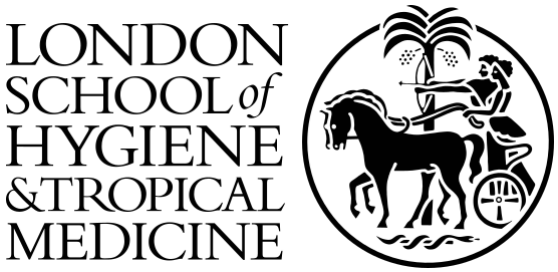

Facing the challenges of high-cost medicines:

Multinational comparison of the pricing and reimbursement decision-making processes for the new Hepatitis C treatments

AMINA SUGIMOTO

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Department of Health Services Research and Policy

Faculty of Public Health and Policy

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Declaration

I, AMINA SUGIMOTO, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Date:

Dedication

I would like to dedicate this Doctor of Public Health (DrPH) thesis to my family.

Arigatou to my father, mother and Mari for your continuous support throughout the programme.

Acknowledgements

First and foremost, I would like to thank Professor John Cairns, my supervisor, for his patient guidance, advice and encouragement throughout my study at the LSHTM. I respect him and have learnt so much not only as an academic but also as a professional.

I would also like to thank my DrPH classmates as well as those who shared the offices with me, for their inspiration and encouragement.

Sincere thanks to my family and friends as well who supported me dearly even during my hard times.

And lastly, I would like to use this opportunity to thank the Joint Japan / World Bank Graduate Scholarship Program (JJ / WBGSP) for financially supporting my study here at the LSHTM. Without this program, I would not have managed to complete the programme.

Integrating statement

This integrating statement is one of the last written assignments for the DrPH programme, which aims for the student to reflect on the learnings from its three distinct components with the emphasis on the linkages between them. I have, therefore, organised this statement into three sections: the first section focuses on my experiences and learnings from each of the three components. The second section explores what impacts it had on my career as a public health professional. Last but not least, the third section discusses how the programme can be improved for prospective students.

1. The DrPH programme:

Taught course, organisation and policy analysis (OPA) project and research project were the three components of the DrPH programme. In this section, I have summarised my experiences and learning from each component.

Taught course: The taught course was comprised of two mandatory modules, which involved attending classes, daily reading and four written assignments during the first three months of the programme. We also had a special retreat as a class, which was a full-day training on leadership and management. One of the unique characteristics of the programme, I believe, is diversity. Not only that the students come from a various cultural background, but we were also diverse in terms of age, professional background and the level of working experience. The teaching itself was thought-provoking led by specialists from various fields. However, as a DrPH student, we were also expected to contribute to discussions based on individual's practical experiences. Being the youngest member of the class, I struggled the most during these first few months. This is because I was feeling that there was a limit to how much I could contribute compared to the classmates considering the level of experience I had prior to joining the LSHTM. Nevertheless, now that I reflect back, the struggle I experienced during this phase greatly enhanced my learning throughout the programme. Being constantly exposed to that level of diversity helped to shape my research interest and to set a clear future vision. Also, I had managed to train myself to self-sustain confidence and motivation. Spending the first three months together with the class also created this sense of unity and a support system, which may

not exist for a PhD student. A frequent check-in with each other was helpful to stay on track and to be inspired throughout the programme.

OPA project: I chose to do my OPA project at the first biotech public-private partnership in Japan called the Global Health Innovative Technology (GHIT) fund. Since my research interest is in “Access to medicine”, I wanted to learn about this new attempt by the Japanese government which collaboratively invests in innovative research for neglected diseases together with the private sector. The biggest challenge was in obtaining an agreement from the GHIT for conducting the project at their organisation. In the end, I had a great support from the school, especially Prof. Peter Piot, who kindly connected me with the GHIT fund. This whole process took four months. I know a few DrPH students who have similarly struggled to identify an organisation for their OPA. It was often the case that the students had misjudged the scale and objective of the project, and failed to obtain an agreement from their preferred organisation. The issue of finding an organisation for OPA was often raised and discussed at the course meetings. However, I think the whole experience of OPA starts from identifying an organisation to negotiation, which is a training process itself for shaping a piece of work that satisfies both parties involved. The programme is, therefore, intentionally designed to be flexible for this purpose. What may be needed is for the school to communicate this clearly to the students and to provide necessary support based on their needs. If I had a clear understanding of the objective and scale of OPA prior to starting my research, I would have chosen a smaller organisation to practice skills on qualitative analysis and to conduct a more in-depth analysis. As I had limited experience working on qualitative analysis, the whole process (analysis and write-up processes was another challenge. However, the assignments from the taught course, especially the mini-OPA assignment, were helpful to get a sense of what was expected.

Research project: I started to prepare for the last component of the DrPH programme, research project, from January 2015. The DrPH review took place in July 2015, and I completed the thesis in July 2017. I, therefore, spent approximately 2 years from data collection to analysis and write up. I chose a similar topic to the OPA “Access to medicine”. However, this time was more specific on “Access to high-cost medicine”, which has become an emerging issue even in the developed countries. Unlike the PhD programme, the first two components of the DrPH programme provided sufficient amount of time to rethink and narrow down my research interest. With support from the supervisors, I had managed to specify my research interest from broad interest on access to medicine to pharmaceutical policy and high-cost medicine. I think that it was advantageous to work on

the same topic for the OPA and research project, and to use similar research techniques. The OPA experience was a perfect opportunity for practising what I have learnt from the taught course, which I could then fully apply for the research project.

2. Career as a public health professional:

The past four years at the LSHTM was a constant struggle with myself, but it was the right amount of time to search for my passion: what I should work on, what I want to work on and what I can work on. As mentioned previously, to have linked the content of the OPA to the research project was helpful. While studying the issue of access to medicine in the developing countries, I have come to realise that the issue of the rising cost of pharmaceutical products in the developed countries has become one of the utmost important and emerging public health issues worldwide. Having spent a year thinking about the issue has helped me to shape my future. Currently (as of July 2017), I work at a public-health think-tank based in Tokyo where it's main focus is on the issues of healthcare spending and pharmaceutical costs. In a few years, I hope to move to the private sector, a pharmaceutical company, to obtain more hands-on practical experiences on how to improve access to medicine in collaboration with the public sector.

3. Future improvements of the program:

The content of the programme has changed and improved greatly during the past four years, and thus the current students must have a different experience to my time. However, if I am to improve anything, I would look more into designing additional management and leadership workshops which are available throughout the programme. What we learnt in the taught course is not something that can be learnt all at once. It would be a good occasion to practice these skills, and also to get to know DrPH students from other cohorts.

Overall, my experience at the LSHTM has been very enriching. When I first started, I had to change my supervisor and had a few months of feeling lost. Even then, I was given enough support and supervision. The way the school is designed, that it is a public health-focused graduate school with specialists from various disciplines, was also helpful in identifying my true research interest. Compared to my experience at the previous university, I find that the door was open to most professors and that there were various multi-disciplinary events. I think that the programme itself was flexible, and although we had to work very hard for it, there was enough support for individual students. The programme structure was also helpful to self-motivate ourselves, that there was a pressure of moving from one component to the other but at the same time there was a sense of

completion and satisfaction. This flexibility was also helpful in making this experience of DrPH unique and different from each other.

It is still difficult to believe that I am about to complete the DrPH programme and that my time at the LSHTM has come to an end. But I treasure the experience I had at the LSHTM, a constant exposure to the world class public health researchers and the network we have built throughout the four years. I hope that this will be my strength to further practice as a public health specialist.

Abstract

The therapeutic landscape of Hepatitis C virus (HCV) infection has changed dramatically since 2013 when “life-saving” direct-acting antivirals (HCV-DAAs) entered the global market. Although behind such a huge biomedical stride, their high prices have been criticised globally as a barrier to patient access and a threat to health care financing.

In order to understand the emerging challenges of high-cost medicines, this study conducted a comparative multinational analysis of pricing and reimbursement decision-making processes for HCV-DAAs in Japan, the U.S. and England.

Overall, the list prices of HCV-DAAs differed largely by country (the U.S.>England>Japan) and by pharmaceutical company.

With respect to reimbursement decisions, the common obstacle was the prediction of and the management of demand. Access to HCV-DAAs was least controlled in Japan and most strictly controlled in the U.S. where certain individuals (those with HIV co-infection, a history of illicit drug and alcohol use) were systematically excluded. In England, access, in theory, was controlled by the disease stage, but in practice, implementation was largely delayed and the number of patients to be treated annually has been strictly managed.

The study found that despite the common obstacle of budget impact, the countries were faced with different challenges. In Japan, there has been a growing recognition of the importance of cost considerations. While this may be a positive development, the implementation of health technology assessment (HTA) must reflect the existing health system, policies and culture. In the U.S., increased focus should be placed on its systematic problems such as its fragmented health system. The challenge for England was more specific, namely, the disparity between the current budget and the cost-effectiveness threshold must be reconsidered, given the ability of the NHS to produce health benefits from existing activities.

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Introduction

With the recent technological advancements in the pharmaceutical sector, highly effective but costly medicines (i.e., high-cost medicines) are becoming more and more available for prevalent diseases such as Hepatitis C virus (HCV) infection: a disease that affects more than 170 million people worldwide (2 to 3% of the world population) and the cause of 54,000 deaths and 955,000 disability adjusted life-years (DALYs) annually [1].

For long, prevention and clinical management of this blood-borne disease had been a challenge due to numerous obstacles including its asymptomatic silent progression, variations in genotype and the high prevalence among the hard-to-reach populations (e.g., injection-pharmaceutical product users (IDUs) and correctional population) [2]. Since the market entry of Direct-Acting Antivirals (HCV-DAAs) in 2013, however, the therapeutic landscape of HCV infection has begun to change dramatically. In contrast to the previous regime that used pegylated interferon (PEG-IFN), HCV-DAAs have a significantly higher sustained virologic response (SVR) in most patient types and it can be administered orally [3][4]. Moreover, HCV-DAAs can now be prescribed as an interferon-free regimen with limited side effects [5]. Accordingly, HCV-DAAs have received positive recommendations from medical associations worldwide including the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and the Japan Society of Hepatology (JSH) [6][7][8]. The World Health Organization (WHO) also issued its first guideline for HCV infection in 2014 and added HCV-DAAs onto its essential medicine list [9][10].

Behind such a huge biomedical stride, however, HCV-DAAs remain out of reach for most patients around the globe. Of many factors that could contribute to inadequate access, affordability is one of the main reasons that undermines it [11]. Olysio® (Simeprevir, Janssen Pharmaceutica); Sovaldi® (Sofosbuvir, Gilead Science, Inc.); Daklinza® (Daclatasvir, Bristol-Myers Squibb); and Harvoni® (Sofosbuvir+Ledipasvir, Gilead Science, Inc) are examples of HCV-DAAs which had an initial price tag of 66.360, 84,000, 63,000 and 94,500 USD per a 12-week treatment course, respectively [12]. With these high prices, despite its high effectiveness, not only low-and-middle-income countries (LMICs), but also high-income countries (HICs) are struggling to ensure access while managing their health care expenditure [13][14][15]. As a result, the high list prices of HCV-DAAs have been criticised globally making the political headlines as a barrier to patient access and a threat to the financial sustainability of the health systems [11][16]. The issue was raised at both the G7 and G20 summits and became a major

consideration for the United Nations (UN) high-level panel on access to medicine [17][18].

While some financial incentives are essential for accelerating medical progress, ensuring affordable access to medicine is a critical part of the health systems for providing services that a patient needs, wants and deserves [14]. Under the growing tension between the provision of health care and the continuous expansion of the pharmaceutical spending, policy makers are becoming increasingly more aware that the appropriate use of pricing and reimbursement policies is the key to maintain a balance that will maximize health outcome and facilitate cost-effective and sustainable access to high-cost medicines [19][20]. To date, countries have applied various policies to control the spending on HCV-DAAs and to ensure timely and appropriate access. However, due to the differences in the design, motives, and rationale behind such policies, how countries have been responding to this challenge is not yet well explored.

With this respect, this research conducted by AMINA SUGIMOTO as a doctorate thesis, as a part of the Doctor of Public Health (DrPH) programme at the London School of Hygiene and Tropical Medicine (LSHTM) investigated countries' response to the challenge of high-cost medicines using an example of HCV-DAAs. Case studies were conducted in Japan, the United States (U.S.) and England from August 2015 to December 2016 with an overarching aim to contribute to the understanding of the emerging challenges of high-cost medicines by conducting a comparative analysis of countries' experiences with ensuring access to HCV-DAAs. Given the fiscal impact of the recent financial crisis and the unprecedented market entry of HCV-DAAs, a summary of the implemented policies by these world economies would be of good use for the future policy making of other countries that are facing a similar challenge.

The thesis consists of three parts: Part 1 frames the challenge to be addressed in this thesis by providing the background information. It also explains the methodology used for the study; Part 2 explains the study findings: and Part 3 discusses the key findings and the main contributions of the study.

Research aim and objectives

The overarching aim of this thesis is to contribute to the understanding of the emerging challenges of high-cost medicines by conducting a comparative analysis of countries' experiences with ensuring access to HCV-DAAs.

To achieve this aim, the pharmaceutical policy of the selected countries (Japan, the U.S., and England) were studied, and their progress towards making pricing and reimbursement decisions for HCV-DAAs were investigated and compared.

The specific objectives are to:

1. Capture the global access situation for HCV-DAAs;
2. Describe the pharmaceutical policy (pricing and reimbursement decision-making processes) of the selected countries;
3. Describe the progress for ensuring access to HCV-DAAs in the selected countries;
4. Identify the obstacles and challenges experienced by the selected countries, and describe how they have responded; and
5. Draw conclusions from objectives 2 - 4 on what lessons can be learnt from the experiences with HCV-DAAs for ensuring access to the forthcoming generation of high-cost medicines.

Part 1: Study background

Part 1 of the thesis aims to provide necessary information for understanding the purpose and methodology used for the study, which is divided into two chapters:

- Chapter 1: frames the challenge to be addressed in this thesis by providing a review of the literature on the current epidemiology, prevention and clinical management of HCV infection worldwide, as well as on the emerging issues associated with access to high-cost medicines.
- Chapter 2: explains the methodology and conceptual frameworks used for this study.

Chapter 1: Background

1.1 Introduction

This chapter provides information necessary for understanding the study, which is divided into four sections. Since the aim of this thesis is to understand emerging challenges of access to high-cost medicines using HCV-DAAs as an example, Section 1.2 explains the epidemiology of HCV infection as well as its preventative and clinical management measures that are currently in use. Section 1.3 further provides additional information about HCV-DAAs including a summary of clinical and cost-effectiveness data and an updated list of HCV-DAAs with a regulatory authorisation (as of December 2016). In Section 1.4, the emerging issues of high-cost medicines are discussed. Finally, in Section 1.5, the structure and objectives of pharmaceutical policy are explained to clarify why and how the pharmaceutical market principally differs from other markets.

1.2 Hepatitis C virus infection

Hepatitis C virus (HCV) infection, first discovered in 1989, is a blood-transmitted infectious disease that until recently did not have effective treatments [21]. It is estimated that close to 3% of the world population is infected, and of those 130 to 170 million people are chronically infected [1][2][22]. In 2013, 1.46 million deaths were reported to have been linked to the infection, and it is estimated that 350,000 to 500,000 people are dying annually from the complications resulting from the infection [1][23]. Despite such a significant global burden, HCV infection has for long been ignored as a public health issue.

Epidemiology of HCV Infection

HCV infection is a global epidemic that has a large degree of geographic variability. Eighty percent of the global burden is found in low and middle-income countries (LMICs) where Egypt, India, and China have the highest incidence and prevalence rates [24]. However, unlike the other infectious diseases such as tuberculosis (TB) and malaria, HCV infection is also highly prevalent in high-income countries (HICs) like the United States (U.S.), Japan and Italy [1][2]. There is also a significant regional variation that exists over its genotypes. Globally, genotype 1 (GT1) is the most prevalent type which accounts for 46% of all the adult infections, followed by GT3 (22%), GT2 (13%), GT4

(13%), GT6 (2%), and GT5 (1%) [25]. Infections in North America and Europe are predominantly GT1, North Africa and the Middle East have a large GT4 population, and Asia is largely GT3 [25].

The disease transmits primarily by percutaneous inoculation of contaminated blood (e.g., unsafe medical practice, illicit drug use and blood transfusion), sexual intercourse and from mother to child infection [2][21]. In LMICs, unsafe medical practice is still the predominant route of infection: in 2000, nearly 40% of injections were performed using already used medical equipment, which caused approximately two million new infections [26]. On the other hand, illicit drug use is the most common route of transmission in HICs, for example, more than two-thirds of the infections in the U.S. in the last decade were in injecting drug users (IDUs) [27].

Disease progression is typically marked by slowly progressive fibrosis from stage 0 (F0: no fibrosis) to stage 4 (F4: cirrhosis), which could take a latent period of over 30 years [28][29]. Once infected, approximately 75 to 85% of the cases develop into chronic infection, and of these 60 to 70% develop into HCV-related End-Stage Liver Disease (ESLD) and Hepatocellular Carcinoma (HCC) [29]. It is estimated that approximately 90% of the new liver cancer incidence, which is the second most common cancer worldwide, is caused by HCC [21][30][31]. The infection, therefore, kills more people than TB (1.2 million deaths) and malaria (0.5 million deaths), and is also a leading cause of death among persons infected with Human Immunodeficiency Virus infection / Acquired Immune Deficiency Syndrome (HIV/AIDS) (1.3 million deaths) [23][31].

In recent years, it is estimated that the incidence rate of HCV infection in most HICs is gradually declining due to concerted disease control efforts [2][21]. For example, blood transfusion accounts for only one-quarter of the source of the new cases worldwide and it is nearly eliminated in most HICs, due to compulsory (if not frequent) testing for HCV-specific antibodies and HCV-ribonucleic acid (RNA) in donated blood samples [21]. Therefore, the current global HCV epidemic is mostly the result of the frequent use of unsterilized medical equipment until the 1980s [2]. For example, the poor sterilisation procedures utilised during the Schistosomiasis infection eradication program in Egypt from the 1950s to 1980s was the cause of the extensive transmission [32]. Egypt, therefore, has the highest prevalence of HCV antibodies of 14.7% [21][32]. Similarly, in Japan, the nationwide schistosomiasis eradication campaign from 1940 to 1980 resulted in an extensive spread of HCV infection [33]. Even in the U.S., 70% of infected persons were born between 1945 and 1965, and thus the government is recommending screening individuals born within this time frame [34].

Accordingly, considering the current epidemiological profile, the majority of infected individuals today are over the age of 65. Since the risk of obtaining liver diseases increases progressively with age and duration of infection, it is expected that the prevalence of severe liver diseases will sharply increase in the next decade [21][35][36][37]. For example, the mortality rates from HCV-related HCC and cirrhosis have increased by 74% and 36%, respectively, from 1990 to 2010 [31][38].

Despite the above statistics, however, there is not yet a reliable estimate of the prevalence of HCV-related HCC and cirrhosis, or the mortality attributable to HCV infection [2]. This is because the high prevalence rate is often found in the hard-to-reach populations and also that the vast majority of infected individuals are spending many years unaware of the infection due to its long latent period [2]. In the subsequent section, challenges associated with prevention and control of HCV infection are explained.

Prevention and control of HCV infection

Both preventative and control (clinical) measures are important for achieving herd immunity and to lower the risk of (re)infection [21][39]. Further details are explained below:

Preventative measures: Preventative measures aim not only to protect individuals from infections, but also to prevent further spread of the disease through behavioural control. The commonly used preventative measures are safe blood supply, safe injection practices, as well as reducing the number of people who initiate drug injection [2]. Such public health efforts, to efficiently identify HCV-infected persons and to direct them to appropriate medical care, are currently underway in many countries (e.g., needle exchange programs in Australia and birth cohort testing in the U.S.) [40]. However, despite these efforts, more than 15% of the infected persons globally are still unaware of the infection, and the high transmission and reinfection rates are persistent amongst the hard-to-reach populations [21]. This is because the control of HCV infection has been challenging due to uncertainties regarding the basic epidemiological data, geographical distribution, risk factors, and co-factors that accelerate its progression [2][29]. A large proportion of the infected individuals has also uniformly reported having suffered from fear and anxiety about stigmatisation and discrimination [21]. Since the majority of the new incidences are found in the hard-to-reach populations, stigmatisation and negative societal attitudes towards these individuals results in under-reporting of HCV-infection. Although studies have found that the reinfection rate among these populations after a successful treatment is relatively low, such under-reporting and low political interest are

both barriers to sufficient resource allocation [21][41]. Moreover, lack of an effective vaccination further lowers public interest over HCV-infection [10]. (Note: Despite the fact that there were a general understanding that the reinfection rate is low after a successful treatment, evidence for HCV-DAAs was not available at the time of the study [42])

Control measures: The success of HCV treatment can be measured using Sustained Virologic Response (SVR), which indicates the proportion of persons with no HCV RNA detected six months after the end of treatment [21]. Since a relapse rarely occurs a few months after the end of treatment, SVR is often used as a proxy for cure. Until 2013, the standard of care (SOC) for HCV-infected persons with GT1 was Pegylated interferon (PEG-IFN) plus Ribavirin (RBV) [10]. However, the global coverage of this regime has been far from the optimal ranging from 21% in the U.S. to as low as 3.5% in Europe because of its complex administration, severe side effects, long duration of treatment (24 to 48 weeks) and the low SVR rate (40 to 50%) [3][38][43][44]. Especially in patients with co-existing conditions (e.g., HIV/AID, autoimmune disorder, solid organ transplant and active substance abuse), PEG-INF often results in a low level of effectiveness and a high rate of adverse effects [40]. For example, close to 50% of HIV patients are intolerant to PEG-INF and many have experienced various side effects [40]. There are also other reasons for the low uptake of the previous SOC for HCV infection. These include: 1) physicians and healthcare staff with special training and experience are required; 2) the most common method of antibody detection cannot distinguish acute and chronic infections; 3) diagnosis is often delayed due to asymptomatic silent progression of the disease; 4) several types of HCV genotypes respond differently to the existing treatments; 5) a high prevalence in regions / areas with limited access to health services (e.g. laboratory testing, refrigeration of pharmaceutical products); and 6) complexities and high costs associated with provision of the treatments [29][40]. Due to the above reasons, most countries have long failed to develop political and public interest in investing in control measures for HCV-infection.

1.3 Direct-acting antivirals (HCV-DAAs)

The first breakthrough in HCV treatment occurred in the early 1990s with the market entry of interferon alpha (INF-a) [45]. In 1998, RBV was added to INF-a, which doubled the SVR rate, and in 2001 PEG-IFN in combination with RBV was introduced to the market [45]. However, as mentioned earlier, this traditional SOC has long been unpopular.

In 2011, the first generation HCV-DAAs ((Victrelis® (Boceprevir, Merck & Co.) and Incivek® (Telaprevir, Janssen Pharmaceutica)) became available [46]. In 2013, the second generation HCV-DAAs ((Olysio® (Simeprevir, Janssen Pharmaceutica) and Sovaldi® (Sofosbuvir, Gilead Science, Inc.)) entered the market, and this had signalled the end of the traditional SOC [46].

In contrast to the traditional SOC, HCV-DAAs are highly effective with a high SVR of over 90%, manufactured as a tablet for simplified administration (e.g., oral and once-daily), requires less than 12 weeks of treatment duration and have minimal toxicity [37][47][48](Table 1). Moreover, the most recent products have a high SVR in all patient subgroups regardless of the genotypes, age, sex, race and liver-enzyme levels [37]. It also has an important public health implication that with simplified administration, it has become much easier to roll out in the hard-to-reach settings.

Sovaldi®, which later became an essential ingredient for the improved combination regimen, was initially discovered by a mid-size pharmaceutical company called Pharmasset Inc. Gilead Science, Inc (hereafter Gilead) bought Pharmasset Inc. for 11 billion USD, in November 2011, while the compound was still undergoing a Phase 2 clinical trial [49]. It was a huge gamble for both companies, but this purchase sent out a clear message that Gilead was intent on becoming the global leader in the HCV infection disease area. Sovaldi® was then considered as the best HCV treatment available, and Gilead stock has more than quadrupled since 2014 [50].

TABLE 1: COMPARISON OF THE SOC FOR HCV INFECTION (PRE AND POST-2013)

	Pre-2013	**Post-2013**
Treatment type	Pegylated interferon	Second generation HCV-DAAs (Interferon-free)
FDA Regulatory authorisation	2001	2013
SVR rate	<50%	>90%
Side effects	Severe	Minimal
Treatment duration	24 to 48 weeks	8 to 12 weeks
Administration	Injection	Oral tablet

Regulatory authorisation (as of December 2016)

Regulatory authorisation (also referred to as market authorisation) is an essential process before a product enters the market. In most countries, a regional / national agency independently conducts this regulatory authorisation process. Typically, the most respected agencies are the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Ministry of Health, Labour and Welfare of Japan (MHLW). They are responsible for pharmaceutical product evaluation, quality control, and registration and control of standards for production, importation and marketing of new prescription medicines [51].

As of December 2016, 15 HCV-DAAs have received regulatory authorisation from at least one of the three regulatory authorities (Table 2). These HCV-DAAs can be categorised into three classes depending on their function: NS3/4A protease inhibitors, NS5A inhibitors and NS5B polymerase inhibitors.

HCV is a positive-stranded RNA virus, and its non-structural proteins which are crucial for viral entry, replication and proliferation are produced by translating a set of genes sequenced in its long open reading frame (ORF) [52]. Each of the genes (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B), therefore, has a function to produce non-structural proteins essential for virus survival, and HCV-DAAs function by terminating these processes (mainly the RNA replication and proliferation processes by inhibiting its translation process of polyproteins to non-structural proteins) [30].

In addition, five multi-class combination regimens (i.e., a combination treatment of two or more HCV-DAAs) are also available. The characteristics of each of the HCV-DAA classes are explained in detail below [46][53][54]:

- **NS3/4A Protease inhibitors:** There are seven NS3/4A protease inhibitors available: 1) Victrelis® (Boceprevir, Merck & Co.); 2) Incivek® / Incivo® (Telaprevir, Janssen Pharmaceutica): 3) Olysio® (Simeprevir, Janssen Pharmaceutica); 4) Sunvepra® (Asunaprevir, Bristol-Myers Squibb); 5) Vanihep® (Vaniprevir, Merck & Co.); 6) Viekirax® / Viekira Pak® (Paritaprevir, AbbVie Inc.) and 7) Zepatier® (Grazoprevir, Merck & Co.). In 2011, Incivek® (EMA: September 2011, MHLW: November 2011) and Victrelis® (EMA: July 2011, MHLW: Not filed) received the FDA regulatory authorisation as the first generation HCV-DAAs. However, despite the high SVR ranging from 68 to 75% in GT1 treatment-naive patients, patients still had to suffer the side effects due to the recommended use of PEG-IFN [55][56]. As more effective HCV-DAAs with fewer side effects became available, NS3/4A protease inhibitors have become less popular and are

gradually disappearing from the market. For example, Victrelis® (Discontinued date: December 2015) and Incivek® (Discontinued date: October 2014) were both discontinued in the U.S. Also in England, both Victrelis® and Incivek® were recently moved to the static list, recognising that there is no new research that would have any material effect on the current guidance [57]. Sunvepra® was filed in the U.S. in April 2014, but it was later withdrawn (October 2014). To date, Sunvepra® has a regulatory authorisation only from the MHLW (September 2014). Vanihep® was only filed and approved by the MHLW (November 2014). One of the suggested reasons for this trend is that the use of NS3/4A protease inhibitors as a monotherapy given in combination with PEG-IFN and RBV had led to the emergence of drug-resistant variants [58]. Olysio® (EMA: May 2014, MHLW: November 2015) was approved in the U.S. in November 2013, and it is the most effective NS3/4A protease inhibitor currently available.

- **NS5A inhibitors:** There are five NS5A inhibitors that are currently available: 1) Daklinza® (Daclatasvir, Bristol-Myers Squibb); 2) Harvoni® (Ledipasvir, Gilead Science, Inc.); 3) Viekirax® / Viekira Pak® (Ombitasvir, AbbVie Inc.); 4) Enclose® (Velpatasvir, Gilead Science, Inc.) and 5) Zepatier® (Elbasvir, Merck & Co.). These new type of inhibitors were first approved in late 2014, and are becoming popular as a potential cure for patients with the genotypes other than GT1. While most of the NS5A inhibitors were approved in combination with other HCV-DAAs, Daklinza® is the first and only inhibitor that was approved as a separate entity (FDA: July 2015, EMA: August 2015, MHLW: September 2014).
- **NS5B polymerase inhibitors:** There are two NS5B polymerase inhibitors available: 1) Sovaldi® (Sofosbuvir, Gilead Science, Inc.); and 2) Viekirax® / Viekira Pak® (Dasabuvir, AbbVie Inc.). Sovaldi® was approved by the FDA in December 2013 (EMA: January 2014, MHLW: May 2015), and this was the first product that could be orally administered without the use of PEG-IFN and had worked well against different genotypes (GT1 to GT6) [59]. Sovaldi® was also the first HCV-DAAs which was approved through the accelerated pathway by the FDA (Similar to adaptive licensing) [60].
- **Multi-class combination drugs:** There are five multi-class combination drugs available: 1) Harvoni® (Sofosbuvir + Ledipasvir, Gilead Science, Inc.); 2) Viekirax® / Technivie® (Ombitasvir + Paritaprevir + Ritonavir, AbbVie Inc.) 3) Viekira Pak® (Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir, AbbVie Inc.); 4) Zepatier® (Elbasvir + grazoprevir, Merck & Co.) and 5) Epclusa® (Sofosbuvir + Velaptasvir, Gilead Science, Inc.). The first multi-class combination drug was

Harvoni® (FDA: October 2014, EMA: November 2014, MHLW: August 2015), which had shown the SVR of close to 100% [40]. Its response rate was equally the same in most patient subgroups regardless of the age, sex, race, liver-enzyme levels, genotypes and pre-existing antiviral resistance variants [40]. In 2015, AddVie Inc. (Hereafter AddVie) also released combination drugs, Technivie® and Viekira Pak®. Although both HCV-DAAs had scored a high SVR, the FDA released a warning in 2015 informing the potential risk of acquiring acute liver injury [61]. The latest combination drugs available are Zepatier® (EMA: July 2016, MHLW: N/A) and Epclusa® (EMA: July 2016, MHLW: N/A), which were approved by the FDA in early 2016. The multi-class combination drugs become the mainstream as it prevents the emergence of resistant variants [62].

As such, the recent trend of the HCV-market shows how competitive the market has become over the past six years. It was estimated that there were approximately 60 or more pharmaceutical products for HCV infection under development (as of March 2013) [63]. The trend is moving toward a regime that is easily administered with less treatment duration and side effects. Although the number of assessment looking at long-term outcomes and potential harms of HCV-DAAs is still limited, the future line-up is looking promising with different viral targets and improved combinations [15][64].

Clinical recommendations

Despite the high effectiveness of HCV-DAAs, the recommended selection and use of HCV-DAAs for patients with specific conditions differs by country. Generally, guidelines published by the major international hematology associations such as the American Association for the Study of Liver Diseases (AASLD), the Infectious Disease Society of America (IDSA), the European Association for the Study of the Liver (EASL), and the Japan Society of Hepatology (JSH) have made favorable recommendations for the use of HCV-DAAs over the traditional SOC [6][7][8]. They recommend the treatment of all infected individuals, except for those with limited life expectancy (e.g., less than a year due to other diseases) [6]. Due to their simplicity and safety, the AASLD also recommends that HCV-DAAs can be prescribed by non-specialist physicians [6].

Furthermore, the World Health Organization (WHO) issued its first guideline for HCV infection in 2014, just in time for the second generation HCV-DAAs [10]. In this guideline, the WHO recommended the use of HCV-DAAs (Sovaldi® and Olysio®) in most conditions instead of PEG-INF and RBV alone (potential impacts of costs were not considered) [10]. At the 67th World Health Assembly (WHA) in the same year, a resolution WHA 67.6 was

passed, which focused on improvement of prevention, diagnosis and treatment of viral hepatitis [65]. Thus, “Combat viral hepatitis” is now listed as one of the specific action plans on the 2030 Agenda for Sustainable Development Plan by the UN [66]. In 2015, the WHO also added Olysio®, Sovaldi®, Daklinza® and Harvoni® on its essential medicine list [9]. Thus combating HCV infection has quickly become a global public health priority, and this has stimulated countries to improve the access to HCV-DAAs. Later in 2016 at the WHA, a strategy that included the very first global targets for HCV infection control was adopted as a Global Health Sector Strategy (GHSS) on viral hepatitis for the period 2016 to 2021 [67].

Cost-effectiveness recommendations

There are several studies on the cost-effectiveness of HCV-DAAs. However, since the calculated incremental cost-effectiveness ratio (ICER) varies widely depending on the context (e.g., targeted population, clinical effectiveness, pricing, and estimated probability of progression), the findings from the National Institute for Health and Care Excellence (NICE) on the cost-effectiveness of Sovaldi® and Harvoni® in the context of the United Kingdom (U.K.) are summarised below [68][69] (Appendix 1).

Assessments of the cost-effectiveness of Sovaldi® and Harvoni® were conducted separately for treatment naïve and experienced groups, those with and without cirrhosis, and also for special groups (e.g., people not eligible for PEG-INF and those infected with HIV/AIDS). Overall, NICE concluded that Sovaldi® and Harvoni® were cost-effective under most scenarios. However, there are some exceptions. For example, NICE does not recommend the use of Sovaldi® in combination with PEG-INF and RBV for people who are not eligible for PEG-INF. For genotypes other than GT1, the use of Sovaldi® for the treatment naïve population (especially without cirrhosis) is not recommended. As for Harvoni®, it is recommended for all types of GT1 and GT4 patients, but it cannot be used for more than 24 weeks. It is also not recommended for those with GT3 and people with the advanced liver disease and after a liver transplant. These appraisal results from NICE resemble most of the independently conducted cost-effectiveness analyses. Except, the Institute for Clinical and Economic Review (ICER), a U.S-based independent nonprofit organisation specialised in conducting clinical and cost-effectiveness analysis of healthcare products, was initially sceptical and gave a negative recommendation to Sovaldi® [70]. However, later in their reports, they recommended both Sovaldi® and Harvoni® as being valuable for individual patients, as well as for most health systems [71].

TABLE 2: LIST OF HCV-DAAS WITH REGULATORY AUTHORISATION FROM FDA, EMA AND MHLW

Brand name	Generic name	Company	WHO Essential Medicine	Regulatory Authority	Approval date
Multi-class combination drugs					
Harvoni®	Sofosbuvir + Ledipasvir	Gilead	Yes	**FDA**	Oct 2014
				EMA	Nov 2014
				MHLW	Aug 2015
Viekirax® / Technivie®	Ombitasvir + Paritaprevir + Ritonavir	AbbVie	No	**FDA**	July 2015
				EMA	Jan 2015
				MHLW	Nov 2015
Viekira Pak®	Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir	AbbVie	No	**FDA**	Dec 2015
				EMA	Nov 2014
				MHLW	Dec 2015
Zepatier®	Elbasvir + grazoprevir	Merck	No	**FDA**	Jan 2016
				EMA	July 2016
				MHLW	N/A
Epclusa®	Sofosbuvir + Velaptasvir	Gilead	No	**FDA**	June 2016
				EMA	July 2016
				MHLW	N/A
NS3/4A Protease Inhibitors					
Victrelis®	Boceprevir	Merck	No	**FDA**	May 2011 DISC**
				EMA	July 2011
				MHLW	N/A
Incivek® / Incivo®	Telaprevir	Janssen	No	**FDA**	May 2011 DISC**
				EMA	Sep 2011
				MHLW	Nov 2011
Olysio®	Simeprevir	Janssen	Yes	**FDA**	Nov 2013
				EMA	May 2014
				MHLW	Nov 2015
Sunvepra®	Asunaprevir	BMS	No	**FDA**	N/A
				EMA	N/A
				MHLW	Sep 2014
Vanihep®	Vaniprevir	Merck	No	**FDA**	N/A
				EMA	N/A
				MHLW	Nov 2014
(Available as Viekirax® / ViekiraPak®)	Paritaprevir	AbbVie	-	-	-
(Available as Zepatier®)	Grazoprevir	Merck	-	-	-
NS5A Inhibitors					
Daklinza®	Daclatasvir	BMS	Yes	**FDA**	July 2015
				EMA	Aug 2014
				MHLW	Sep 2014
(Available as Harvoni®)	Ledipasvir	Gilead	-	-	-
(Available as Viekirax® / ViekiraPak®)	Ombitasvir	AbbVie	-	-	-
(Available as Epclusa®)	Velpatasvir	Gilead	-	-	-
(Available as Zepatier®)	Elbasvir	Merck	-	-	-
NS5B Polymerase Inhibitors					
Sovaldi®	Sofosbuvir	Gilead	Yes	**FDA**	Dec 2013
				EMA	Jan 2014
				MHLW	May 2015
(Available as Viekira Pak®)	Dasabuvir	AbbVie	-	-	-

Source: Homepage of FDA, EMA and MHLW

*: SRV differs by clinical trial. This means most of the clinical trials had scored above the value indicated. **: Discontinued

1.4 Emergence of high-cost medicines

The economic burden of pharmaceutical products contributes substantially to the overall healthcare cost, and thus it is a major concern for policy-makers worldwide [19]. For some time, however, the percentage of total health expenditure devoted to medicine did not change despite the rising cost of new medicines [13]. For example, the Organisation for Economic Co-operation and Development (OECD) countries have been maintaining the expenditure on pharmaceutical products at 15% of Gross Domestic Product (GDP) [72]. However, due to the rising overall health expenditure since 1970, the total spending on pharmaceutical products has also been increasing inevitably [72]. Between 2000 and 2001, total spending on pharmaceutical products increased by 16% in the U.S. and Canada, 14% in Australia and 12% in Italy [13]. One of the main reasons for this was the rapid increase in the prevalence of chronic diseases induced by the recent demographic changes. In addition, the recent rapid development and diffusion of advanced health technology, as represented by HCV-DAAs, also played a crucial role. These highly effective medicines tend to be techno-intensive and thus expensive. Furthermore, as the world gets wealthier, the increasing consumer demand for better treatments accelerated the FDA approval rate from 56% to 88% from 2008 to 2015 [16]. Therefore, while providing more options for governments to deliver high-quality of care to meet their population needs, it also created further financial pressure [73]. In the section below, four theories that explain reasons for the increasing cost of medicines are explored.

Simple chemicals to complex pharmaceutical products

The research & development (R&D) strategy of the pharmaceutical industry has been changing over the past years [74]. In the past, the industry's focus was on producing products that are made of simple chemicals for treating common diseases and infections (e.g., antibiotics, cholesterol lowering tablets). However, in recent years, they have begun to concentrate more on smaller markets for conditions that affect fewer people (e.g., medicines tailored to treat specific diseases). These medicines are often complex, and thus require more investment for R&D as well as for production.

"Evergreening" patents and expensive generics

Intellectual property rights (IPRs) are essential for supporting the industry to generate income to reinvest in R&D to ensure that there is a continuous supply of new pharmaceutical products [75]. However, the system can also be a barrier to encouraging

more price competition within the market [75]. For example, some pharmaceutical companies are exploiting the patent system to list their existing products as a new patented product with slight adjustments, pressured by the fact that some of their profitable products are soon going off patent [13]. This phenomenon is called “evergreening”, creating a cycle of “effectively the same but slightly adjusted” versions of their products to be protected by a new patent for another prolonged period of time [13]. In addition, the generic market is also growing, but the pace of conversion from brand to generics or biosimilar has been slowing down and thus prices of generic products are also going up [16].

High spending on R&D

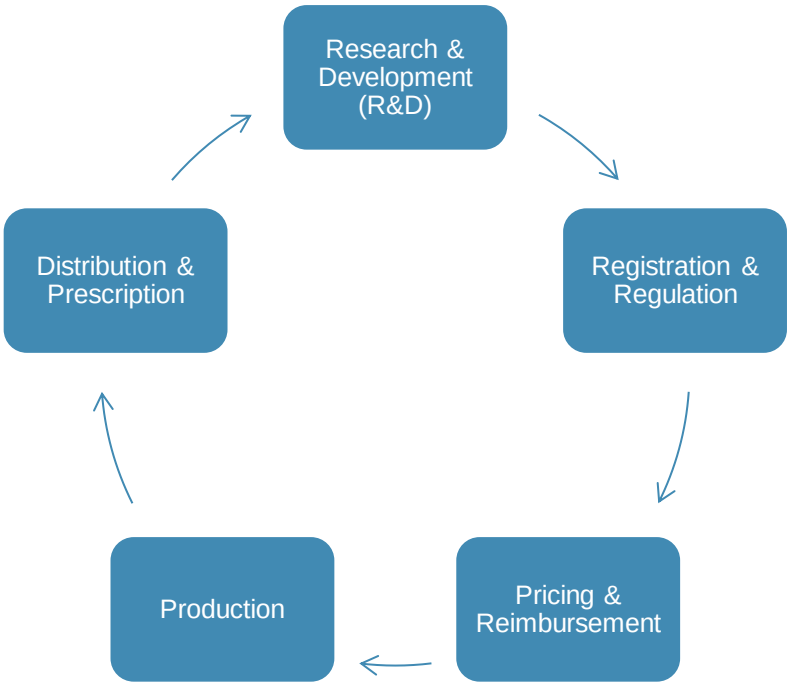
Throughout the pharmaceutical product life cycle, the process of R&D is most expensive costing an average of 800m USD per product (Figure 1) [13]. As such, the industry generally spends a significant proportion of their net profits on R&D: in 2000, the major pharmaceutical companies claimed that they have spent on average of 16% of their expenditure on R&D, which was substantially higher than the 4 % of other industries [13]. Thus, the industry claims that the high spending on R&D is one of the main reasons for the rising prices of pharmaceutical products. However, the actual amount spent on R&D is often a black box and thus it is not publically available information.

High spending on marketing and mergers:

Despite the industry-claimed high spending on R&D, studies have found that a large portion of the spending is actually being used for product promotion and marketing, and more recently for mergers with other pharmaceutical companies [13][72]. One of the possible motives behind this movement is the uncertainty associated with the future of the industry. The pharmaceutical industry used to be one of the most profitable businesses with an average profit of 16%, but in recent years their net income growth has begun to decline and the value of pharmaceutical product stocks has been revised [13]. The factors inducing this trend are the expanding generics businesses, the imminent expiry of patents for several very profitable products and the increasingly demanding customers, but most importantly constrained expenditure on pharmaceutical products by the governments [76]. It is estimated that the number of major international pharmaceutical companies will drop from over 30 to 12 in the next ten years [13]. Such operational costs are increasing the cost of pharmaceutical products. With respect to the

case of HCV-DAAs, a study has claimed that the high costs of HCV-DAAs were result of the 11 billion USD acquisition of Pharmasset Inc. by Gilead [77] . Gilead, therefore, was under pressure to gain a return on their investment. In addition, the fact that HCV infection was one of the most prevalent diseases worldwide, and that the disease suddenly became possible to be eliminated resulted in a rapid increase in demand, and enabled the high product prices.

FIGURE 1: PHARMACEUTICAL PRODUCT LIFE CYCLE



1.5 The pharmaceutical market and policy

It is a well-known fact that the pharmaceutical market is plagued by market failure with conditions such as 1) a lack of timely, independent and accurate information available to patients; 2) limited price competition within the market and 3) external benefits to those who are not receiving health services [13]. In contrast to a regular commodity, pharmaceutical products can save lives and improve health, but at the same time, they can be harmful and even fatal. Pharmaceutical products can also be costly to the health systems, but at the same time, their availability can promote public trust [76]. Therefore, in most countries, government involvement in the pharmaceutical market has been common. In order to secure equitable and safe access to quality medicines, governments can inform, regulate, mandate, finance, and provide medicines [76]. Although financing system and policies used by the government to regulate the market differ by country, the overall ideas are explained in the following section.

Financing systems

The pharmaceutical market is a very complex system involving a heterogeneous array of agencies, companies, organisations, and individuals. Whereas, the pharmaceutical supply chain is simple involving only three entities (Pharmaceutical company, wholesale distributors and pharmacies), the market itself holds a complex triangular relationship of the consumers, the providers and the agencies (i.e., Third-party payer (TPPs)) (Figure 2). Instead of upfront payment for its full cost, patients pay taxes or premiums either to governments or TPPs, which then channel the collected funds to the healthcare providers. TPPs are responsible for reimbursement decision-making and defining a formulary list [76]. Examples of such agencies are government agencies, social insurance organisations and private insurance organisations. A completely free market, therefore, does not usually exist in the health sector since patients are usually separated from the actual transaction and TPPs are paying on behalf of consumers.

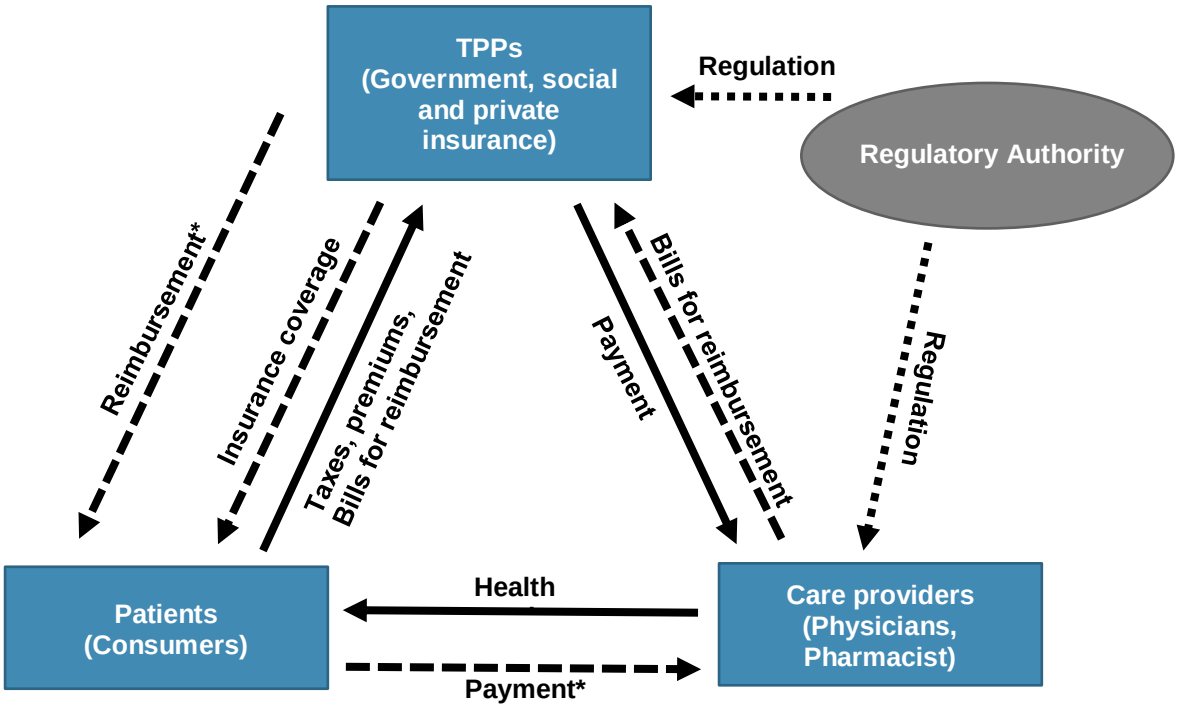
The pharmaceutical financing by a TPP can take two forms [72]:

- **Private financing:** Out of pocket payment (OPP), private health insurance schemes, and financing through other non-governmental entities.
- **Public financing:** Social and national health insurance schemes managed by public agencies based on government budget (central, regional and local), usually with exemptions of the poor and chronically sick.

Most countries have a mixed system, however, the public financing of pharmaceutical products is a standard model used in most HICs, although less prevalent in North America and LMICs [13] For example, the proportion of government subsidisation among HICs varies from the U.S. being the lowest at 15% to 80% or more in Norway, Turkey and the Czech Republic [13]. Therefore, depending on the extent of government involvement, the type of problems and dilemmas in the pharmaceutical policy vary.

In countries with a public insurance system, cost containment of pharmaceutical products is the key concern. This is because although the consumer's demand for pharmaceutical products is usually sensitive to price despite the fact that the sensitivity can vary across different patient groups, such economic factors do not influence physicians' prescribing behaviours [72]. Therefore, in countries with established healthcare systems, it is often challenging to control the volume of prescriptions. On the other hand, for countries with a system that has an extensive involvement of the private sector, protecting individual patients from catastrophic OPP is the foremost challenge.

FIGURE 2: TRIANGULAR RELATIONSHIP OF CONSUMERS, PROVIDERS AND PAYERS IN THE PHARMACEUTICAL MARKET



Source: Adapted from WHO framework "Public-Private Roles in the Pharmaceutical Sector"

*: the actions may only apply on certain occasions or health systems

Pharmaceutical policy

Universal access to medicine can only be achieved when the amount of OPP by patients can be partially or fully reimbursed by TPPs [78]. Therefore, obtaining a regulatory authorisation is of little use to the industry if it is not reimbursed otherwise access to pharmaceutical products will effectively be precluded for most patients [79]. Although prices of pharmaceutical products do not play a crucial role in the physician's decision-making processes in most countries (where partial or full reimbursement is available), it is one of the most important considerations for a TPP to make a reimbursement decision [76]. Hence, pricing mechanism and reimbursement decision-making are additional barriers to the industry, often referred to as the fourth hurdle [79][80]. Countries, therefore, use various policies to control pricing (pricing control policy) and spending (reimbursement policy) on pharmaceutical products [13][81]:

- **Pricing control policy:** Dialectics over price often takes place between a pharmaceutical company and TPPs who are large buyers of pharmaceutical products. They use their purchasing powers to enforce price control by using financial and / or health outcome based Managed Entry Agreements (MEAs). In this thesis, initial prices set by a pharmaceutical company is referred to as list prices, and final agreed prices after some negotiation with a TPP is referred to as effective prices.
- **Reimbursement policy:** Countries use different analysis and decision-making approaches (i.e., Health Technology Assessment (HTA)) to make decisions on formulary list, cost-sharing scheme, coverage decisions and reimbursement reviews.

While the WHO has published a guideline on Country Pharmaceutical Pricing Policies and there are similar pricing and reimbursement policies commonly used especially by the EU countries, the design, motives, and organisation of such policies remain largely different in details by the health systems [80][82][82][82][82][81][81][81][79][79][79][79][79][81][82]. Especially the reimbursement decision-making mechanism is a complex and context-dependent process due mainly to the differences in the political and economic systems as well as the health systems. For example, the obvious differences may be the type and number of available TPPs. In the U.S., there are multiple TPPs from both private and public sectors, but in most European countries a single public sector TPP dominates [79]. Another example of the evident difference is its cost-sharing mechanism. The details of different pharmaceutical policies used in practice will be discussed in the result section (*Part 2*).

It is also a process that has profound implication on patients access to medicines and for the system's fiscal well-being. It is practically a process that determines whether and how much to pay from the pool of fund by balancing the product's ethical and economic values to the society. Therefore, it requires the multifaceted evidence and balancing of benefits and risks in order to determine what level of coverage is appropriate for whom, under what conditions and in what settings [83]. However, the above concept is often difficult for stakeholders (especially patients) to understand that they tend to focus more on potential benefits rather than risks or cost to the TPPs.

Consequently, the decision makers involved and the evidence required for an assessment differ greatly from country to country [79][84]. For example, HTA is an evaluative method identified in the 1970's for systematically assessing properties, effects and impacts of health technology in order to provide evidence-based input to policy making [80][73]. It is a process to evaluate social benefits of a product / service when compared with the existing materials. Although the potential benefits of HTA have been widely recognised, its use by decision makers differs greatly: Japan has a concentrated focus on clinical effectiveness and safety and less focus on budget impact whereas England has an independent institution called NICE that conducts HTA [80].

Therefore, affordability and availability of pharmaceutical products at the patient level are largely dependent on the pricing scheme and reimbursement decision-making mechanism of a country. Due to the public sector spending limits and political and economic instability worldwide, the sustainability and efficiency of these processes have become a common challenge for countries for achieving cost-containment of pharmaceutical expenditure as well as the equitable access to pharmaceutical products [3][43][81].

1.6 Conclusions

HCV infection is highly prevalent worldwide, where 130 to 170 million people are chronically infected, and thus the discovery of HCV-DAAs substantially increased the patient demand. However, due to their high prices, not only LMICs but also HICs are struggling to ensure access. The GHSS for hepatitis calls for at least 3 million people to be treated by 2020, and the treatment coverage to reach 80% of the eligible population by 2030 [67]. However, to meet these goals, the real crux of the challenge ahead is how to provide access to such high-cost medicines while managing budget impact on the health systems [29]. While numerous policy changes are on-going with respect to price reduction (e.g., IPRs), controversial market prices of high-cost medicines and the resulting high pharmaceutical spending are increasing the gap between the volume of effective treatments available and the ability of TPPs to cover the cost. Therefore, more work on pricing and reimbursement policies may be needed at the country level for cost-effective and sustainable access to high-cost medicines.

Chapter 2: Methodology

2.1 Introduction

This chapter describes the study design, the methods and the conceptual framework used for this thesis (Table 5). Rationales and limitations for each of the study designs are also discussed. The final sections explain the ethical consideration and the justification for the thesis.

2.2 Study design

The overarching structure of this thesis takes the approach of retrospective qualitative analysis and consists of three study designs, as explained below:

Design 1 Baseline study (Part 2, Chapter 1): Before diving into a specific case, it is important to have a good understanding of the global situation with respect to pricing and access to HCV-DAAs. Therefore, this descriptive study documented and compared the facts about pricing and access controls applied to HCV-DAAs by the HCV endemic countries worldwide. The study was also essential for selecting the countries to be explored later as a case study.

Design 2 Single case study (Part 2, Chapter 2, 3 and 4): A case study was selected as the backbone of this thesis because it analyses contextual conditions in relation to the case, often defined as “precise description of reconstruction of cases” [85]. In this respect, countries were selected as a case for analysing the access situation to HCV-DAAs (contextual condition). A benefit of conducting a single case study is that it allows a very detailed and exact explanation of the case to be captured as a typical or particular example of a more general case. On the other hand, there is a high chance that the case chosen may not represent the general case or is not helpful in answering the initial research aims. Design 1 was, therefore, an essential step prior to conducting case studies for avoiding this from happening. In the end, case studies were conducted in Japan, the U.S., and England.

Design 3 Multi-case study (Part 3, Chapter 1): An explanatory descriptive multi-case study, also known as a comparative study, was conducted to compare the countries' responses to the challenge of HCV-DAAs. This type of study design has recently gained popularity in the social sciences as it provides evidence that is considered more compelling and robust [86]. While a single case study is useful in making a strong argument about a phenomenon observed in a certain case, a multi-case study allows the investigator to draw more general conclusions from the analysis. In order to identify common challenges faced by countries in improving access to HCV-DAAs, a multi-case study was needed to draw general lessons learnt from the experiences from Japan, the U.S. and England. Despite the advantages, it is a challenge to determine how many cases are deemed sufficient for a quality study. This problem is further explored in the following section (*2.4 Data analysis*).

2.3 Data collection

Data collection was conducted from the August 2015 to December 2016. One of the challenges with respect to data collection was access to accurate data. Since the topic of this thesis has received wide media and academic attention, it was expected that there would be abundant documentary data available. However, data validity was an issue since a dialogue about pricing and reimbursement is often confidential between the TPPs and pharmaceutical companies. Therefore, several data types were explored for the purpose of within / between-methods triangulation. In the section below, the data sources used for the study are explained in further detail.

Document data: Three types of document data were collected:

- **Internet documents:** Although collecting internet documents can sometimes be challenging as there are seemingly endless materials available and Internet site can disappear as the time passes, it is the most timely form of data that exist today.
- Since the pricing and reimbursement decision-making process for HCV-DAAs was an on-going process in most countries during the study, it was expected that academic publication on the topic would be limited. Therefore, the Internet documents were collected as the main source of data. Data was systematically searched and collected from the top most read general and industry-focused news websites (in English and Japanese) and the official websites of

stakeholders of interest (Appendix 2, 3). Social media such as Twitter and Facebook were excluded from the search because they are mostly comprised of subjective perspectives and thus lacking in data consistency and accuracy. The search was limited to a time period from November 2013 (when the first second-generation HCV-DAAs obtained FDA approval) up to December 2016.

To ensure the highest possible level of information coverage, the following search syntaxes were developed and used in Google search, on top of the search of the news websites, to identify relevant and publicly available news articles:

- Search Syntax 1: (Hepatitis C or Hep C or Hepatitis C virus or HCV or Hepatitis virus) AND (treatment or pharmaceutical product or cure or medication or medicine or regimen or prescription) AND (Cost* or pric*)
- Search Syntax 2: (Hepatitis C or Hep C or Hepatitis C virus or HCV or Hepatitis virus) AND (treatment or pharmaceutical product or cure or medication or medicine or regimen or prescription) AND (approv* or reimburs* or registration)

- **Printed documents:** Relevant published and grey documents were collected. To do so, the relevant website of the stakeholder organisations were thoroughly checked.
- **Published journal articles:** Published journal articles were also searched. As mentioned previously, it was expected that the data available from academic journals would be limited.

Semi-structured interview data: Semi-structured interviews were conducted when needed to obtain valid and accurate data directly from stakeholders and specialists. The findings were then contrasted with the data obtained from document data. This was an important step since talking to key informants can provide rich, sensitive and up-to-date information that is otherwise not available from document review [87]. Homogeneous sampling, a type of purposive sampling method, was used to identify relevant stakeholders for the interviews. Once the initial interviewee list was developed and data collection had begun, the snowball technique was used to add additional potential interviewees from a referral. The number of interviews required to obtain satisfactory information for a case study depended on the chosen country. Therefore interviews were continued until the stories began to repeat themselves. Examples of interviewees were the public TPPs, the pharmaceutical industry, academia and professional associations (Appendix 4). Each interview was conducted following the interview guide developed with a list of appropriate open-ended questions (Appendix 5). When a face-to-face

interview was not possible, an interview was conducted by phone. For a phone interview, a set of questions was sent to the interviewee prior to the interview. As mentioned previously, the main source of data for this study was document data. The data obtained from the interviews were, therefore, used to verify the findings from the document analysis. When there was no document data available, but the findings from the interviews were considered relevant, a citation noting that the data came from an interview is included.

Since the efforts to collect accurate data, however, since most of the data used in this thesis come from non-peer-reviewed sources, it is particularly important to assure the data quality. This was achieved by the following approaches. Firstly, most of the internet and printed documents were collected from well-respected websites/organisations/individuals. Secondly, the collected document data was cross-checked with journal articles once published. Thirdly, interviews were also conducted to make sure that the collected document data was accurate. And lastly, the comparison of the three developed countries using the same variables, facilitated quality control of the data across the three studied countries.

2.4 Data analysis

A theoretical thematic analysis was the main analytical method used in this study as it is suitable for identifying, analysing and reporting patterns within data [88]. A coding framework, with a list of themes, was developed based on the conceptual framework (*2.5. Conceptual Framework*), and a computation program called NVivo 11 (QSR International, the U.S.) was used for the analysis. The methods used for data analysis are explained further in the following sections.

Design 1 Baseline study (Part 2, Chapter 1): A descriptive analysis was performed based on document data, and the analysis was undertaken in ten HICs (Italy, Portugal, Spain, Australia, Japan, the U.S., Canada, Germany, England and France) and LMICs. These countries were selected based on the ranking of HCV prevalence and incidence rates [25][89][90]. Moreover, although they were not studied in depth, having an understanding as to how these high HCV prevalence countries responded to the challenge of HCV-DAAs (i.e., prices of HCV-DAAs, pricing schemes, access restrictions and co-payment rates) offers additional insights to the global access situation to HCV-DAAs. This process was essential for selecting the countries for the case study, and also important for determining whether the findings of the case studies were typical or particular trends observed at the global level. Since the reimbursement data from LMICs was limited, only the overall access situation was summarised and presented.

The framework for Managed Entry Agreements (MEAs) was used to categorise various forms of pricing schemes used by the selected countries. An MEA is *an arrangement between a pharmaceutical company and payer / provider that enables access to (coverage / reimbursement of) a health technology subject to specified conditions* [91]. The ultimate goal of MEAs, therefore, is to maximise cost-effectiveness and to minimise the budget impact of a new technology introduced into the health systems [91]. To achieve this, there are three intermediate target variables that need to be well managed, which are the uncertainties related to Effectiveness, Price and Use of the product [92].

Design 2 Single case study (Part 2, Chapter 2, 3 and 4): Based on the criteria developed and after careful consideration, an embedded and descriptive case study was conducted in three countries (Japan, the U.S., and England) (Table 3). There are three main reasons for this selection: First, these three countries share a few convenient commonalities that could function as independent variables for conducting a comparison.

For example, Japan, the U.S., and England are among the largest economies (i.e., high-income countries) and are the three major regions where most branded pharmaceutical products are being developed. These three countries also have a relatively high prevalence of HCV infected individuals. Therefore, any trends, reactions or decisions made in these countries can be expected to have influence worldwide. Second, the differences in the structure of their health systems and in their pharmaceutical policies facilitated analysis of approaches that worked and did not work against ensuring access to HCV-DAAs. Third, another important consideration was convenience for collecting sufficient data for the analysis. Since the investigator is bilingual in English and Japanese, and currently a resident of England, it facilitated access to sufficient data in England and Japan. To ensure the same quality of data to be obtained for the U.S., a trip was also made to the U.S.

Using the conceptual framework, the pattern matching technique was used with the existing pharmaceutical policy being an independent variable and any changes made being the independent variables.

TABLE 3: CRITERIA FOR COUNTRY SELECTION

Priority	Criteria	Variables	Description
1	Data accessibility and availability	▪ Language ▪ Potential interviewees ▪ Travel restriction	Indicator for assessing the possibility of conducting a case study
2	Severity of HCV endemic	▪ Prevalence rate ▪ Incidence rate ▪ High-risk groups ▪ HCV genotypes	Indicator for determining the demand size for HCV-DAAs
3	Economic background	▪ Gross National Income (GNI) ▪ % health spending ▪ % pharmaceutical spending ▪ Willingness to pay for medicine	Indicator for determining the purchasing power of the selected country
3	TPPs characteristics	▪ Number of TPPs ▪ Type of the TPPs	Indicator for determining the purchasing power of TPPs of the selected country

Design 3 Multi-case study (Part 3, Chapter 1): An explanatory analysis was conducted based on the results and data available from the case studies. There are two means of replication of case studies: literal and theoretical. Literal replication predicts similar results while theoretical replication looks into contrasting but anticipatable results [93]. As for this study, literal replication was selected since the study was conducted based on the same preliminary theory. Also, to perform theoretical replication often requires two to three replications of each case, which was not possible considering the scale of research expected as part of the DrPH programme. One of the limitations of this method is that since the analysis is mainly text and framework based, other important aspects (e.g., interviewees' emotion and meeting atmosphere) that cannot be described by the conceptual framework may be missed. In order to minimise this effect, not only semantic themes, but also latent themes (e.g., underlying patterns, assumptions and ideas) were investigated. Similar to Design 1, the MEA's framework was used for the comparison.

Note that for the purpose of this thesis, policies that were implemented at the national level and the decisions made by the public TPPs were considered (decisions made at the regional and hospital levels and by the private TPPs were excluded). This is because, in most countries, both private and public TPPs exist, and price and access to pharmaceutical products are controlled at all levels depending on the system, which further complicates the comparison.

Currency conversion: In order to conduct a detailed comparison, the Purchasing Power Parity (PPP) was used, a commonly tool for comparing a product value between different currencies [19]. As for this study, the 2015 PPP is used (Table 4) [94].

TABLE 4: PURCHASING POWER PARITY (2015)

Country	PPP (2015)
The U.S.	1.000
Japan	102.516
The U.K	0.688
France	0.80
Italy	0.73
Spain	0.67
Germany	0.77
Canada	1.25
Australia	1.46
Portugal	0.58

Source: The World Bank

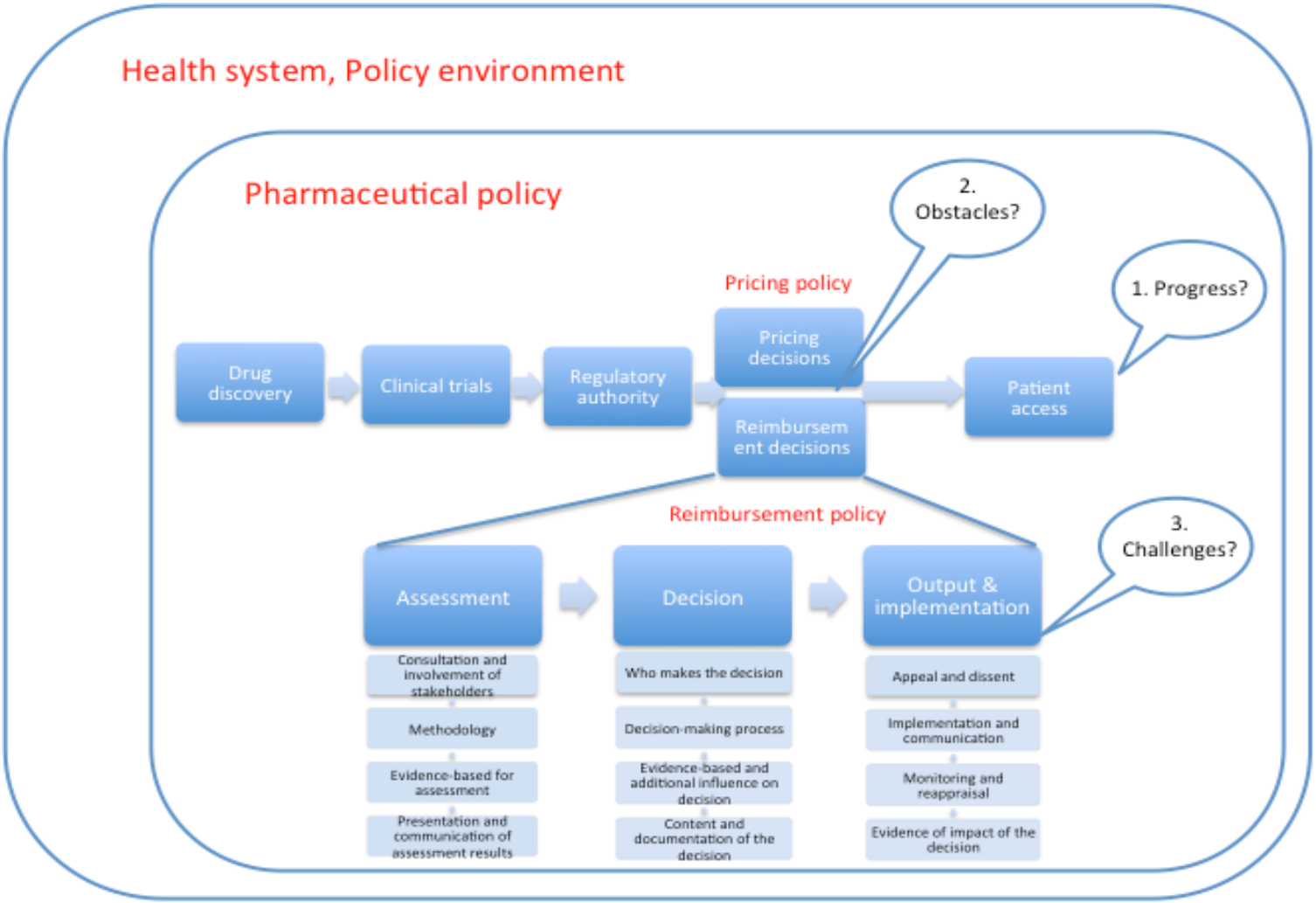
2.5 Conceptual framework

The conceptual framework used in this study was developed based on the existing concept called "*Elements of a Fourth Hurdle System*" (Figure 3). This concept was developed by Hutton et al., in 2006 as a mean to conceptualise the mechanisms of the reimbursement decision-making process at the national level for a new health technology [80]. He describes that the requirements to be fulfilled by the pharmaceutical companies, when obtaining a reimbursement approval from TPPs as a fourth hurdle in the process of pharmaceutical product development, consists of three processes: Assessment, Decision-making and Output and Implementation [80].

For countries that conduct an HTA (e.g., cost-effectiveness analysis), there is another process adjutant to Assessment, which is Appraisal. However, due to the extensive differences in the health systems between the countries selected, the Appraisal process was assumed similar to Assessment in order to simplify the comparison. Furthermore, prior to analysing the situation at the pharmaceutical policy level, a well-informed understanding of the health system (its policy objectives, health insurance system, the type of stakeholders and their relationship with each other, and with other public and private sector bodies) and the policy environment for HCV treatments (the level of demand, public and political support, and resources available) are crucial especially for conducting a multi-case study. The framework, hence, also takes this into consideration.

In the context of this research, the focus is to understand and compare the pricing and reimbursement decision-making processes of the selected countries. One of the challenges was that the framework has not been used previously in Japan and the U.S., but had been used in the European Union (EU) member states [92]. Thus, the framework was not used to develop a new conceptual theory, but instead to explain and compare the observed phenomena, and to uncover some of the challenges facing pharmaceutical policy in the three countries.

FIGURE 3: CONCEPTUAL FRAMEWORK



2.6 Ethical consideration

Research ethics approval was obtained from the LSHTM ethics committee.

For conducting a semi-informant interview, information about the research was sent to all the interviewees prior to the interview and a written consent form was collected at a face-to-face interview (Appendix 6). A verbal consent was recorded from all interviewees if an interview was conducted over a phone or Skype call. The right of all interviewees to refuse the participation without giving any reasons was respected, and all the participants were allowed to withdraw from the study at any time without any reasons. The investigator was responsible for the confidentiality of participants who take part in the study. This is registered under the Data Protection Act (The United Kingdom, 1998).

The storage and accessibility of the data gathered were strictly regulated to secure confidentiality. The collected data was stored on the investigator's work computer with a password, and she was the only person who had the access to the data collected. Data was anonymised prior to the analysis, except in certain cases where individuals or organisations need to be quoted in the final report. In this case, individuals or organisations were informed about the quotation prior to the publication and additional informed consent was also collected.

2.7 Conflict of interest

The investigator's tuition fee and living expenses were covered by the Joint-Japan World Bank Graduate Scholarship Program (JJ / WBGSP). There was also no specific sponsor for this study and, thus, no issue of conflict of interest.

TABLE 5: METHODOLOGY SUMMARY

Chapter	Objectives	Research questions	Data collection	Data analysis
Part 2 Chapter 1	1. Capture the global access situation for HCV-DAAs	**High-income countries:** ▪ Which of the HCV-DAAs have obtained the regulatory authorisation by the FDA, EMA and MHLW (as of December 2016)? ▪ At what price HCV-DAAs become available? ▪ What types of pricing schemes have been applied? ▪ What access restrictions and co-payment rates have been introduced? ▪ What are the expected pros and cons of each of the policy implemented? **Low and middle-income countries:** ▪ Which of the HCV-DAAs are currently available at what price?	Document review	**Baseline study** Thematic analysis Descriptive analysis
Part 2 Chapter 2,3 and 4	2. Describe the pharmaceutical policy (pricing and reimbursement decision-making processes) of the selected countries 3. Describe the progress for ensuring access to HCV-DAAs in the selected countries 4. Identify the obstacles and challenges experienced by the selected countries, and describe how they have responded	**Institutional:** ▪ What is the overall policy environment for HCV infection? ▪ Which stakeholders are involved, how are they related to each other and to the health system, and to what degree did they have an influence over the decision-making process? ▪ Who is responsible for making decisions regarding pricing and reimbursement? **Methodological (Pricing Control):** ▪ How are costs considered in countries with or without economic assessment? ▪ What are the rules, processes and criteria used for the pricing decision and negotiation? ▪ Were there any product specific agreements for HCV-DAAs? **Methodological (Reimbursement decision-making):** ▪ What are the rules, processes and criteria used for reimbursement decision-making? ▪ How the decisions are implemented, and accountability of the process is ensured? ▪ What were the obstacles experienced during the decision-making process?	Document review Semi-structured interview	**Single-case study** Thematic analysis Descriptive analysis
Part 3 Chapter 1	5. Draw conclusions from objectives 2 - 4 on what lessons can be learnt from the experiences with HCV-DAAs for ensuring access to the forthcoming generation of high-cost medicines	▪ How the challenges and experiences of HCV-DAAs differ from those of Antiretroviral Therapy (ARVs) and other high-cost medicines? ▪ What are the similarities and differences in approaches that worked and did not work? ▪ What lessons can be learnt from HCV-DAAs?	Document review	**Multi-case study** Thematic analysis Explanatory analysis

2.8 Thesis justification

The market entry of highly effective HCV-DAAs was a game changer for the therapeutic landscape, and thus combatting HCV disease has quickly become a public health priority in many countries. However, the high prices of HCV-DAAs were equally received as a shock to many, which brought out the issue of access to high-cost medicines as an emerging public health concern not only in LMICs but also in HICs.

Despite this recognition, few studies that have looked into the countries' responses to the HCV-DAAs and / or the challenge of high-cost medicines as a whole. This is possibly because many of the high cost medicines have been for diseases with a relatively small population and thus the response has been minor. In contrast, the case of HCV-DAAs has led to an aggressive public outcry. HCV-DAAs, therefore, provide a great opportunity for exploring how the pricing and reimbursement decision-making processes of different countries have responded to the challenges of providing timely access to high-cost medicines. In addition, although the reimbursement mechanism differs from country to country, a detailed comparison of countries' responses can provide an overview of the similarities and differences in approaches that worked and did not work. The pharmaceutical pricing and reimbursement decision-making procedures were selected as the core focus of the study because, whilst global harmonisation of the regulatory process is on-going, pricing and reimbursement decisions are still unique to each country. Therefore, these procedures have been and will continue to be an important determinant for the patient's ultimate access to medicine. The study of pharmaceutical economics and policy investigates just a single section of health economics. However, with an aim to foster efficiency and equality in access to medicine while promoting further innovation in the industry, it also naturally leads to a study of the appropriate roles of public and private sectors in managing a rapidly advancing health technology [95].

Accordingly, this study is one of the first that conducts case studies to document and compare countries response to the challenge of the high price of HCV-DAAs. Especially, given the impacts of the recent financial crisis, it is thus anticipated that the outcome of this study will be a useful resource for decision makers to obtain a heuristic understanding of the current progress worldwide in terms of access to HCV-DAAs which might help to improve the operation of existing systems and provide guidance for further policy development in improving access to high-cost medicines.

2.9 Conclusions

In total, 588 documents were retrieved and 18 interviews were conducted. Within and between methods triangulations were used to ensure construct validity, and the final case studies were also reviewed by the key informants. Internal validity was ensured by using an analysis technique called pattern matching. The use of a conceptual framework for each case study and replication logic to conduct multiple case studies were useful for ensuring external validity.

Part 2: Results

Part 2 is divided into the following four chapters:

- Chapter 1: summarises the global access situation of HCV-DAAs. The pricing and access control schemes applied were separately investigated for HICs and LMICs.
- Chapter 2, 3 and 4: present the findings from the case studies conducted in Japan, the U.S., and England, which document in detail the pricing and reimbursement processes used and their responses to the obstacles faced. Each case study is organised as follows: Section 1 explains the health system and the pharmaceutical pricing and reimbursement processes. Section 2 describes the current access situation and the pricing and reimbursement decisions made for HCV-DAAs. Section 3 then identifies obstacles experienced during the decision-making process that have influenced existing pharmaceutical policy. Finally, section 4 discusses the future challenges for each country with respect to access to high-cost medicines.

Chapter 1: The global access situation

1.1 Introduction

This chapter, as an opening chapter, delivers a global story about access to HCV-DAAs from 2014 to 2016. It is based on a documentary search focused on HCV endemic countries, and the investigation was conducted separately for HICs and LMICs.

Despite the differences in health systems and in pharmaceutical policies, a global summary of the pricing schemes applied and the reimbursement decisions made, as summarised in this chapter, serves as a good starting point for understanding the issues around access to high-cost medicines. This chapter, therefore, serves as an introduction to the subsequent case studies where the consequences of the market entry of HCV-DAAs are examined in more detail.

1.2 Access in HICs

In this section, the prices of HCV-DAAs in ten HICs (Italy, Portugal, Spain, Australia, Japan, the U.S., Canada, Germany, England and France) are compared and the pricing schemes used for negotiation and the final reimbursement decisions made are explored (as of December 2016). To facilitate multinational comparison, initial prices set by a pharmaceutical company are referred to as list prices, and final agreed prices after some negotiation with a TPP are referred to as effective prices.

Prices

To make a multinational pricing comparison possible, four HCV-DAAs (i.e., Olysio®, Sovaldi®, Harvoni® and Daklinza®) were selected (Figure 4, 5, 6, and 7). All prices were recalculated into cost-per-pill using PPP at the quantity recommended by the FDA. Because of commercial confidentiality, accurate prices of the selected HCV-DAAs were not available in most countries. Therefore, the prices presented here are the figures reported in the public domain, and thus may not accurately represent the effective prices. Despite the limitations, however, it provides some understanding of the level of transparency in each country and how that may have affected pricing decisions of the other countries. Furthermore, due to

limited data availability, the product prices in Spain and Canada were excluded from the following comparison. To improve the accuracy, potential discounts that may have applied to a TPP (that represent each of the selected countries) are indicated in red as an error bar. The findings were also contrasted with other studies that have summarised the global list and effective prices of HCV-DAA, which were published during the course of this study [96][97][98][99][100][101].

Of the four products, Harvoni® (Mean:829 USD, SD:196 USD) was on average the most expensive HCV-DAA, followed by Sovaldi® (Mean:804 USD, SD:146 USD), Olysio® (Mean: 415 USD, SD:204 USD) and Daklinza® (Mean:421 USD, SD:215 USD). Note that a product price in this context indicates cost-per-pill and not cost-per-treatment-cycle. This is because the cost-per-treatment-cycle could differ not only by the type of HCV-DAAs but also by indication (e.g., combination therapy with RBV) and duration, further complicating the comparison.

In general, the prices of HCV-DAAs differed substantially by country. The highest prices were reported in the U.S., where HCV-DAAs became available at the list prices of 790 USD (Olysio®), 1,000 USD (Sovaldi®), 1,125 USD (Harvoni®), and 750 USD (Daklinza®) per pill [12]. To accurately estimate the effective prices of HCV-DAAs was difficult, especially in the U.S., due to the complexity of its health system and the confidential deals made separately with TPPs. While one study found that the effective prices of HCV-DAAs were largely similar across HCV, another study reported that the average effective price of HCV-DAAs in the U.S. was 36% higher than that of the EU member states, despite the availability of rebates and discounts [101][102].

With respect to the U.S. public sector, the precise data on their effective prices were also not available. However, it can be estimated that the price of Sovaldi® in 2015 ranged from 540 to 770 USD per pill. This is because, on top of the mandatory rebate of 23% for the public services, Gilead had announced that both private and public TPPs had received an average discount of 46% in 2015 [103][104]. It is also reported that the U.S. Department of Veterans Affairs (VA) received an overall discount of approximately 40%, when Sovaldi® became available at the price of 594 USD per pill [105]. Similarly, it is expected that the price of Harvoni® ranged from 491 to 865 USD per pill in 2015. Detailed information on non-Gilead products in the U.S. was not available (*Part 2, Chapter 3*).

Among the EU member states, the prices in Portugal were the highest for all of the four HCV-DAAs. It is reported that Italy, Germany, and France were initially offered similar list

prices [106]. Although the effective prices in Italy were also confidential, the reported prices reflect that the deals were closed at relatively high prices (except for Sovaldi®). France from the beginning was very active at pressuring the pharmaceutical companies to lower their prices and managed to negotiate an average discount of 45% from what was initially offered, achieving one of the lowest prices agreed for Sovaldi® and Harvoni® in Europe [107]. Germany also received close to 30% discount for Sovaldi®: the pharmaceutical company initially listed 56,500 EUR (73,377 USD: 874 USD per pill) per a 12-week treatment course, but it was substantially reduced to 41,000 EUR (53,247 USD:618 USD per pill) [108]. The prices in England were relatively low compared to the other EU member states (*Part 2, Chapter 4*).

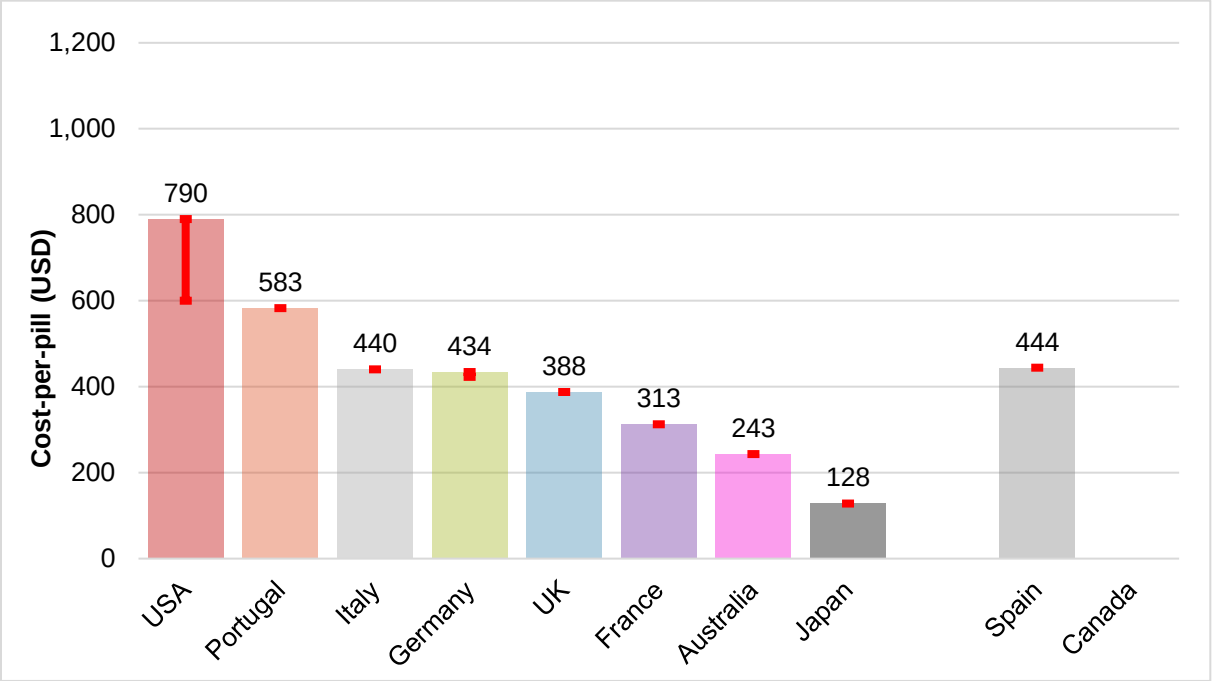
An exception here was Japan where the system allows the pharmaceutical companies to indicate their wish prices, but the effective prices are determined by the government using a set of rigorous rules (*Part 2, Chapter 2*). As a result, the costs of pharmaceutical products are usually lowest in Japan and HCV-DAAs were not an exception.

As previously mentioned, detailed information about the negotiations that took place in Spain and Canada were not available. However, it was reported that the Ministry of Health in Spain has managed to obtain more than 58% discount for both Olysio® and Sovaldi®, settling at the effective price of 431 USD per pill [109]. Further details on the pricing in Canada was not found because the Canadian pharmaceutical prices are set under different provincial laws and are confidential just like in the U.S. [110].

It is interesting to note that when ranked by price, the differences among the selected countries become wider for the non-Gilead products (Olysio® and Daklinza®) compared to the Gilead products (Sovaldi® and Harvoni®): this trend may indicate that Gilead had a unique marketing strategy targeting a few selected countries. Studies also found that although there was a positive correlation with SVR and the price of HCV-DAAs, there was no correlation with GNI, clearly indicating the different marketing strategies and negotiations applied regardless of country's wealth [97][100].

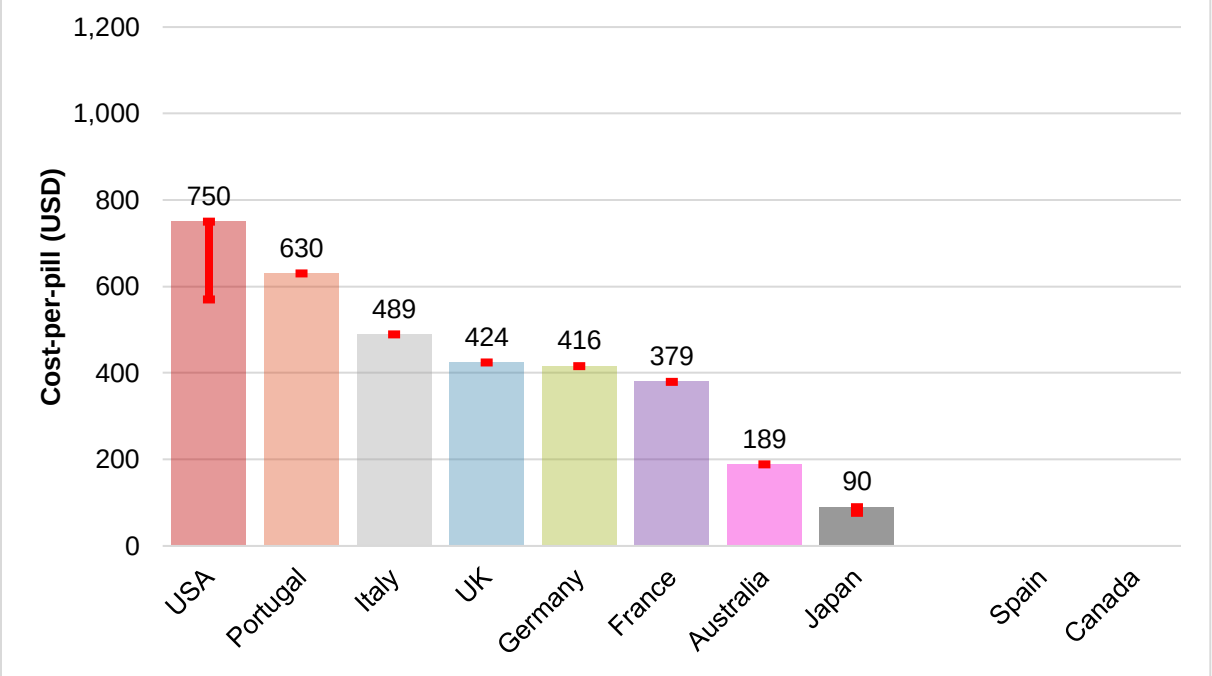
A pricing war seems to have begun in late 2014 when AbbVie joined the race with their products such as Viekira Pack® and Viekirax® [111]. However, a clear drop in product prices did not occur until late 2016. Since the data collection for this study ended in December 2016, the extent of price reduction resulted from the competition was not assessed (Further details on price reduction due to competition are mentioned in Part 2 and Part 3 (Chapter 3).

FIGURE 4: PRICES OF OLYSIO® (BY COUNTRY)



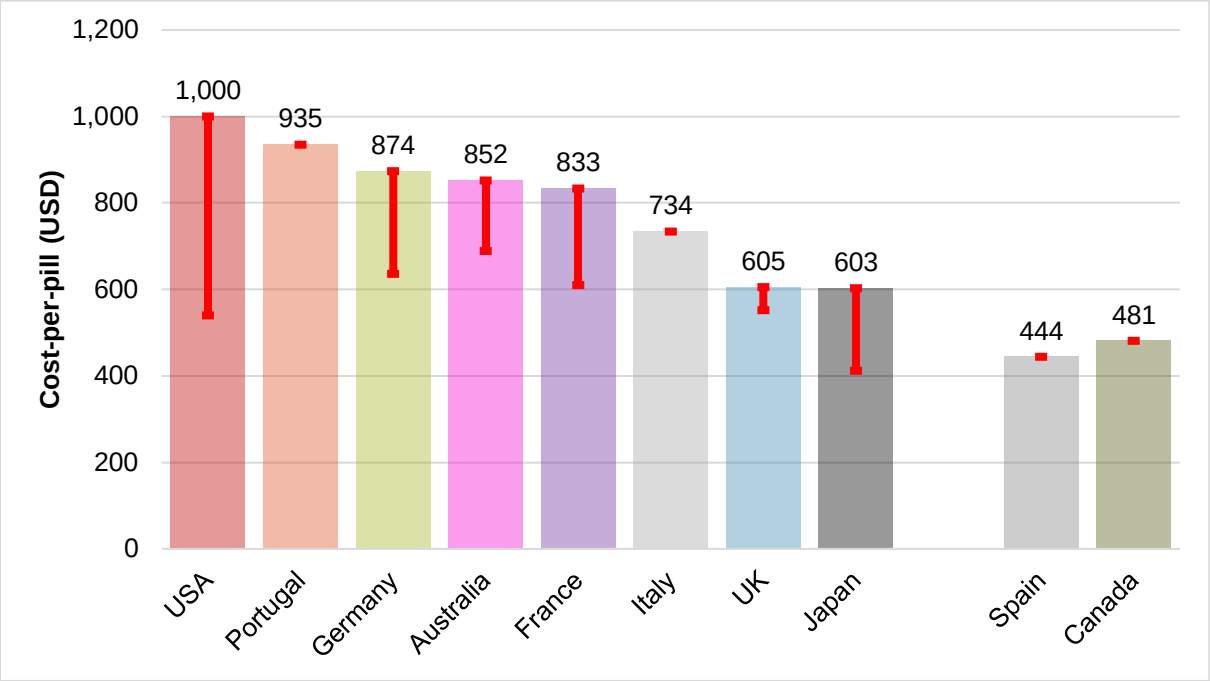
*Sufficient data not available

FIGURE 5: PRICES OF DAKLINZA® (BY COUNTRY)



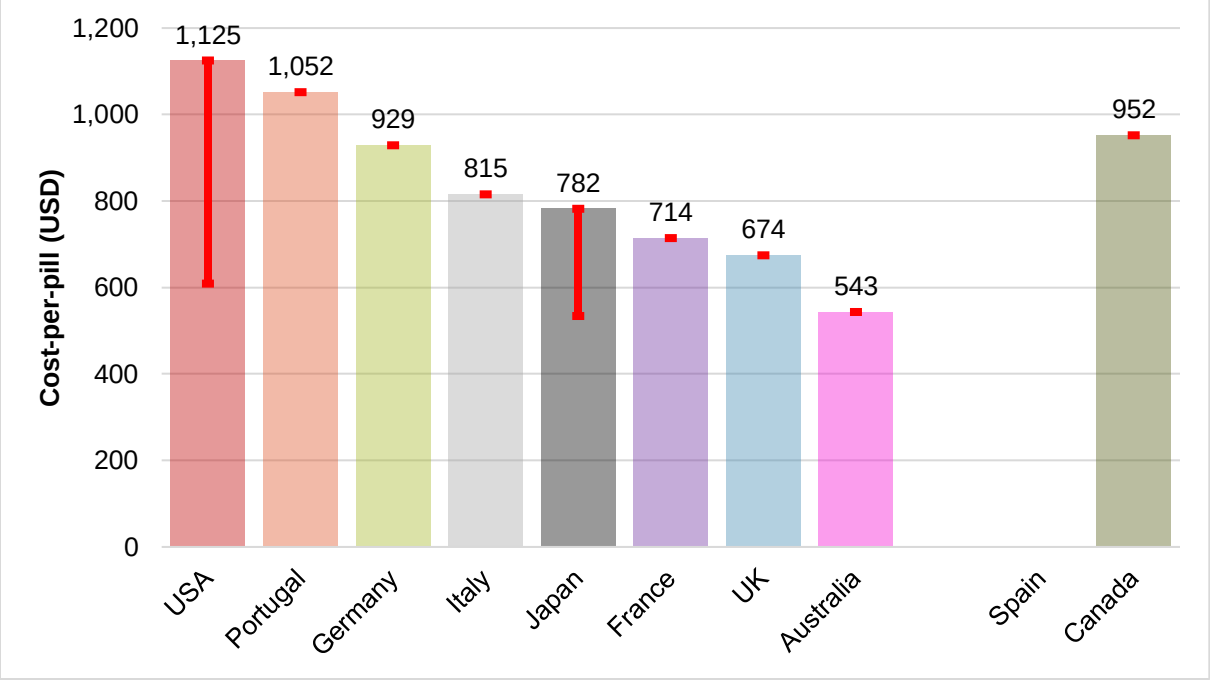
*Sufficient data not available

FIGURE 6: PRICES OF SOVALDI® (BY COUNTRY)



*Sufficient data not available

FIGURE 7: PRICES OF HARVONI® (BY COUNTRY)



*Sufficient data not available

Pricing schemes

In this section, the MEA framework was used to categorise various forms of pricing schemes used by the selected countries for HCV-DAAs. The type of MEAs can be categorised into Financial-based or Health-outcomes-based, as discussed below.

Financial-based MEAs:

According to the framework, there are four types of financial-based MEAs (Discount and rebates, Free doses, Price-volume agreements (PVAs), Dose / time-cap) [92]. Of these four MEAs, three were identified as being used by the selected countries for price negotiation with the pharmaceutical companies:

- **Discount and rebates:** Mandatory discount is the most common and traditional MEA used by the government / TPPs. For example, as previously mentioned, the U.S. public TPPs are given a mandatory discount of 23 to 24% on the list prices of newly marketed pharmaceutical products [112][113][114]. Similarly, in Germany, a 7% discount is applied to products reimbursed by both private and public TPPs [115]. As for England, 15% of the rebate is applied when the statutory scheme is used, which was the case for Sovaldi® and Harvoni® [116].
- **PVAs**: This type of MEA is a common approach used by EU member states where a pharmaceutical company offers discounts for a promised volume of sales or for a promised volume of patients [81]. It essentially achieves price discrimination just like discount and rebates as explained above, but the mechanism is different since the negotiation takes place per volume of sales or patients.
    - **Promised volume of sales:** With this type of MEA, pharmaceutical companies are expected to return a part of their revenue to the government when a pre-specified budget ceiling is exceeded, based on an assumption that pharmaceutical companies can steer the volume of sales, and thus should be held responsible for volume increases [17]. For example in England, pharmaceutical companies can decide to join a voluntary and non-contractual scheme with the government (i.e., Pharmaceutical Price Regulation Scheme (PPRS)). PPRS 2014 left the companies free to determine list prices but set annual limits on the growth of NHS expenditure on branded drugs. Participating manufacturers return money to the Department of Health (DoH) when revenue

growth exceeds the agreed limit [116]. With respect to the manufacturers of HCV-DAAs, Gilead was not listed as a voluntary scheme member, but Janssen Pharmaceutica (Hereafter Janssen) and Bristol-Myers Squibb (hereafter BMS) were [117]. Therefore, as mentioned above, Sovaldi® and Harvoni® were negotiated using the usual statutory scheme [116]. France also has a progressive contribution scheme, which was applied for HCV-DAAs in 2015, where annual spending for HCV infection is capped and pharmaceutical companies are taxed based on the excess revenue they gain in a particular year [118][119]. France so far is the only country that has made this type of tax-based deal with Gilead, and the caps were set at 450m and 700m EUR (563m and 875m USD) in 2014 and 2015, respectively [118].

  - **Promised volume of patients:** Under this agreement, the price per unit volume is negotiated and thus often preferred by the industry as it leads to a larger profit as the size of patient group increases. For example, Italy was one of the first to commit to the purchase of Sovaldi® by volume in 2014 [120]. By 2015, Olysio®, Harvoni® and Daklinza® were subsequently negotiated under this scheme [120]. Spain also purchased HCV-DAAs by volume, but the arrangement was slightly different: the price of Sovaldi® will be negotiated again when the sales reach the initially promised volume of purchase, and Olysio® will be distributed locally free of charge once the sales exceed the promised volume assigned to each region [109]. In Germany, a tier-based pricing scheme which calculates a price by unit purchased was agreed with Gilead [108]. Australia also closed the deal with Gilead and BMS under a tiered pricing scheme with an annual treatment cap of 10,000 to12,000 people [121].

- **Dose / time cap:** Caps on doses and duration of the scheme are often used in combination with PVAs. For example, a tier-based pricing scheme used by Germany with Gilead is set to be valid for three years, started retrospectively with the purchases made since January 2014 [108]. France applied a temporary approval for Harvoni® at a slightly reduced price to limit the budget impact while the final reimbursement decision was being made [119]. Patient access schemes, where a pharmaceutical company grants free or reduced price access to their product for a limited time period, is common in the U.S. (mostly among the private TPPs). England has used this scheme for Daklinza® and Harvoni® and made the effective prices confidential [122][123].

Health-outcomes-based EMAs:

There are three types of health-outcomes-based MEAs (Payment by the result, Registry and coverage with evidence development) [92]. Of these three MEAs, only *Payment by result* was identified as being used by the selected countries:

- **Payment by results:** This type of arrangement is also called the "Pay if you are clear" scheme, where a TPP does not pay for the total treatments used, but for the number of successful treatments attained. This innovative scheme is an effective cost-saving measure as it allows TPPs to select and pay for most appropriate treatment options. However, the downside is that it might lead to access restriction for those who may be cured if the treatment were provided (but were excluded due to a negative screening result). It was first adopted by the Scottish Medicines Consortium (SMC) for Olysio® in 2014, which only comes into effect when treated patients reach the SRV after 12 weeks [124]. Under this negotiation, Janssen is expected to pay for the cost of prior-HCV screening tests used to identify the patients who are likely to show effective outcomes with HCV-DAAs [124]. They are also expected to pay for alternative treatments if their products were not effective [124]. NHS England adopted the same scheme with Janssen in 2014, followed by Portugal in 2015 [125]. The deal made in Portugal forces the pharmaceutical company to provide additional treatments until a patient is cured [126]. France also reported that they have adopted a similar deal, but the details are not open to the public.

Others forms of pricing schemes:

In addition to the above pricing schemes, some countries have undertaken further steps to manage the impacts of HCV-DAAs:

- **Joint negotiation**: This form of EMA is uncommon, but it is an effective negotiation method as it allows sharing of timely and accurate information about on-going negotiations among collaborating countries. The price negotiation between Gilead and the Pan-Canadian Pharmaceutical Alliance (pCPA), an association of Canadian provinces for conducting joint price negotiation for both brand and generic prescription pharmaceutical products, took place for Sovaldi® and Harvoni® in 2014 and 2015, respectively [127]. This seemingly effective approach, however, has not been too popular in the EU. For example, France attempted to create a joint force to

compare the prices of HCV-DAAs. However, their effort was diminished because of the lack of price transparency and the weak political will among the member states [102]. On the other hand, countries with relatively small patient populations, Belgium and the Netherlands, have announced that they have started a joint negotiation for high-cost and rare medicines from 2015, and this included HCV-DAAs [128][129]. For their future negotiations, they plan to strengthen their bargaining power by implementing a system that allows more information exchange, sharing of registries and coordination of evaluation methods [130].

Accordingly, finance-based MEAs have been more popular than health-outcomes-based EMAs, and the most commonly used finance-based MEAs were PVAs. This is because countries rely on the regulatory authorities for information on product effectiveness and safety, but the information on product pricing and use (i.e., demand) are often inaccurate and insufficient. The financial-based MEAs, therefore, provide some level of security and control over total spending. PVAs, especially, are a powerful tool for maximising control over the uncertainties on pricing and use. Since it does not directly influence the list prices, it can also prevent parallel importation and thus is preferred by the industry. However, the downside is that without accurate demand data, it is challenging to approximate a budget line as it may lead to over consumption of pharmaceutical products or penalising the industry by not returning what they have invested [81]. Other forms of innovative MEA may be needed to appropriately speed up and maximise the access to products for high priority diseases, especially when it has become more and more difficult to obtain sufficient and generalisable clinical data due to the recent movement towards acceleration and harmonisation of the regulatory process [81].

Reimbursement decisions

In most HICs where the national level purchasing power is relatively high (except in North America) and with an established health system, only about a quarter of pharmaceutical expenditure is OPP. However, the coverage has been decreasing over time due to recent fiscal consolidation [72]. Therefore, reimbursement decisions made by TPPs are important considerations for patient access. In this section, the level of access restriction (free or restricted) and co-payment (with or without co-payment) in the selected countries are compared by categorising them into the following four groups.

Free access with no co-payment: France

Given the high prices, France once restricted the access to HCV-DAAs only to the most severely ill patients [131]. However, this policy was withdrawn in mid-2014 to enable access to HCV-DAAs free of charge without co-payment, making it affordable for anyone who wishes to be prescribed [131]. This was an unusual decision made by the government considering that co-payment for pharmaceutical products is the usual practice in France.

Free access with payment: Portugal, Australia, Japan, Canada and Germany

Five out of ten countries (Portugal, Australia, Japan, Canada and Germany) have free access but with some level of co-payment. The type of pharmaceutical co-payment scheme differed by country depending on the reimbursement policy: Japan, Canada, and Portugal require patients to contribute 10 to 40% of the prescription cost often with a maximum cap on payment. In contrast, Germany and Australia require patients to pay a set prescription fee for each prescription where the amount differs by the type of beneficiary arrangement.

While most of the countries applied the existing co-payment scheme for HCV-DAAs, Japan was the only country that developed and applied an alternative funding scheme separately from their usual reimbursement policy. Under this special subsidisation scheme, HCV-DAAs are available at the cost of 10,000 to 20,000 JPY (98 to 195 USD) per treatment cycle depending on patient's socioeconomic background [132]. Since 2015, patients can access HCV-DAAs at least twice in their lifetime, instead of the previous once [133]. This scheme is financed by both central and local government with the total cost reaching 8.6b JPY (84m USD) in 2015, separate from the usual cost-sharing scheme which is financed by the social insurance system [133]. Such investment was needed in Japan because of the high prevalence of HCV infection, due to the nationwide schistosomiasis eradication campaign which resulted in an extensive spread of HCV infection (1940 to 1980) [33]. Although this additional funding improved the access substantially, it also resulted in a significant budget impact to the health system (*Part 2, Chapter 2*).

Similarly, Australia invested in an extra funding to provide access to HCV-DAAs: a 1b AUD (680m USD) investment under the Pharmaceutical Benefits Scheme (PBS) came into effect in 2016 for five years [121]. This was their biggest purchase since the funding of the Human Papillomavirus (HPV) vaccine, and the government is currently working with the state and territory governments to make HCV-DAAs available for the prison population as well

[134][135]. Under this investment, patients can receive Sovaldi®, Harvoni®, Daklinza® and RBV irrespective of disease stage at the subsidised cost of the normal PBS co-payment (37.70 AUD (25.82 USD) for general patients and 6.10 AUD (4.18 USD) for concessional patients) [121]. These reimbursement decisions came into effect with a substantial delay of two years, but the government claims that the time was necessary for preparing for the provision of barrier-free access to HCV-DAAs [121].

Germany was also hesitant and initially excluded HCV-DAAs from its formulary list because the Institute for Quality and Efficiency in Healthcare (IQWiG) did not approve its additional clinical benefits [108]. Due to the increasing public pressure, however, GKV-Spitzenverband (a statutory health insurance that covers approximately 90% of the German population) had eventually agreed to list them on their formulary list in February 2015 as an exceptional case [136][137]. Meanwhile, they also spent six months negotiating with the pharmaceutical companies and preparing an appropriate infrastructure for the provision of HCV-DAAs.

Restricted access with no co-payment: Italy

HCV-DAAs are available free of charge in Italy, but access is strictly restricted to those with the most severe form of the disease (above F3) due to the limited public funds [138]. Similarly to Japan and Australia, Italy also invested 1b EUR (1.4b USD) in 2015 to cover the excess cost of HCV-DAAs [138].

Restricted access with co-payment: Spain, England and the U.S.

Three countries (Spain, England and the U.S.) fall under this category, i.e., the access to HCV-DAAs is restricted due to the reimbursement decisions made by the TPPs and the cost of co-payment.

Within the EU member states, the strictest access restriction was found in Spain. With the maximum co-payment rate of 40%, only the patients with the condition above fibrosis (F2) can access to HCV-DAAs [139]. Patients who are tolerant to PEG-INF-based treatments are still receiving them, despite the side effects [140]. The government initially had set aside 125m EUR (186m USD) to treat 4,000 - 7,000 with Sovaldi® in 2014 [140]. Due to the high demand, HCV infection management policy was revised and the government announced 727m EUR (1b USD) investment in 2015 as a three-year strategic plan [139].

In England, the access to HCV-DAAs was less strict than Spain since patients were not denied access by disease severity and also the co-payment was relatively low at the cost of 8.20 GBP (11.92 USD) per item [141]. However, due to the potential high budget impact, NHS England had deliberately requested a delay in the appraisal decision-making and guidance implementation [142]. As a result, they only treated approximately 500 patients with Sovaldi® in 2014 who had less than a year to live [143]. This was funded by the emergency HCV fund of 18.7m GBP (27.2m USD) [143]. They then expanded the already existing NHS Hepatitis C treatment fund from 40m GBP (58m USD) in 2014 to 190m GBP (276m USD) in 2015 with the coverage of approximately 3,500 patients [143]. This was the single largest investment in 2015, apart from the Cancer Drugs Fund [144]. By March 2016, NHS England had implemented an access control scheme with a set quota to treat 7,000 to 10,000 patients per year across the 22 new operational delivery networks [18][36] (*Part 2, Chapter 4*).

The situation in the U.S. was highly criticised by the public, as well by Congress. Although the level of accessibility differs greatly by TPPs, patients are generally denied access if unable to afford the co-payment. For example, according to a recent study, there has been a considerable heterogeneity with respect to access to Sovaldi® within the Medicaid programs [103]. Under the federal regulation, each state has some freedom in administering its own health program, but they are also obliged to cover all the FDA-approved pharmaceutical products without any discrimination [146][147]. In practice, many of the Medicare programs are actively restricting access by the level of disease severity: one-third of the states denied access to persons with advanced severe fibrosis (F3) or cirrhosis (F4) [103]. Moreover, co-infection with HIV/AIDS infection and alcohol and drug addiction are reasons for denying access in many of the states [103]. The access situation in Medicare Part D is not as strict as that of Medicaid, but they are also faced with an issue that they are strictly prohibited by the law to conduct price negotiation [148]. Therefore, they are left with the only option of increasing premiums and / or deductibles to manage the budget impact [148]. It is, thus, estimated that their premium increased by 8.6% in 2014, and the deductible has gone up from 320 to 360 USD in 2016 [149][150] (*Part 2, Chapter 3*).

1.3 Access in LMICs

In LMICs where purchasing power is low at the national and household levels, the complexity of patent management (i.e., the availability of generic products) is one of the major barriers to access to medicine. Even with generics, patients are often faced with catastrophic OPP due to the weak health system and the inadequate reimbursement policy. In this section, the access situation to HCV-DAAs in LIMCs is briefly summarised in order to provide a global understanding of the impact of HCV-DAAs.

Access to HCV-DAAs, is urgently needed, especially in the emerging markets, due to the high prevalence and increasing incidence in the region. However, the availability of HCV-DAAs is still limited and varies largely within LMICs: it is estimated that less than 1% of the infected individuals are receiving the treatments globally [151]. As a result, numerous charities including Medecins Sans Frontieres (MSF), have been strongly advocating against the high prices, arguing that HCV-DAAs should be available for 500 USD per treatment course in LIMCs [152]. A recent study also highlighted that the generic production cost of HCV-DAAs can be lower than 200 USD [153][153][154][155].

To manufacture generics, however, a product patent has to have expired. Under the current IPR, the patents of Olysio® and Sovaldi® are due to expire in 2026 and 2029, respectively [156]. Therefore, it was estimated that 6 to 7.5 million patients could lose their life as the result of the restricted access and the high prices given the current death rates and the increasing epidemic [156].

In early 2015, India's patent office rejected an application from Gilead for local production of Sovaldi® citing that it was not inventive enough compared with the previous formulations, in an attempt to encourage local generic production [157]. As a result, the pharmaceutical companies (i.e., Gilead and BMS) developed access programs by late 2015 to provide generic versions of their products at low cost [158][159].

Under the Gilead Access Scheme, a deal was made with 11 Indian generic makers to provide generic versions of Sovaldi® and Harvoni® [160]. The number of countries covered under this scheme increased from 91 countries in 2014 to 101 in 2015, and 105 in 2016 [158][161][162]. The product prices of Sovaldi® and Harvoni® have also dropped from 300 and 400 USD per bottle in 2015 to 250 and 300 USD per bottle to 2016, respectively [161][162].The access scheme prepared by BMS, which signed a licensing agreement with

the Medicines Patent Pool (MPP) allows generic makers to produce copies of Daklinza® without any royalty fee [159].

These schemes, however, were heavily criticised by the civil society because of the exclusion of a few emerging markets with high HCV infection (e.g., China, Russia, Brazil, Mexico and Ukraine) [160]. Overall, there were twenty middle-income countries (MICs) and three LICs that were under one of the two access programs, and at least eleven MICs were excluded from both. Consequently, the price of HCV-DAAs in LMICs was generally lower than in HICs, but also differed by the availability of the access schemes [97]. It is estimated that the price of Sovaldi® in LMICs ranges from 2,000 to 15,000 USD for a three-month regimen [163].

Examples of countries with and without access schemes:

Countries with access schemes

- **India:** As of January 2016, the generic version of Sovaldi® and Harvoni® are available at the price of 200 to 400 per USD per pack (7 to 14 USD per pill) [164].
- **Egypt:** Egypt is included in the Gilead access program, but excluded from the MPP. At first, the deal was made to price the 12-week treatment of Sovaldi® at 900 to 1,000 USD per pill [165]. As of 2017, it is available at 250 USD per bottle (approximately 9 USD per pill) [166]. The Ministry of Health has made the product available at specialised government clinics from late 2014 [166].
- **Georgia:** An HCV infection elimination program was launched in Georgia in April 2015, which planned to make discounted diagnostics and Sovaldi® available to all patients [167]. The Ministry of Labour, Health, and Social Affairs in collaboration with Gilead provided 5,000 treatments during the first stage of the program, followed by 20,000 treatments annually free of charge [167]. As of July 2015, 2,042 people were treated out of over 7,600 people who screened positive [167].

Countries excluded from access schemes

- **China:** China has one of the largest HCV populations of nearly 30 million people [160]. Sovaldi® is not yet approved in China, but the country is currently under negotiation with Gilead as they stand outside of their access program (as of April

2015) [160]. China rejected Gilead's product patent for the inactive form of Sovaldi® in June 2015. However, since Gilead still holds its patent for the active ingredient, it did not lead to generic production right away [160]. They have also avoided implementing compulsory licensing despite the pressure from the civil organisations [168].

- **South American countries:** The health ministers of Mercado Comun del Cono Sur (MERCOSUR: Argentina, Bolivia, Brazil, Paraguay, Uruguay, Venezuela, Chile, Peru, Colombia, and Ecuador) have managed to purchase Sovaldi® at the lowest price in the region, 81.85 USD per pill [169]. This purchase was conducted through by the Pan American Health Organization (PAHO)[169].

1.4 Conclusions

The market entry of HCV-DAAs in 2013 changed the therapeutic landscape of HCV infection, which raised hopes for the eradication of the disease worldwide. However, the exceptionally high list prices initially announced by the pharmaceutical companies costing upwards of 1,000 USD per pill for Sovaldi® were heavily criticised worldwide, and highlighted not only the issue of the ethics of pharmaceutical pricing but also raised questions about the functionality of current pharmaceutical pricing control and reimbursement policies. This chapter, therefore, provided an overview of the global access situation for HCV-DAAs and a summary of pharmaceutical policies used by the HICs from 2013 to 2016.

The subsequent chapters, discuss the issues of access to HCV-DAAs using Japan, the U.S. and England as case studies.

Chapter 2: Case study: Japan

2.1 Introduction

Japan has one of the highest HCV prevalence rates worldwide where 1,900,000 to 2,300,000 people are infected, that is 1.5 to 2.0% of the entire population [170][171]. Of these, the majority are above the age of 40 years, and around 70% are infected with GT 1b and the rest with GT 2a/b [172]. This high prevalence among the older population is a result of the post-1800's modern medicine and public health: an extensive transmission began in Japan with the discovery of the hypodermic needle and a treatment for schistosomiasis [33][173]. By the 1970's, it is estimated that approximately 10 million injections were given out with a used or unsterile hypodermic needle [171]. The intensive use of methamphetamine during the pre-and post-World War 2 further spread the infection [173]. Because of the high HCV prevalence among the older population, the mortality rates of HCV-related ESLD and HCC have begun to increase in the recent years [171]. According to the Japanese government, HCC became the 5th leading cause of death in 2014 with the death toll almost reaching approximately 30,000 deaths per year [174].

To combat the endemic, the government has been making concerted efforts on prevention, especially among the younger generation: The initial attempt began in 2001 and a free HCV screening test became available in 2008 [171]. In 2009, the "Basic Act on Hepatitis Measure" was formulated with a clear statement emphasising the human rights of Hepatitis patients to receive quality care and treatments [171]. In 2011, the MHLW further implemented an extensive awareness campaign namely "Shitte Kanen Project (Get to know Liver Cancer Project)" involving numerous artists and celebrities as supporters [175]. By 2012, 70 medical facilities across the 47 prefectures were selected as a liver disease designated hospital, and the MHLW also expanded the financial assistance for HCV treatments on top of the existing national health insurance [171]. Accordingly, HCV infection has been one of the major public health priorities in Japan. The total budget allocated for hepatitis in 2014 was 18.7b JPY (182m USD), but it was increased to 20.7b JPY (202m USD) in 2015 with a supplementary budget of 3.5b JPY (34m USD) [176]. By 2016, the total budget reached as high as 22.2b JPY (217m USD) [176].

With the above information in mind, this chapter discusses access to HCV-DAAs in Japan and the potential impacts HCV-DAAs have had on pharmaceutical policy.

2.2 Health system and pharmaceutical policy

The health system in Japan, and specifically its pharmaceutical pricing and reimbursement decision-making processes, are described below prior to an analysis of the impact of HCV-DAAs on their system.

Health system

Japan achieved universal health coverage in 1961 [177]. Since then, the country has performed extensive health system reforms alongside the post-war economic miracle, and thus attained a high health status and longevity for the population in a fairly short time [178]. As a result, despite its high old-age dependency ratio, health expenditure as a percentage of GDP in Japan (2014: 10.2%) has been lower than the OECD average (2014: 12.4%) [179]. Behind such achievements, however, its health spending has reached 42t JPY (409b USD) in 2015 and it has become the greatest financial challenge to the economy [180]. As opposed to the other OECD countries where health spending has been constant or on a gradual decline, that of Japan is constantly rising. The year-on-year growth rate of the national medical expenditure was 3.8% and that for the elderly (75 and over) was 4.6% [180]. The situation has been further complicated by the last twenty years of major political and economic stagnation where the national debt has now reached 1,000t JPY (9.8t USD), that is twice GDP [181].

Health insurance societies

The health insurance system in Japan is built on a social health insurance scheme through compulsory subscription and premium contributions [182]. There are close to 3,500 public TPPs across the country, and the proportion or amount of insurance premiums differ largely depending on the type of TPP a person is insured with [182][183]. Broadly speaking, there are two types [182]:

- **Employees' Health Insurance** (*Koyousya hoken*): Managed by independent healthcare societies / organisations for corporate employees, central and local government employees, private school teachers; and

- **Community-based Health Insurance** (*Chiiki hoken*): Managed by the central / local governments for those who are self-employed or engaged in agriculture, forestry and fisheries.

Premiums

On top of the monthly premium determined by each of the TPPs, beneficiaries are also expected to cover 30% of their total medical costs as an over-the-counter payment [184]. However, this cost-sharing rate varies depending on a patient's age and socioeconomic background: 70 years and older (10 to 30%), children younger than 6 years (no charge), and low-income (no charge) [184] (Table 6).

In response to the increasing healthcare cost, the high-cost medical care benefits scheme (*Kougaku ryouyouhi seido*) was set up in 1973 in order to minimise the amount of monthly OPP [185]. This is because with the above cost-sharing scheme, the monthly OPP a beneficiary has to bear can be substantial for certain medical products / services. Under this benefit scheme, a patient can claim for reimbursement if their monthly OPP (10 to 30% of the total medical fee) exceeds a set monthly cap of 100,000 JPY (975 USD) [186]. The exact monthly cap varies depending on a patient's age and socioeconomic background, as well as on the treatment duration (Table 7).

TABLE 6: THE COST-SHARING SCHEME UNDER THE JAPANESE HEALTH SYSTEM

Category (age)	Benefit ratio (Coverage by the insurance)
Below 6	80%
From 7 until 69	70%
Above 70	90%
Low-income	100%

Source: Kemporen - National Federation of Health Insurance Societies (2015)

TABLE 7: THE HIGH-COST MEDICAL CARE BENEFITS SCHEME (*KOUGAKU RYOUYOUHI SEIDO*)

Category (Income JPY)	Monthly cap (1st to 3rd month)	Monthly cap (4th months on)
11.6m and over	252,600 + (Medical costs – 842,000) * 1%	140,100
7.7m – 11.6m	167,400 + (Medical costs – 558,000) * 1%	93,000
3.7m – 7.7m	80,100 + (Medical costs – 267,000) * 1%	44,400
Less than 3.7	57,600	44,400
Exempted from tax	35,400	24,600
Persons above 70	80,100 + (Medical costs – 267,000) * 1%	44,400

Source: MHLW (2015)

Medical fees

Built on the premise of egalitarianism and community-based health care, the Japanese health system is designed, in principle, to enable every beneficiary to have access to health care services at their choice of healthcare facility [187]. Medical fees are centrally determined and uniformly applied to all medical facilities in Japan using a "fee-for-service" scheme where every medical service is assigned a number of points, each of which is worth 10 JPY (0.1 USD) [182].

Pharmaceutical policy

What characterises the Japanese pharmaceutical policy in contrast to the other HICs, is that it places a stronger emphasis on the premise that all products approved for clinical use by the regulatory authority must be made universally available at an affordable cost across the country [183]. In other words, once a pharmaceutical product obtains a regulatory authorisation for clinical use, almost all products get listed on the formulary list (i.e., Drug Price Standard) under the strict pricing control by the MHLW (i.e., a positive listing approach) [180][188].

This, in turn, means that the definitions of the list and effective prices have a slightly different meaning in Japan. Whilst in most HICs a list price is an initial market price determined by a pharmaceutical company and an effective price is that with discounts, a list price in Japan is determined by the MHLW and thus it directly denotes the cost to the government [180]. An effective price under this context is, therefore, the final price (with or without discounts on the list price) given to medical institutions and pharmacies (to make a distinction, hereafter

referred to as a market price) [180]. Regardless of the market price, medical institutions and pharmacies are reimbursed based on the list price listed on the Drug Price Standard. Patients also pay 0 to 30% of their prescription cost based on the Drug Price Standard. Therefore, the cost difference between the list and market price becomes an additional profit for medical institutions and pharmacies, but the market price has no implications for the MHLW and the patients.

As of December 2016, there were 19,876 pharmaceutical products listed on the Drug Price Standard [189]. Pharmaceutical spending had reached 9.2t JPY (90b USD) in 2015, of which 7.2t JPY (70b USD) was spent on branded medicines (78%) [189].

In the section below, the pricing and reimbursement decision-making processes in Japan are explained in a sequence of decision-making, assessment and output and implementation processes (Table 9).

Decision-making process

The decision-making process in Japan is a straightforward process to be completed within the time frame of 60 to 90 days [190]. The main organisations involved are the MHLW and the Pharmaceutical and Medical Devices Agency (PMDA: an agency that conducts regulatory control on behalf of the MHLW) [180]. Within the MHLW, there are also several independent expert groups such as the Drug Pricing Organisation (DPO) and the Central Social Insurance Medical Council (*Chuikyo*) that play a central role in decision-making [180]. Another important stakeholder to consider is the industry. Although their voice is heard less during the decision-making process, the pharmaceutical company decides whether to put their product on the formulary list and their requests are communicated in a report format [191]. Similarly, there is also no official opportunity available for patients to express their requests. In some cases, for example for an orphan drug, petitions can be collected and submitted [180]. However, the incentive to reflect the patient voice in decision-making is limited since the current situation with respect to access to medicine is relatively satisfactory for most diseases in Japan.

The decision-making process is comprised of the following six steps (Figure 8) [180]:

Step 1: Application for formulary listing by a pharmaceutical company: After a product obtains a regulatory authorisation, the pharmaceutical company applies for formulary listing. They do this by completing a formatted report that summarises their request to the Health

Insurance Bureau (Medical Economic Division, which has a role in pricing) via the Health Policy Bureau (Economic Affairs Division, which has a role in representing and supporting the industry). This includes all information required for calculating the product price [191]. Evidence not mentioned in this report would not be considered further.

Step 2: Preparation of a provisional pricing report by the Health Insurance Bureau: The Health Insurance Bureau develops a provisional pricing report based on the reports submitted by the PMDA (via the Pharmaceutical and Food Safety Bureau) and the pharmaceutical company (via the Health Policy Bureau). The Health Insurance Bureau can ask for additional data if the evidence presented at this stage is insufficient.

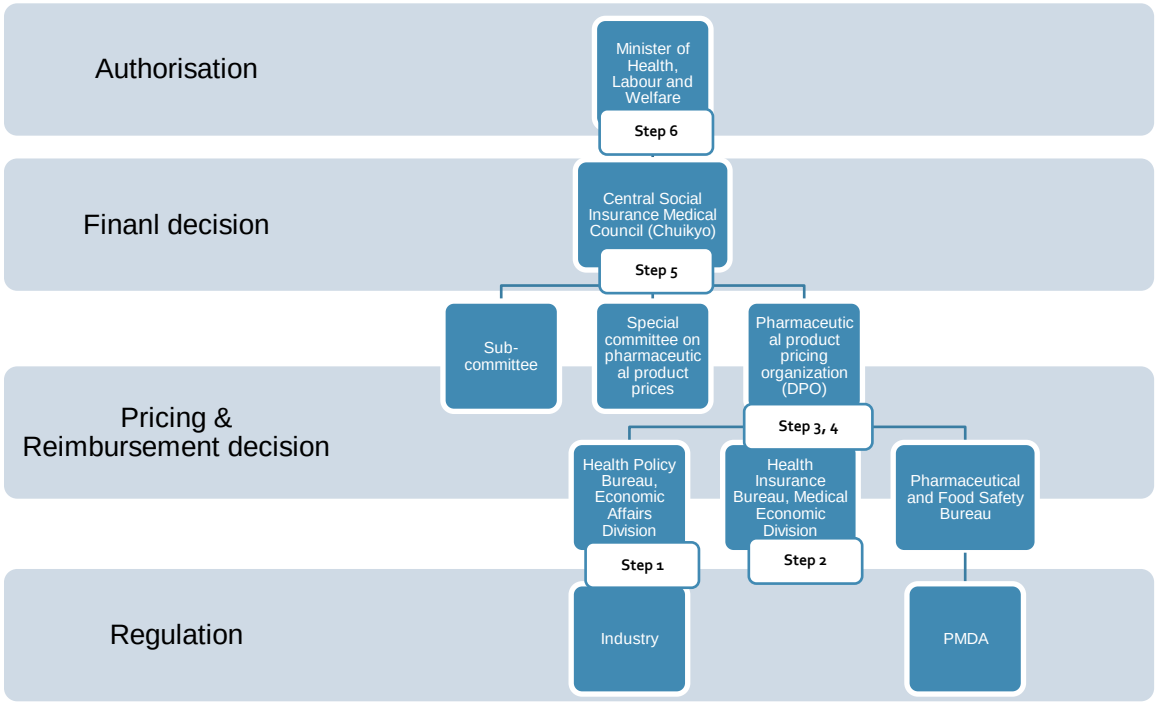
Step 3: Finalisation of the pricing report at the DPO: The Health Insurance Bureau then submits the provisional pricing report to the DPO, an independent expert body (a group of experts from the fields of medicine, dentistry, pharmacology and economics). The minutes from this meeting are not available to the public [192].

Step 4: Revision of the final pricing report: After the first meeting at the DPO, the pharmaceutical company receives the preliminary pricing decision. If the company does not agree with the decision, they can submit additional data and call for a second DPO meeting.

Step 5: Final decision-making at *Chuikyo*: The final pricing report is submitted as a product of the Health Insurance Bureau to *Chuikyo*, an advisory panel / pricing authority at the MHLW. The pharmaceutical company can attend the meeting. However, they are prohibited from contributing. In principle, a further discussion can take place at this meeting, but in practice, this rarely happens since it is used more as a formality to gain permission from the council. Most of the meeting minutes and necessary documents are available from the MHLW's website [192].

Step 6: Authorisation by the minister of Health, Labour and Welfare: The final approval for the listing is then obtained by the minister of Health, Labour and Welfare.

FIGURE 8: SIX STEPS IN THE PHARMACEUTICAL PRICING AND REIMBURSEMENT DECISION-MAKING PROCESS IN JAPAN



Assessment process

The assessment process in the context of Japan refers to the use of a set of comprehensive formulas developed by the MHLW to calculate pharmaceutical product prices [180]. There are two main steps as explained below:

Step1: Product price calculation [180]**:** Product price can be calculated by using two different methods depending on the availability of comparable drugs, which largely affects the final price. Comparable drugs in this context are defined as branded pharmaceutical products that were listed within the last ten years, no generic available, and are similar to the new product with respect to a) indication; b) pharmacological mechanism; c) active ingredients and structural formula; and d) route of administration:

- **Cost-calculation method**: used when there is no comparable drug. A product price is determined based on the estimated cost of production (based on the data provided by a pharmaceutical company); and
- **Comparative method:** used when there are comparable drug(s). A product price is adjusted to that of comparable drug(s), and then five types of the premium are added if applicable (Table 8).

The product price is usually set as a cost-per-day price (*Box 1*). The main evidence used for the calculations are clinical efficacy and safety data (including the list of potential comparable drugs) and some cost data (including production cost, projected market and sales, foreign list prices). Pharmaceutical companies are also recommended to submit a report to explain which methods / premiums should be applied and if possible, cost-effectiveness data [191]. However, in practice, the number of pharmaceutical companies that submit cost-effectiveness data has been limited (3% in 2006) due to the lack of expertise at the MHLW and the lack of clarity to what extent it affects the final pricing decision [193][194].

Step 2: Further price adjustment with the reference countries [180]**:** The final price adjustment is then performed with the average product prices of four reference countries (the U.S., England, France and Germany). If the product price after Step 1 is more than 1.25 times higher than the averaged foreign prices, the final price is reduced. If it is more than 0.75 times lower than the average foreign prices, the final price is increased. A foreign price is considered an outlier when it is three times higher or lower than the calculated product price after Step 1. In this case, they are omitted from the calculation. The price is only adjusted when foreign list prices are available from at least two of the reference countries.

TABLE 8: SUMMARY OF PREMIUMS UNDER THE JAPANESE HEALTH SYSTEM

Type of premium	Aim and the conditions to be considered
Innovation premium (70 to 120%) **Value premium (35 to 60% / 3 to 30%)**	To reward an improvement in drug value. Conditions considered are: ▪ New clinically beneficial mechanism of action ▪ High efficacy or safety compared to other similar pharmaceutical products ▪ Significant improvement in treatment ▪ High clinical efficacy by improved drug formulation
Marketability premium (10 to 20% / 5%)	To increase the incentive for developing pharmaceutical products that have a small potential market ▪ Orphan drugs designated by the pharmaceutical affairs law ▪ Primary indication shows a certain pharmacological effect for a small market
Pediatrics premium (5 to 20%)	To increase the incentives for developing pharmaceutical products for children ▪ Paediatric indication / dosage / administration are shown explicitly in the major indication (including small children, infants, newborns, and low-birth-weight infants) ▪ Comparable drugs do not have Pediatric Premium
***Sakigake* premium (10%)**	To increase the incentive for pharmaceutical companies to obtain a regulatory decision in Japan before other countries ▪ A pharmaceutical product has new indications than other products that have already been approved in Japan as well as other industrialised countries (The U.S., England, Germany, and France) ▪ A pharmaceutical product that was listed in the formulary list in Japan prior to other countries ▪ It has been proven based on clinical trials that the product is not going to be distributed in Japan ▪ A pharmaceutical product that has already obtained either innovation or value premium

Source: Kemporen - National Federation of Health Insurance Societies (2015)

Outputs and implementation process

Once a product is listed on the Drug Price Standard, there is usually limited restriction for patients to obtain it's prescription [180]. However, the list prices are revised every once in two years by the MHLW for the purpose of controlling the total health spending by adjusting the list prices to the market prices, and also for improving the simplicity and transparency of the whole process [180]. The revision is based on the results of the drug pricing survey, which collects data on the market prices of the listed products from approximately 4,000 wholesale pharmaceutical distributors and 3,400 selected medical institutions [195]. The following formula is used for the recalculation of the list prices:

$$\begin{aligned} &Revised\ drug\ price \\ &\quad = [Weighted\ average\ of\ the\ market\ price\ (Distribution\ of\ the\ market\ prices)] \\ &\quad \times [Consumption\ tax\ (1.08\%)] \times [Adjustment\ (1.02\%)] \end{aligned}$$

In theory, the system is designed to gradually lower the list prices over time [180]. This is because, for example, *a weighted average of the market price* is calculated based on the distribution of market prices, which is usually lower than the list prices [180]. However, if the total pharmaceutical spending needs to be further controlled, the MHLW can apply additional rules that can induce a price reduction by a larger amount [180]. When to conduct a revision is not bound by law, hence it can happen at any time when needed. For example, *Repricing for Market Expansion* is applied for a product which has been on the market for less than 10 years and has its sales exceeded the initial estimate [180].

There are two types of *Repricing for Market Expansion*:

Type 1: For the products with its price calculated using the Cost-calculating method, the maximum of 25% price reduction can be applied if:

- the market size exceeded 15b JPY (146m USD) and the sale increased by twice more than the initial estimate; or
- the market size exceeded 10b JPY (98m USD) and the sale increased by 10 times more than the initial estimate.

Type 2: For the products with its price calculated using the Comparative method, the maximum of 15% price reduction can be applied if:

- the total sales increased significantly due to a change in its indication; and
- the market size exceeded 15b JPY (146m USD) or the sale increased by twice more than the initial estimate.

TABLE 9: SUMMARY OF REIMBURSEMENT POLICY IN JAPAN (PRIOR 2014)

	Assessment	Decision	Outputs and implementation
Constitution and governance	Discussion within the MHLW The industry sits as an observer Limited involvement of patient groups	The final decision is made at *Chuikyo* The minister of health is responsible for the final decisions	99.9% of the products for clinical use are listed Patients have the right to receive products that are listed on the formulary
Methods, Processes	Positive listing: all regulatory approved products are listed if requested by the pharmaceutical company Product price is determined based on a set of comprehensive formulas	The non-independent appraisal committees at the MHLW conduct the pricing decision-making process The industry can object, but it would only induce another cycle of pricing process for the maximum of twice	Fixed decision-making period of 60 to 90 days from the point of the regulatory authorisation to the formulary listing
Use of evidence	The main consideration: ▪ Effectiveness ▪ Safety The pharmaceutical company and the PMDA provide data	Evidence that is not listed in the report is not considered Socio-economic aspects of the products are usually not considered	Pricing revision usually takes place once in two years to reflect the market prices on the list prices
Transparency and accountability	Well documented	Well documented Except for the minutes of the DPO meetings	Pricing formulas revision usually take place once in two years to improve the transparency

2.3 Access to HCV-DAAs

There are eight HCV-DAAs available in the Japanese market, of which Vanihep® and Suvepra® are only available in Japan (as of December 2016) (Table 10). The pricing decisions made for these eight HCV-DAAs and their access situation in Japan are explained below. Note that the prices listed here are the list prices and not the market prices because the prime interest of this study is to explore the impacts of HCV-DAAs at the national level.

Pricing decisions

The PMDA approved HCV-DAAs via an expedited review, and the list prices were then calculated using the comparative method without any delay [196][197][198][199] [200][201][202]. When compared by the cost-per-day, the products of Gilead (i.e., Harvoni® and Sovaldi®) had the highest list prices of 80,171 JPY (782 USD) and 61,799 JPY (603 USD), respectively [200][201]. Followed by Viekirax®, Olysio®, Incivo®, Vanihep®, Daklinza® and Sunvepra®: 53,602 JPY (523 USD), 13,134 JPY (128 USD), 12,422 JPY (121 USD), 11,248 JPY (110 USD), 9,186 JPY (90 USD) and 6,561 JPY (64 USD), respectively [196][197][198][199][202]. Interestingly, the price difference between the first and second generation HCV-DAAs was not as obvious as in the other HICs.

A cost-containment rule, *Repricing for Market Expansion*, was applied in January 2016 for 45 products including Daklinza®, Sunvepra® and Viekirax® [203]. The prices were then reduced by 13.2% for Sunvepra® and 14% for Daklinza® and Viekirax®, and thus the re-calculated price became 5,695 JPY (56 USD), 11,295 JPY (110 USD), and 46,098 JPY (450 USD), respectively [203][204]. In addition, a new rule *Special Repricing for Market Expansion* was applied for Sovaldi® and Harvoni® lowering the price down by 31.7% to 42,209 JPY (412 USD) and 54,757 JPY (534 USD), respectively [203][204].

BOX 1: EXAMPLE OF DRUG CALCULATION (THE CASE OF SOVALDI®)

Step 1: Basic Price Calculation: Using the comparative method, the initial price of Sovaldi® was calculated to be 23,397 JPY (228 USD) based on the list prices of the selected comparable drugs (Incivo®, Interferon, and RBV).

Step 2: Premium calculation: The innovation premium of 100% was applied which increased the price to 46,793 JPY (456 USD). Note that the use of this type of premium is rare, and the last time it was applied was 13 years ago.

Step 3: Foreign price adjustment: The price was further adjusted by foreign prices, and the final price was set at 61,799 JPY (603 USD).

Reimbursement decisions

Separate to the usual cost-sharing scheme (10 to 30% of the total medical fee with a monthly cap), a special subsidisation scheme is available for the treatment of Hepatitis C and B [132]: The amount of co-payment depends on the individual's socioeconomic background, but the majority of households (average annual salary below 7,700,000 JPY (75,110 USD)) can receive the treatment for a maximum cost of 10,000 JPY (98 USD) per treatment cycle. For those with high-income (average annual salary above 7,700,000 JPY (75,110 USD)), their co-payment is slightly higher at 200,000 JPY (1,951 USD) per treatment cycle (12 weeks). This scheme was developed in 2008 for providing financial support for interferon-based treatments when the cost of the HCV treatments began to increase [133]. Since 2011, interferon-free treatments were also listed eligible for the subsidy [133]. The scheme is financed both by the central and local governments at a 1:1 ratio [133]: the total operation cost is 17b JPY (166m USD) and the budget for 2015 was 8.6b JPY (84m USD).

The MHLW lists three reasons why they provide such additional financial support for HCV patients [132]:

- Japan is a country with one of the highest HCV prevalence rates;
- An active promotion of the latest available treatments is important for controlling the prevalence of ESLD and HCC; and
- The latest treatments are too expensive for an average patient to purchase.

To have access to HCV-DAAs, patients must be enrolled in the substitution scheme and for this, an approval from a local government is needed [132]. Once approved, they can receive the treatments prescribed by a specialist regardless of the route of transmission if a patient has shown some symptoms of a liver disease caused by HCV infection [132]. Initially, a patient could receive an interferon-free treatment only once, and only for the treatment duration listed in the regimen [132]. If needed, the scheme provides an additional subsidy for interferon-based treatments [132].

Under this scheme, 16,658 people (high income: 2,022; others: 14,636) submitted the application and 14,394 people (high income: 1,787; others: 12,607) received the first generation HCV-DAAs in 2014 [205]. The official data for the following year after the market entry of the second generation HCV-DAAs are not yet available. However, a substantial increase in the total prescription number can be expected considering that the first year

sales for Sovaldi® and the first seven months sales of Harvoni® had reached 1,509b JPY (15m USD) and 2,693b JPY (26b USD), respectively [206]. This roughly calculates into prescriptions to have been made for approximately 290,689 and 399,889 treatment cycles, respectively. If there were some discounts available at the medical institution level, the total prescription number can be expected to be higher than this estimate.

TABLE 10: SUMMARY OF HCV-DAAS AVAILABLE IN JAPAN (AS OF DECEMBER 2016)

Product name (Chemical name)	Listed date (Company name)	Price / day (JPY)	Indication	Regime	Price determination	Price adjustment	Expected market size		Cost-effectiveness data	# of meeting
							Population	Spending (JPY)		
Viekirax®	Nov 2015 (AbbiVIe)	53.602	GT 1 Compensated cirrhosis	Daily oral intake (2 tablets) for 12 weeks	Similar Efficacy Comparison Method Daklinza® / Sunvepra®	Foreign Price Adjustment	14,000	61 billion	Unknown	2
Harvoni® (Sofosbuvir, Ledipasvir)	August 2015 (Gilead)	80,171	GT1 Compensated cirrhosis	Sofosbuvir (400mg) with Ledipasvir (90mg) Daily oral intake for 12 weeks	Similar Efficacy Comparison Method Daklinza® / Sovaldi®	None	18,000	119 billion	Submitted	1
Sovaldi® (Sofosbuvir)	May 2015 (Gilead)	61,799	GT 2 Compensated cirrhosis	Sofosbuvir (400mg) with RBV Daily oral intake for 12 weeks	Similar Efficacy Comparison Method Incivo® / Interferon / RBV	Innovation premium (100%) Foreign Price Adjustment	19,000	99 billion	Submitted	2
Vanihep® (Vaniprevir)	Nov 2014 (MSD)	11,248	GT1 (Untreated patients with a high HCV RNA rate or who cannot tolerate interferon treatments)	Vaniprevir (300mg) with interferon and RBV Twice oral daily intake for 12 to 24 weeks	Similar Efficacy Comparison Method Olysio®	None	3,500	3 billion	Unknown	2
Daklinza® (Daclatasvir)	Sep 2014 (BMS)	9,186	GT1 Compensated cirrhosis	Asunaprevir (100mg) with Daclatasvir (60mg)	Similar Efficacy Comparison Method	Value premium 1 (A=40%)	17,000	22 billion	Unknown	1

			(For patients cannot tolerate interferon treatments)	Twice oral daily intake for 24 weeks	Olysio®					
Sunvepra® (Asunaprevir)	Sep 2014 (BMS)	6,561	GT1 Compensated cirrhosis (For patients cannot tolerate interferon treatments)	Asunaprevir (100mg) with Daclatasvir (60mg) Twice oral daily intake for 24 weeks	Similar Efficacy Comparison Method Olysio®	None	17,000	16 billion	Unknown	1
Olysio® (Simeprevir)	Nov 2013 (Janssen)	13,134	GT1 (Untreated patients with a high HCV RNA rate or who cannot tolerate interferon treatments)	Simeprevir (100mg) with interferon and RBV Daily oral intake for 12 weeks	Similar Efficacy Comparison Method Incivo®	Value premium 2 (A=5%)	16,000	18 billion	Unknown	1
Incivo (Telaprevir)	Nov 2011 (MSD)	12,422	GT1 (Untreated patients with a high HCV RNA rate or who cannot tolerate interferon treatments)	Telaprevir (750mg) with interferon and RBV Three times daily oral intake for 12 weeks	Similar Efficacy Comparison Method RBV	Value premium 1 (A=40%)	16,000	17 billion	Unknown	1

2.4 Impacts of HCV-DAAs

When the second generation HCV-DAAs became available in 2014, the high list prices were questioned and discussed at *Chuikyo,* but it did not lead to a nationwide debate [207]. The pricing and reimbursement decision-making processes for HCV-DAAs were carried out just like any other pharmaceutical products without any delay, and for most patients, the access was guaranteed under the special subsidisation scheme. However, many patients were initially postponing their one-time chance of receiving a prescription, waiting for better HCV-DAAs to become available.

The situation changed in late 2015 when the MHLW revised and changed the eligibility from the one-time chance of receiving HCV-DAAs to twice [133]. This change had induced a sharp increase in the prescription number of Sovaldi® and Harvoni® [206]. Accordingly, by early 2016, the impacts of HCV-DAAs at the national level became gradually obvious and were recognised by the decision-makers as well as by the media.

In the following sections, obstacles identified and resulted policy changes are discussed.

Obstacles

An attempt was made to identify obstacles experienced during the process of pricing and reimbursement decision-making process for HCV-DAAs in Japan. However, to identify such obstacles was a challenge due to the structure of the formulary listing system in Japan where these processes take place almost automatically. However, accountability of the MHLW and justification for the high prices were identified as one of the main obstacles as the wider public gradually became aware of the high cost of HCV-DAAs and its potential budget impact.

There were three reasons to why accountability and justification became an issue:

- **Uncertainties in demand:** The actual demand for HCV-DAAs was approximately 15 to 20% higher than the initial estimate (calculated based on the initial sales estimate provided by the MHLW and the actual sales). These estimates are usually calculated by a pharmaceutical company based on their data [180]. As for the case of HCV-DAAs, both the pharmaceutical companies and the MHLW had failed to accurately predict the demand size, and thus the potential budget impact. To predict the demand size of HCV-DAAs was also a challenge for the other HICs (*Chapter 3 and 4*). This may highlight the need for the MHLW to develop an internal capacity to conduct epidemiological analyses

(including the development of accurate databases) rather than simply relying on the analysis provided by the pharmaceutical companies.

- **Calculation for the cost-per-day**: On the official documents available on the MWHL website, regardless of how a treatment is prescribed (i.e., daily, durational), the product price is listed as the standardised cost-per-day [190]. As for HCV-DAAs, this had led to a public confusion. For example, the cost-per-day for Harvoni® was calculated by using a rule called "Adjustment by Treatment Cycle (*Kuru-awase*)". In other words, it was calculated by adjusting the cost of Harvoni® per treatment cycle (12 weeks) with that of the comparable drugs (Sovaldi® (61,799 JPY (603 USD) per day for 12 weeks) and Daklinza® (9,186 JPY (90 USD) per day for 24 weeks)):

$$\text{Sovaldi } (61{,}799.30 \text{ JPY}) + \text{Daklinza } (9{,}186.00 \text{ JPY} * 2) = \text{Harvoni } (80{,}171.30 \text{ JPY})$$

  The logic behind the above calculation is that for the 24-week treatment with Daklinza® to have a similar effect as the 12-week treatment of Harvoni®, the dose has to be doubled hence the price should be doubled as well. From the MHLW and the industry perspectives, the above rule was perfectly legitimate and needed to reward the shortened treatment duration that was achieved by the pharmaceutical company's efforts, so that it would lead to more incentives for further innovation. The MHLW also reasoned that the above rule was explained in *the 1982 Discussion Report on Drug Price Calculation of New pharmaceutical products* [208]. However, at the meeting held at *Chuikyo* in August 2015, one of the council members accused the government for using the pricing rule formulated 30 years ago as a justification for its high price [207]. This dialogue has led to one of the first extensive public questioning of the legitimacy of the drug pricing methods used by the MHLW. The use of rules / formulas may seem to be the simplest way to achieve justification; however, this episode highlighted the need for appropriate explanation to the public by the MHLW of their choice of methods used and decisions made.
- **Consideration of preventive benefits:** The preventive benefits of HCV-DAAs (prevention of disease progression and HCV transmission) are widely recognised in numerous studies (*Part 1, Chapter 1*). The MHLW also clarifies on their website that it was one of the core reasons for providing an extra subsidy for HCV-infected individuals [132]. However, under the current pharmaceutical policy, preventive benefits of a pharmaceutical product are not considered for formulary listing [180]. Greater clarity is thus needed with respect to how preventive benefits are valued and used as evidence for providing extra subsidy by the MHLW.

Policy changes

As mentioned previously, HCV-infected individuals in Japan have relatively easy access to HCV-DAAs and are protected from catastrophic expenditure under the generous subsidisation scheme. However, the total budget impact of HCV-DAAs to the government has become substantial as the demand increased.

In the following section, major policy changes that came into effect after April 2016 are listed:

- **Revision of the list price will be conducted annually instead of every two years** [209][210]**:** The list price of all products on the formulary list will be revised annually (instead of every two years). In addition, the market prices of products of the major wholesalers will also be investigated in detail every year. Specific criteria for this revision will be drafted in 2017, and the plan is to be implemented in 2018.

- **Revision of "*Repricing for Market Expansion"*** [211]**:** As described previously, this policy allows a forced reduction of a product price if its sale exceeds the initial estimation. Prior to 2016, *Repricing for Market Expansion* could not be applied to HCV-DAAs. This is because the rule states that when the Comparative method was used, the policy can only be applied when the increase in its annual sales was induced by a change in its indication.

  As a response to the overwhelming budget impact of HCV-DAAs (and of the other high-cost medicines), a new policy *Special Repricing for Market Expansion* was developed and applied. The concept behind this new policy is similar to the previous one, but the MHWL now has substantially more control over managing the list price. Under this policy, the following rules apply:

  a) **Maximum 25% price reduction**: when its annual sales reach 100 to 150b JPY (975m to 1.5b USD) and the initial estimate is exceeded by 1.5 times;

  b) **Maximum 50% price reduction**: when its annual sales reach 150b JPY (1.5b USD) and the initial estimate is exceeded by 1.3 times.

  This new policy was applied to six products, and specifically b) was applied to Sovaldi® and Harvoni® [204]. As a result, the revised list prices of Sovaldi® and Harvoni® since 2016 became 42,000 JPY (410 USD) and 55,000 JPY (537 USD), respectively [203][204].

- **Growing interests over HTA** [212]**:** The agenda for implementation of HTA in decision-making has been around since 1992. Since then the pharmaceutical companies are recommended to submit an HTA report (mainly, cost and cost-effectiveness data) when

applying for formulary listing, but the number of pharmaceutical companies that actually submit such a report has been limited. A pilot implementation was scheduled in 2014, but the plan was postponed due to the strong opposition from the medical association [213]. The opponents argued that the implementation of HTA may further lead to a disincentive for the industry to invest in innovation and for rationing of patient access [214]. Some also claimed that it is unnecessary because the prices of pharmaceutical products in Japan already reflect the foreign prices by the use of the currently used external referencing system [215].

Since the market entry of HCV-DAAs, however, the need for HTA was often mentioned at Chuikyo using the example of Sovaldi®. Subsequently, the pilot implementation began in 2016 for seven pharmaceutical products including Sunvepra®, Daklinza®, Viekirax®, Harvoni® and Sovaldi® [216]. Therefore, the introduction of economic analysis in the current pricing system has been under discussion in the MHLW. Details of this progress are not yet clear, but a few pilot studies to recalculate product prices (for rare diseases) using economic analysis took place in 2016.

It is important to note here it is not yet clear to what extent the market entry of HCV-DAAs had resulted in the above policy changes. What is known at this stage, however, is that the government has strengthened price control against the will of the industry, which may reflect the government's desperate need to contain the pharmaceutical spending [217]. Interestingly, the policy changes implemented in 2016 were not restricted to the above policies [211]. For example:

- **A newly-added Sakigake premium**: adds 10% to products that have not yet marketed elsewhere (under the comparative method); and
- **The new foreign price adjustment**: lowers the price if the calculated list price exceeds 1.25 times the foreign average price (instead of 1.5 times previously).

Conceivably, these policy changes could be seen as being implemented to compensate for the potential damages caused by the strengthened pricing control policy. These damages include the potential decline in the industry’s incentive to innovate, as well as in their interest in the Japanese marketplace.

2.5 Challenges and reform proposals

As a response to the economic recession and the increase in health spending since the 1990s, the Ministry of Economy, Trade and Industry (METI) has been pressuring the MHLW to reduce healthcare spending [218]. The increase in insurance premiums since 1997 is a good example of cost-containment policy implemented by the MHLW [218]. Similarly, pharmaceutical policies have been revised over the years. However, the revisions made were often on an ad-hoc basis in response to immediate issues, and there has not been an extensive reassessment of the existing system.

To that extent, the market entry of HCV-DAAs had unprecedented impacts on the system: one of the major changes induced by HCV-DAAs was an accelerated movement towards implementation of HTA. This was new considering that the current approach to cost-containment with respect to pharmaceutical spending is achieved via implementation of a compulsory price reduction policy rather than focusing on product specific cost-effectiveness assessment. While this may be a positive step forward, the current dialogue on HTA implementation has been dominated by the traditional view of the use of cost-effectiveness as a cost-containment measure rather than its use as an access optimisation measure. The current debate also lacks an understanding of potential implications of HTA when adopted in the already established Japanese pharmaceutical policy landscape.

To assess the appropriateness of the MLHW's approach in implementing HTA is beyond the scope of this study, and practical challenges associated with the full implementation of HTA are well documented elsewhere [214]. Nevertheless, in the following paragraphs, overall potential future challenges that Japan may face with respect to the growing financial pressure from high-cost medicines beyond the discussion of HTA are discussed:

Firstly, **the bureaucratic culture and system of the MHLW that works against cultivating an understanding of and incentives for cost-containment among decision-makers, physicians and the public must be reconsidered.** The strong egalitarian characteristic of the Japanese health system and the financial flexibility of the social insurance scheme with a vaguely set budget ceiling, have shaped the bureaucratic culture of policymakers whereby they have fewer incentives to react to the potential impacts of high-cost medicines. This is because high-cost or high budget impact are not a barrier to formulary listing under the existing decision-making process where a set of rules are used for price calculation. For example, HCV-DAAs were not seen as the forefront of high-cost medicines because HCV infection has traditionally been an expensive area and that there were many other high-cost medicines on the market (i.e., the field of cancer). The

seriousness of the issue was further diluted by the fact that the HCV epidemic has long been one of its public health priorities. Therefore, despite the substantial financial impacts of HCV-DAAs, the MHLW took the responsibility to provide equitable access and had no initial intention of limiting their spending. The Japanese public, including physicians, also believe that medicines must be affordable for all due to the misconception developed from the universal health coverage. At present, physicians can use any pharmaceutical products listed on the formulary, and there is even an incentive to use high-cost medicines. Clinical guidelines are written for the purpose of clinical benefits and not for societal benefits, and there is no educational program for improving their cost awareness. Therefore, even with an effective cost-containment measure at the national level (e.g., HTA), if the people on the ground are not following the decision, true cost-containment is difficult to achieve.

Secondly, **the existing methods to determine a product price must be redesigned to reflect its true value within the Japanese context.** An advantage of the existing pricing procedure with the use of a set of calculation formulas is that it provides a shared (mis)conception that it is simple and highly transparent. However, the system is also inflexible and lacks in evidence-based approach with several disadvantages:

- **Premium calculation:** The current point system for calculating the premiums uses a regression model based on the database of the previously listed pharmaceutical products [219]. For example, the last time *the innovation premium of 100%* was used was over 13 years before Sovaldi®, and clearly, the level of innovation at the time to receive this type of premium is fundamentally different from that of today [220]. Therefore, the model may not be suitable for assessing an innovative product like HCV-DAAs, which had achieved exceptional technological advancements.
- **Adjustment with foreign prices:** The current method used to adjust the Japanese list prices to the global market may go against the global trend of assessing a product's value. As previously explained, the meaning of list and effect prices can be different in different health systems, but the MHLW still uses the averaged foreign list prices without considering the potential price discounts that may have been granted in the reference countries.
- **Preventive benefits:** While future high-cost medicines are expected to possess both clinical and preventive benefits, preventive benefits are not yet reflected in the considerations.

Thirdly, **the existing levels of transparency and accountability in decision-making by the MHLW must be reassessed**. As explained, a product price in Japan is determined using a set of rules, thus the whole system can be seen as highly transparent. However, the

publically available information is limited to the final decisions made under the closed door of the MHLW, and there is insufficient explanation regarding the assessment process (i.e., how and why such price calculation method or comparable drugs were used). There is a lack of involvement of important stakeholders such as the patient groups, and the minutes from the DPO meetings are also not available to the public. Some argue that the pharmaceutical pricing process in Japan is seemingly transparent, but the actual decision reflects a sensitive balance between what is considered “an appropriate price” for both the MHLW and the pharmaceutical company (Data from interviews). This may be why in some cases, the selection of comparable drugs can be slightly odd. In business, some level of confidentiality may be required. However, when spending the taxpayer’s money, it is important to be transparent about the evidence and reasoning underlying the decisions made, especially for obtaining public support and understanding.

Lastly and most importantly, **further clarity is needed for the use of assessed product value in the pricing and reimbursement decision-making processes (especially with respect to the use of HTA).** Despite the scheduled pilot project, there are numerous questions to be answered such as to what extent the HTA evidence will affect the premium calculation and how the appraisal results will affect the compulsory-price-controlling rules such as *Repricing for Market Expansion*. As such, it is still unclear to what extent the use of HTA will affect the existing system. These questions are being raised because, as mentioned previously, the understanding of HTA in Japan still sits around the notion of cost-containment. When Japan has already achieved the high treatment coverage, an alternative option may be to consider access optimisation rather than cost-containment. HTA should, therefore, be used for access optimization, as part of an evidence-based approach that enhances transparency in the price setting process, stakeholder involvement, evidence-based prioritisation and public education. Access optimisation rather than cost-containment has already been a common approach in other HICs, such as England, yet effective implementation has long been a global challenge. Similarly, in a country like Japan, where patients and physicians have an understanding of health security as everyone to have the equal access to virtually all health care and services available, implementation of effective access optimisation will be a challenge. Nevertheless, the fact that the discussion of HTA has been ongoing since 1992 and yet, there has not been a convincing plan of implementation may suggest that the current approach may not be suitable for the Japanese context. A way forward, therefore, may be to develop an alternative strategic approach to optimise the access to high-cost medicines based on the existing pharmaceutical pricing and reimbursement system developed in Japan.

2.6 Conclusions

Pharmaceutical policy in Japan is built on a strong egalitarian system. Product prices are determined under the strict control of the MHLW, and physicians can freely select a pharmaceutical product listed on the Drug Price Standard. Patients also have equitable access at an affordable cost without strict access restrictions. These successes in the health sector have long been at the core of Japanese diplomacy, however, it now faces a substantial financial challenge that can no longer be avoided.

This study revealed that until the end of 2015, the impacts of HCV-DAAs were not visible in Japan. The high costs of HCV-DAAs were not seen as a barrier to formulary listing, and the subsidisation scheme specifically set up for hepatitis was available to encourage more prescription. The MHLW was aware of the high costs of HCV-DAAs, but the delay in managing the budget impact occurred because the system was lacking a mechanism to exclude HCV-DAAs from the formulary list. Gradually but definitively, the MHLW began to realise the potential financial impacts of HCV-DAAs. As a response to the unprecedented budget impact, the MHLW implemented policy changes that primarily strengthened their control over pricing. These newly added rules, such as *Repricing by Market Expansion*, enabled the MHLW to further control pharmaceutical spending. However, it was again another ad-hoc approach to solving the immediate issues, which led to extensive resistance from the industry.

Accordingly, the market entry of HCV-DAAs evidently impacted the Japanese health system and also served as a strong stimulus for the MHLW and TPPs to reconsider the current system. However, it also created an illusion that the country needs to adopt a worldly popular HTA (understood as a cost-containment measure). While this may be a positive move forward and the pilot project is ongoing since 2016, there are still limited studies on how HTA can / should be adopted by the Japanese health system. Instead, as identified in this study, there are wider issues to be addressed beyond the need for HTA, such as transparency and accountability. Thus, when Japan has already achieved sufficient coverage of health care but with the growing ageing population, it may now be the time to consider access optimisation, rather than cost-containment. In order to achieve this, prospective policy changes require a good understanding of the existing system and a careful consideration of the need and culture of the Japanese people.

Chapter 3: Case study: The United States

3.1 Introduction

HCV infection is one of the most serious public health issues in the U.S. It is estimated that approximately 3.5 million people (1 to 2% of the population) are currently infected, and 4.6 million are carrying the antibody [221]. Of these, a large majority are infected with GT1 [25]. Despite the difficulty in obtaining accurate epidemiological data, the Centers for Disease Control and Prevention (CDC) has estimated that approximately 30,500 acute HCV cases occurred in 2014 giving an overall incidence rate of 0.7 infections per 100,000 population [222][223]. The prevalence is highest in the poorest segment of the U.S. population, and also among the elderly population due to unprotected medical procedures that were common in the 1970s [224][225]. New infections are predominately high among young white male living in non-urban areas, especially within the communities of IDUs and correctional populations [224][226]. For example, the state of Kentucky has a prevalence rate seven times higher than the national average [224][227]. However, despite the on-going transmission among young people, deaths associated with HCV infection are sharply increasing among the elderly population [228]. The reported mortality related to HCV infection reached an all-time high of 19,659 deaths in 2014, killing more than any other infectious disease [229].

Accordingly, HCV infection is disproportionally concentrated among Americans who are likely to be insured under the public TPPs such as Medicare, Medicaid and the VA. Challenges are, just like in any other HICs, to expand the screening program and to increase the proportion of infected individuals receiving appropriate care and treatments [230]. To achieve this, the CDC is recommending one-time HCV screening for adults born during 1945 to 1965 [225]. The federal government is also providing high-quality counselling, care and treatments for infected individuals [230]. Under the 10-year national plan, the aim is to increase the proportion of people who are aware of their infection from 45 to 66% and to reduce newly reported cases by 25% [230][231]. Nonetheless, the reality of access to HCV treatments in the U.S. has been far from the optimum. It is estimated that only 10% of the diagnosed population have received treatments due not only to poor patient adherence, but mainly because of the limited access to available treatments [232][233].

This chapter discusses access to HCV-DAAs in the U.S., as well as the impacts that the market entry of HCV-DAAs had on their health systems.

3.2 Health system and pharmaceutical policy

In 2014, total U.S. health expenditure reached three trillion USD (17% of GDP) [234]. In response, per person expenditure also increased from 7,212 to 9,523 USD from 2011 to 2014 [235]. The reported OPP for all income levels is now the highest among all HICs reaching 11% of total spending, that is more than 1,000 USD per capita accounting for 329.8 billion USD [236][237]. This recent sharp increase in health spending is partially the result of the 2010 Patient Protection and Affordable Care Act (ACA), which was launched under the Obama administration to expand the insurance coverage, but is also caused by the increasing prices of prescription drugs [234]. With the current status quo, it is expected that the health spending will continue to grow faster than the economy, at an average rate of 5.8% per year from 2015 to 2025, raising the total health spending of GDP up to 20.1% by 2025 [236].

Prior to the analysis of the impacts of HCV-DAAs on the U.S. health system, an understanding of the nature of the U.S. health system, as well as its pharmaceutical policy, is crucial. Since the U.S. health system is extremely fragmented and thus complicated, this section provides an overview.

Health system

Without a single payer system, the U.S. health system is closer in structure to a free market system where health services are owned, operated and delivered predominantly by distinct private organisations [238]. Approximately half of its population is covered by employer-sponsored insurance (ESI) plans run by private healthcare insurance companies [235]. The rest is either insured through independent private insurance programs or otherwise covered by the three major public TPPs: Medicare, Medicaid and the VA [235]. Despite the availability of the public TPPs, amplified by the financial crisis in 2008, almost 18% of the entire population was uninsured in 2013 (mainly from the poor and minority population segments) [235][239]. The ACA significantly saved this situation, but 11% of the population are still uninsured without appropriate access to health care [239]. In the U.S., geographic, social and economic factors, therefore, play an important role in determining the availability of and access to affordable healthcare [148]. Note that despite the dominant presence of the private sector, this study solely focuses on the following three public TPPs (Table 11). This is because the private sector is too fragmented and it is also difficult to obtain data due to commercial confidentiality.

Medicare: A federal owned insurance program that subsidises health care costs for individuals aged 65 or above and younger people with disabilities [240]. Under the Medicare Modernisation Act in 2003, Medicare's voluntary outpatient benefit, known as Part D, was implemented as a prescription drug benefit (self-administered pharmaceutical products only) [240]. The total number of Medicare beneficiaries in 2014 was 55 million (Part D: 40.5 million) with a budget of 597 billion USD (Part D: 11%) [241][242]. The delivery of Medicare Part D benefit plans has been almost exclusively conducted by private Managed Care Organizations (MCO) such as Medicare Advantage plan with Prescription Drug Coverage (MAPDs) and the standard Prescription Drug Plans (PDPs) [243]. There are three phases in the standard benefit package (2014): initial coverage (annual deductible 320 USD followed by 25% co-insurance), coverage gap (once the total spending exceeds 2,960 USD, 45% co-insurance for branded drugs and 65% for generic drugs) and catastrophic coverage (once the total spending exceeds 6,690 USD, 5% co-insurance) [244]. Additional subsidy is possible if a beneficiary is from a low-income background or has a dual subtraction with Medicaid. That is: income <=100% of the federal poverty line (FPL) (co-payment of 1.2 USD for generic and 3.80 USD for branded products), >100% FPL (co-payment of 2.65 USD for generic and 6.60 USD for branded products), <=135% FPL (co-payment of 2.65 USD for generic and 6.60 USD for branded products) [244]. However, if a beneficiary has income <150% FPL, a 66 USD deductible followed by 15% co-insurance is unavoidable until OPP spending reaches 4,700 USD. After that, 2.65 and 6.60 USD co-payments for generic and branded product applies, respectively [244]. If monthly spending on pharmaceutical products exceeds 600 USD, the product is then categorised under a 'speciality' tier with a higher co-sharing scheme [244].

Medicaid: A state-owned insurance program that subsidises healthcare costs for individuals with low-income. Under the ACA, the Medicaid coverage was expanded in 31 states [245]. In 2014, Medicaid had 64 million beneficiaries including 4.3 million newly eligible adults with the budget of 497 billion USD [246]. The program is jointly funded by the state and federal governments with an average federal medical assistance percentage of 57% [247]. The delivery of Medicaid benefit plans is likewise performed by MCOs, but there is also a fee for service system [248]. Co-payment schemes for prescription drugs are determined separately by the states including specification of which pharmaceutical products to be considered as "preferred" or "non-preferred" (to be listed on its formulary) and also for co-payment schemes for generic and branded drugs [249]. The state programs use OPP charges to

promote cost-effective spending, but co-payments are limited to nominal amounts for those <150% FPL and less than 20% for those >150% FPL [249].

Veteran Health Administration (VA) program: The VA program is funded by the Federal Supply Schedule (FSS), which also funds the public insurance schemes such as the Department of Defense, Public Health Services, Indian Health Service and federal prison [112]. In 2014, the VA program had 9 million veterans enrolled with a budget of 59 billion USD [250]. Health services are delivered through 21 Veteran Integrated Services Networks (VISNs) which is one of the largest integrated health systems in the U.S. [251]. While the majority of the veterans are eligible for free health care, those with an income above the VA limit are required to co-pay 8 to 9 USD for 30-day or less supply of prescription drugs [250].

TABLE 11: SUMMARY OF PUBLIC TPPS IN THE U.S.

	Medicare Part D	Medicaid	VA Program
Description	Federal owed insurance program for individuals aged 65 or above and younger people with disabilities	The state-owned insurance program for individuals with low-income	Federal owed insurance program for all veterans
Annual budget (USD)	597 billion (Part D: 65.7 million)	497 billion	59 billion
Number of beneficiaries	55 million (Part D: 40.5 million)	64 million	9 million
Co-payment	Initial coverage (annual deductible 320 USD followed by 25% co-insurance) Coverage gap (once the total spending exceeds 2,960 USD, 45% co-payment for branded drugs and 65% for generic drugs) Catastrophic coverage (once the total spending exceeds 6,690 USD, 5% co-payment for the total pharmaceutical spending)	Differs by the state: Individuals income >150% FPL (max co-payment 20%) Individuals income <150% FPL (nominal co-payment)	Free of charge Except for individuals with high-income co-pay 8 to 9 USD for 30 days or less of supply

Pharmaceutical policy

As explained previously, much of the information about pricing and reimbursement decision-making processes, available in other HICs, are hidden in the U.S. due to the strong presence of the private sector. Therefore, this section provides an explanation about the overall process rather than discussing the policies set by different TPPs (Table 12).

Price setting

In the U.S., pharmaceutical prices are fully determined by a pharmaceutical company [252]. The government has a little control over this process as the industry holds one of the most influential lobbying presences domestically [252]. Pharmaceutical product prices are therefore determined entirely based on a company's interest, i.e., what they believe that the market can bear to maximise their profit [252].

The initial price determined by the industry is called the Wholesale Acquisition Cost (WAC) [112]. Although WAC is often used by other HICs as a proxy for the pharmaceutical prices in the U.S., it hardly represents the final effective prices as it is used as a basis for confidential price negotiations [112]. For certain public TPPs, the industry provides a special pricing consideration in return for listing their products on their formulary list [112]. For this type of calculation, the Average Manufacturer Price (AMP) is used, which is the average price paid to pharmaceutical companies by wholesale distributors (AMP is also confidential) [112]. In most cases, a Pharmacy Benefit Manager (PMB) plays an important role in negotiating financial transactions on behalf of the public TPPs [252]. Generally, discounts negotiated by larger private TPPs or federal / public TPPs are higher than those of private plans or small-scale TPPs as they have more negotiating leverage.

The current approaches to discount / rebate for public TPPs are summarised below [112][113][114]:

- **Medicare Part D:** Private plans can negotiate prices (e.g., the average rebate was 15% in 2011). The law prohibits further price negotiation by the Federal government.
- **Medicaid:** A compulsory rebate of 23.1% based on AMP, or the lowest price offered to other purchasers. Further negotiation is possible.
- **The VA program:** A compulsory rebate of 24% based on AMP, or the lowest price offered to other purchasers. Further negotiation is possible.

Reimbursement decision-making

Without a single payer system, there are great variations in the reimbursement decision-making processes undertaken by the public TPPs. Restricted by commercial confidentiality, available information on this process varies by the TPPs. The decision-making process in Medicare Part D and Medicaid are explained here, but not that of the VA program due to the limited information available.

Medicare Part D: The Centers for Medicare & Medicaid Services (CMS) website states that "*Medicare coverage is limited to items and services that are reasonable and necessary for the diagnosis or treatment of an illness or injury*" [253]. Until recently, there was no clear definition of what counts as "reasonable and necessary", and thus often it was interpreted as reflecting the prevailing views of the physician community [83][254][255]. In 2000, however, the CMS eventually clarified that the phrase refers to safety, effectiveness and appropriateness of a health technology and whether it leads to improved health outcomes or not [254]. Accordingly, a technology now has to have reliable scientific evidence that supports potentially improved outcomes in relevant populations, and be accepted by the medical community, in order to gain a reimbursement decision [83]. The evidence here refers to FDA information, clinical guidelines written by specialist societies as well as systematic reviews conducted externally or on their own [83][255]. Interestingly, FDA information itself is not considered sufficient and does not lead to an instant recommendation [256]. Despite the large amount of cost-effectiveness analysis studies published in the U.S., consideration of cost and cost-effectiveness in reimbursement decision-making is prohibited by the law [148]. Also, no literature was found that explicitly articulated how social factors such as stigmatisation play a role in decision-making. Many argue that such a passive stance is strongly associated with American political and cultural values that generate emotional arguments about the rationing of care [257][258].

The quality of evidence is judged based on the quality of individual studies and by the relevance of the findings to their beneficiaries [254]. Despite the difficulty in obtaining data, the CMS so far has been shown to be consistent with the strength of evidence [83][259]: a study found that overall 16% of the assessed technologies had good supporting evidence, 42% had fair and 33% had poor evidence, which implies that Medicare is gradually moving towards an evidence-based approach. Based on the collected data, multi-tiered formularies are used to characterise preferred (with low-cost sharing) and non-preferred (with high-cost sharing) drugs [240]. Since the benefit plans are delivered by MCOs, they can independently

develop and modify the access schemes as long as they meet the value of the standard package specified by the CMS [244][240].

Medicaid: The Medicaid reimbursement decision-making process differs greatly by the state. In general, they are expected to follow the Federal Medicaid requirements (i.e., provide access to all FDA-approved products of the pharmaceutical companies that are a member of the federal drug rebate program), and to coordinate with the decisions made by the other states [146][147]. A drug utilisation review board uses package labelling, national and international treatment guidelines, and peer-reviewed literature to determine the medical necessity of a new product [146]. In a complex situation, they also commonly seek advice from an expert consensus panel [146]. However, one study found that their decision-making process is less structured based on a mixture of scientific evidence, cost considerations and unmeasured preferences [260].

It is important to note here that the theoretical process of the U.S. reimbursement decision-making as discussed above does not necessary reflect its practical application. For example, whether or not the cost consideration is formally listed as a factor influencing the decision, the availability of more rebates / discounts can sometimes be a determinant of formulary listing (e.g., a PBM is likely to list a product with a larger discount on their formulary regardless of the therapeutic differences).

TABLE 12: SUMMARY OF REIMBURSEMENT POLICY IN THE U.S. (MEDICARE PART D) (PRIOR 2014)

	Assessment	Decision	Outputs and implementation
Constitution and governance	The CMS lay out the initial policy. Medicare local contractors (i.e., MCOs) also conduct their assessment and can seek more information from a pharmaceutical company Limited involvement of stakeholders including patient groups	MCOs can independently develop and modify the access schemes as long as it meets the value of the standard package specified by the CMS	Depends on the product
Methods, Processes	Overall, there is no clear guidance for the assessment process Multi-tiered formulary is used for preferred drug selection Quality is judged by the quality of individual studies and its relevance to their population	Internal discussion with advice from the external experts	Unclear
Use of evidence	Main consideration: ▪ Effectiveness ▪ Safety ▪ Appropriateness in relevant community Data source: ▪ FDA labels ▪ Clinical guidelines ▪ Peer reviewed literature	Non-clinical factors that affect the decision: ▪ Cost and possible rebates ▪ Acceptance by the medical community Social factors such as stigmatisation tend to have minimum effect	Unclear
Transparency and accountability	Not transparent	Not transparent	Not transparent

3.3 Access to HCV-DAAs

In this section, the pricing and reimbursement decisions made for HCV-DAAs in the U.S. and the access situation as of December 2016 are explained.

Pricing decisions

There are currently eight second-generation HCV-DAAs available in the U.S. market (Table 13). Two HCV-DAAs, which were filed prior to 2013, are now discontinued (Victrelis® (Boceprevir) and Incivek® / Incivo® (Telaprevir)).

The highest WAC price reported in the U.S. for HCV-DAAs was Harvoni® (1,125 USD per pill), followed by Sovaldi® (1,000 USD), Viekira Pack® (991 USD), Viekirax® (912 USD), Epclusa® (890 USD), Olysio® (790 USD), Daklinza® (750 USD) and Zepatier® (650 USD). The Gilead products were generally more expensive followed by AbbVie.

In the case of HCV-DAAs, increasing market competition did not bring down the prices substantially [243]. This is because the current patent system in the U.S. allows Gilead and other pharmaceutical companies to use monopoly pricing power to set the prices high [261]. This tendency became clear when AbbVie was expected to reduce markedly the price of their new product, Viekira Pack®, to obtain more share, but instead they set the price at just 12% below the Gilead products [262]. In late 2015, Merck also released a new product, Zepatier®, with a price 48% lower than the Gilead products. Such price setting was initially considered to result from market competition. Although, later it became clear that these prices were set to match the discounted prices of the Gilead and AbbVie products [243]. The recent pricing trends for HCV-DAAs may therefore reflect the possibility of mutual forbearance existing between the pharmaceutical companies. Nevertheless, it is also true that Gilead has begun to engage more in meaningful negotiations with Medicare Part D and Medicaid after the release of Viekira Pack® [263][264]. Initially, they offered a modest supplemental rebate on the condition that no prior authorization (PA) and prescription written by a medical specialist would be required [146]. However, by 2015, they have provided an average of 46% discount on the WAC list price [263].

Based on the information available, effective prices for each of the three TPPs are estimated below. WAC prices are used instead of the confidential AMP.

Medicare Part D: With an assumption that the rebates negotiated by MCOs would be marginal, the effective prices of HCV-DAAs were estimated to vary less from the WAC prices. However, the Medicare trustees reported that the average rebate for all Part D products in 2014 was 14.3%, thus it can be expected that the total rebate for HCV-DAAs must have been slightly higher than this figure considering its high prevalence rate [265]. Therefore, the effective prices of HCV-DAAs were estimated using a 15% rebate. There was a limited number of studies that examined the prices of HCV-DAAs in Medicare Part D, but a study that estimated per-duration spending based on the 2014 WAC found that Sovaldi®, Harvoni® and Viekira Pack® were 84,000, 94,500 and 83,319 USD, respectively [244]. These estimates seem to reflect the total Part D spending in the same year [244]. Furthermore, it is possible that Medicare Part D plans obtained lower discounts than the other payers, especially for higher-priced pharmaceutical products. This is because Medicare Part D has a weaker incentive to negotiate higher discounts due to the large share of costs above the catastrophic threshold that can be picked up by Medicaid through reinsurance (as described below) [265]. Also, there are regulatory limits to how much the formulary list can be modified during the business year [265].

Medicaid: Prices paid by Medicaid are difficult to estimate since the independent state programs conduct separate negotiations. However, it is expected that most of the programs have received a maximum rebate of 46% or more from Gilead. Other products are also entitled to at least a 23.1% rebate. Therefore, the effective prices of Harvoni® and Sovaldi® are estimated to range from 608 to 865 USD and from 540 to 769 USD, respectively. Other studies found that the price of Sovaldi® ranged from 595 to 600 USD, which accords with this estimate [266][267].

The VA program: Negotiation details were also not available from the VA program. However, they announced that a 44% rebate was given by Gilead in 2014 making the effective prices of Sovaldi® and Harvoni® 594 and 829 USD, respectively [261][105]. Another study conducted in 2016 indicated that they spent 25,128 USD (299 USD per pill), 68,627 USD (817 USD per pill) and 41,280 USD (491 USD per pill) for Viekira Pak®, Sovaldi® and Harvoni®, respectively [262]. This indicates that the VA program has received substantially more discounts than the other public TPPs [262]. The discount was also prominent and changed overtime for Harvoni®, as it is currently used for two-thirds of the HCV treatments in the VA program [262].

TABLE 13: SUMMARY OF HCV-DAAS AVAILABLE IN THE U.S. (AS OF DECEMBER 2016)

Product name (Chemical name)	Listed date (Company name)	WAC per pill (USD) (12 weeks)	Effective price per pill (USD)		
			Medicare Part D	Medicaid	VA program
Epclusa® (Sofosbuvir + Velaptasvir)	June 2016 (Gilead)	890 (74,760)	757	684	676
Zepatier® (Sofosbuvir + Velaptasvir)	Jan 2016 (Merck)	650 (54,600)	553	500	494
Viekira Pak® (Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir)	Dec 2015 (AbbVie)	991 (83,300)	842	762	753 (299)*
Viekirax® / Technivie® (Ombitasvir + Paritaprevir + Ritonavir)	July 2015 (AbbiVIe)	912 (76,653)	775	701	693.12
Harvoni® (Sofosbuvir + Ledipasvir)	Oct 2015 (Gilead)	1,125 (94,500)	956	608 – 865	855 (829)* (491)**
Daklinza® (Daclatasvir)	June 2015 (BMS)	750 (63,000)	638	577	570
Sovaldi® (Sofosbuvir)	Dec 2013 (Gilead)	1,000 (84,000)	850	540 to 769 (595 to 600)*	608 to 855 (594)* (594)**
Olysio® (Simeprevir)	Nov 2013 (Janssen)	790 (66,360)	672	608	600

*Published data (2014)

**Published data (2016)

Reimbursement decisions

A study estimated that if these HCV-DAAs were not marketed in the U.S., annual health care costs associated with the disease would nearly triple over the next 20 years from 30 to 85 billion USD, due mainly to the continuous expansion of infected population and the accumulated prescription costs of the traditional SOT and liver transplantation [231]. It is also reported that if more patients are treated with HCV-DAAs, the number of patients and the associated spending will level off by 2016 [268]. Nevertheless, the current access situation in the U.S. for HCV-DAAs has been inconsistent and largely limited, but also has improved overtime (Table 14). The summary of reimbursement decisions made by the public TPPs and their access situation to HCV-DAAs are provided below:

Medicare Part D: The second-generation HCV-DAAs became available in some Medicare Part D programs from 2014. By 2015, all programs included Olysio® and Sovaldi®, and 98% provided Harvoni® [244]. In contrast, only 30% of PDPs and 33% of MAPDs provided coverage for Viekira Pak® [244]. However, most of the plans placed the second-generation HCV-DAAs in the specialty tier which is designed to charge higher OPP by requiring co-insurance instead of co-payment: the average co-insurance rate was lower in PDPs (28.7%) than MAPDs (31.4%) [244]. Although these co-insurance rates were found to be relatively higher for the second-generation HCV-DAAs than the previous treatments, most of the coverage plans differed little from each other, implying that the effectiveness or therapeutic value of the second generation HCV-DAAs had less impacts on the decision-making [244]. It may also imply that it was Medicare's intention to minimise adverse selection (attracting more sicker HCV patients) by leaving beneficiaries with limited options [231]. Most of the plans used PAs and specialist prescription, and nearly half of them also used quantity limits [243]. The details of such access restrictions were not available.

It is estimated that there are at least 350,000 HCV infected Part D recipients [269]. In 2014, a total of 57,400 patients were treated with HCV-DAAs, and it is estimated that over half of the currently infected individuals will be treated by the end of 2016 [265]. Under the current speed of treatment provision, it is estimated that the demand for HCV-DAAs is expected to decline by the end of 2016 [265]. However, this has resulted in the total spending on HCV-DAAs increasing from 4.7 billion USD in 2014 to 9.2 billion USD in 2015 [265]. Note that these figures do not take rebates and discounts into account since such data are not yet available from the CMS.

Most of the Part D recipients are struggling from sizable OPP, despite the fact that some levels of catastrophic coverage do exist. In theory, patients who qualify for the low-income subsidy are protected from financial hardship. However, even the enrollees from the low-income background had to pay from 1,080 to 1,191 USD for a full course of HCV-DAAs [244]. Unsurprisingly, with an expensive product like HCV-DAAs, a patient's catastrophic coverage can easily be reached with the first few pills [244]. Therefore, patients without such a subsidy are faced with significant financial burdens, such that the spending goes up to 6,297 USD for Viekira Pak® used alone and 10,889 USD for Sovaldi® with RBV [244].

Medicaid: The state Medicaid programs have a wide discretion in administering their own program, and thus had heterogeneous reimbursement criteria for HCV-DAAs [103]. A study found that in 2014, only 17 out of 50 states and the District of Columbia listed Sovaldi® as a preferred drug [260]. The remaining 33 states listed Sovaldi® as a non-preferred drug requiring a specialist to prove "medical necessity" as stated in their state law [260].

In 2014, most of the state programs had placed access restrictions on HCV-DAAs including PAs to control the total number of prescriptions (i.e., only Nevada did not require PAs) [103]. The common access restriction was based on the scoring of liver fibrosis, which runs counter to the recommendations by the AASLD / IDSA guidelines [6]. Although, the guidelines list persons with F3 or F4 (indicative of severe liver disease) as the top priority group and those with F2 as the second-order priority group, 33 programs required patients to have a score of F3 or F4 to receive Sovaldi®. Five of these states required patients to undergo liver biopsy as a condition to receive the treatment, instead of much less invasive methods (e.g., liver biopsy or transient elastography were the only way to demonstrate cirrhosis in Tennessee) [6][103][243].

The PAs for most states required abstinence from the use or abuse of illicit drugs, alcohol or both for a period of one to twelve months [260]. Many required a urine test to prove non-use of illicit drugs and alcohol, and patients could be denied of access if they had a previous diagnosis of substance misuse [243]. In some states, physicians were even required to watch people collect their own urine [103]. Co-infection with other infectious diseases, such as HIV/AIDS, also incurred a high risk of access denial [260]. Due to the misconception that individuals with the history of alcohol and illicit drug use have a lower treatment adherence rate, the patient's likelihood of completing treatments was also being subjectively rated by physicians and prior pharmacy refill record was used to control their uptake [260]. These access restrictions were again inconsistent with the FDA-approved labelling, as well as the

IDSA / AASLD guidelines. Furthermore, close to 30 states required HCV-DAAs to be prescribed by or in consultation with a specialist (e.g., heptologist, gastroenterologist, infectious disease physician) [260]. This policy was also different from the recommendations by the IDSA / AASLD, as they only recommend collaboration with a specialist when the responsible physician lacks knowledge and experience [260]. Although, to what extent the difficulty in finding a specialist would pose a barrier to access is yet to be investigated: some Medicaid directors have expressed their concerns for delaying access for patients living in rural areas [260].

Overall, despite the rebates and discounts provided, most of the programs continued to restrict access. A study that looked at patient access in the state of Pennsylvania in 2014 found that 46% of Medicaid patients were denied access, compared with 10% by the private TPPs [270]. Although a precise estimate of the HCV infected Medicaid population is not available, the total number of treated patients also differed greatly by the state: a few states treated only a limited number, and the others like California have treated a large number of patients [271][272]. It has also been reported that Medicaid purposefully denied access to elderly patients, waiting for them to turn 65 to be insured by Medicare Part D (Data from interviews). Therefore, there was a fear amongst Medicaid directors that if they were to treat all the HCV-infected individuals, the total pharmacy budget would triple [273].

Limited access to HCV-DAAs continued in 2015 and 2016. However, many of the state programs now have begun to loosen their access restrictions: the fibrosis level of F3/F4 is still a common access requirement, but some states have began to include IDUs in their eligibility (Data from interviews). Nevertheless, patients are still being denied access and have no choice but to participate in clinical trials to receive treatments or to use off-labels products (Data from interviews). The extent of this trend is yet to be investigated.

The VA program: The VA program estimated that there are 129,000 veterans with a potential HCV infection (approximately 89,000 with the diagnosis without treatments, and 40,000 with potential infection) [262]. In 2014, the VA program treated approximately 8,500 veterans [105]. However, since they did not have enough budget to provide sufficient access, they requested the Congress for 1.3 billion USD to treat another 30,000 patients [105]. In 2015, due to a close to 3 billion USD budget shortfall, the VA program began to provide access to HCV-DAAs only for veterans with advanced liver disease (F3/F4) [262][274]. This increased the number of veterans on the waiting list for over one month by 50% [274]. The situation changed when the VA program was given a 46% discount from

Giliead (expected to save 6 billion USD), and by the end of 2015, 42,000 veterans were treated [275]. In 2016, the VA program decided to expand access to all veterans (regardless of disease stage) aided by the new funding from the Congress of 15 billion USD, of which about 1 billion USD was used for prescription drugs [262]. They are now treating 1,100 veterans per week (double the figure than in 2015), hoping to increase the number to be treated to 2,000 veterans per week by the end of 2016 [262]. In 2017, they plan to spend 1.7 billion USD to treat 35,000 veterans with HCV infection [262]. The VA program, therefore, expects a larger discount in the coming years since more budget means more incentive for pharmaceutical companies for negotiation.

TABLE 14: SUMMARY OF REIMBURSEMENT DECISIONS IN THE U.S. (2014-2016)

		2014	2015	2016
Medicare Plan D	**Access restrictions**	▪ Olysio®, Sovaldi® and Harvoni® (Specialty Tier) ▪ PAs ▪ Quantity limits ▪ Specialist prescription	Limited changes	Limited changes
	Spending	4.7 billion USD	9.2 billion USD	N/A
	OPP	Standard cost-insurance (25 to 33%) Low income: 10.8 to 1,191 USD	Limited changes	Limited changes
	Treated	57,400	N/A	125,000 (estimated total treated since 2013)
Medicaid	**Access restrictions**	33 states listed Sovaldi® as a non-preferred drug ▪ F3/F4 patients ▪ PAs (Abstain from alcohol and illicit drug use, urine test, and HIV/AIDS infection) ▪ Quantity limits (One-time treatment, weekly refill, and investigation of patient's adherence and readiness) ▪ Specialist prescription	Loosened restrictions in some state: California: F2 or above. Any patients with other hepatic conditions regardless of the fibrosis level Connecticut: No access restriction Texas: All second-generation HCV-DAAs are covered	N/A
	Spending	N/A	N/A	N/A
	OPP	N/A	N/A	N/A
	Treated	Washington: 350	Texas: 1,200 Washington: 8,000	
The VA program	**Access restrictions**	F3/F4 patients	F3/F4 patients	All infected
	Spending	Extra 1.3 billion	696 million	1 billion
	OPP	Free	Free	Free
	Treated	8,500	42,000 (by the end of 2015)	1,100 / week 2,000 / week (by the end of 2016)

3.4 Impacts of HCV-DAAs

Accordingly, the public TPPs, especially the state Medicaid programs, reacted aggressively to restrict access to HCV-DAAs [148]. One of the major obstacles to providing wide access was exaggerated concerns over a potential increase in the pharmaceutical spending, which was generated by several uncertainties that made it almost impossible to predict the overall cost [146]. This section, therefore, discusses the obstacles identified for conducting assessments, making reimbursement decisions and implementing such decisions.

Obstacles for assessment

There were five obstacles identified for conducting assessments:

1. **Unexpected and sudden change in the clinical conversation:** The arrival of highly effective medicines for a prevalent condition like HCV infection at unaffordable prices was unexpected for most public TPPs [146][273]. Until late 2014, their focus was still on prioritising the sickest patients since the majority of patients were not eligible or unwilling to go through the interferon treatment. However, with the arrival of the second-generation HCV-DAAs, the conversation became much more about accessibility and pricing, now that a cure is straightforwardly possible for most patients with limited side effects. The health care authorities began to consider the possibility of eradicating the disease, and every infected person now wants to be treated at an affordable cost. This unexpected and sudden change in the clinical conversation created a demand that was much higher than expected. As a result, it was difficult for the TPPs to control the demand, and also to make a sound judgement on the timing for switching from the traditional SOC to the new regimen.
2. **Unpredictable size of the target population:** Three unique features of HCV infection made prediction of the size of the HCV-DAAs eligible population difficult [146]. First, some patients were delaying their treatment to wait for better HCV-DAAs to enter the market in the near future. Second, the CDC recommendation on one-time screening increased the early detection rate. Third, the direct and excessive consumer marketing by the industry using television and the Internet promoted the use of HCV-DAAs. These features had synergistic effects making estimation of the potential target population by the TPPs very difficult, and amplified the concerns over the budgetary impact.
3. **The poor quality of evidence:** The HCV-DAAs obtained regulatory authorisation through the accelerated FDA approval process as a breakthrough therapy [276][277]. One of the consequences of this fast approval process is the unavailability of quality data

since the clinical trials are often a minimal single-arm trial with a short period of use in the general public [261]. Also, since these trials do not take co-morbidities into consideration which are common in the Medicaid and VA populations, an assessment of treatment efficiency for HCV-DAAs (e.g., reinfection and resistance) was a challenge. Therefore, the TPPs had no choice but to make reimbursement decisions based on the limited evidence, especially during the initial phase of implementation. Moreover, to conduct a randomised control trial of second-generation HCV-DAAs to assess their incremental benefits was considered unethical since the latest treatments provide a cure. When patient's symptoms are too fluid to decide whether they are eligible for HCV-DAAs or not, eligibility must be determined based on up-to-date data. However, there was also no system to monitor sufficiently HCV-DAA uptake and patient progress. Therefore, despite the seemingly obvious clinical effectiveness of HCV-DAAs, there was not enough evidence initially, upon which the TPPs could rely when making a decision to spend such a large portion of their budget on a single disease.

4. **The use of cost-effectiveness data:** This obstacle is identified separately from the *Poor quality of evidence* because one of the principle focuses of this study is to assess the potential impacts of pharmaceutical prices in decision-making. As explained previously, the law in the U.S. prohibits the consideration of cost and cost-effectiveness by the public TPPs. However, the consideration of cost in a case like HCV-DAAs is unavoidable. Because the consideration of cost in decision-making was not clearly stated in the product assessment and policy interpretation guidelines, it further led to the issue of accountability.
5. **Stigmatisation and prioritisation:** Stigmatisation against and the lack of evidence about substance use disorders (e.g., the rate of treatment adherence and reinfection) played negatively in making reimbursement decisions. While the veterans, the most sympathetic population in the U.S., had almost no access restrictions, strict PAs were laid out by the state Medicaid programs and the others to limit the access of socially vulnerable populations (e.g., IDU and correctional populations) [260].

Obstacles for reimbursement decision-making

There were three obstacles identified for making a reimbursement decision:

1. **Inefficient and insufficient rebate systems:** Under the U.S. health system, in theory, active negotiation is one of the strongest forces that can reduce pharmaceutical prices. However, this system often results in many exclusive deals making it difficult to evaluate its efficiency in price reduction. Also, it is one of the causes of access inequality as it

creates biased reimbursement decisions to purchase certain products over others when a large discount is available, irrespective of the product's effectiveness. While most of the TPPs can independently negotiate prices, it is prohibited for Medicare Part D creating a further divide in access. The current system, therefore, has been an obstacle for decision-makers because the availability of HCV-DAAs was largely affected by the purchasing power of a TPP resulting in biased and delayed reimbursement decisions.

2. **Increasing pressure from the pharmaceutical industry:** The pharmaceutical industry has a strong presence as a stakeholder within the U.S. health system. The pressure from the industry to improve the coverage has been stronger than ever for HCV-DAAs. Pharmaceutical companies encourage patients to demand new medicines, either using monetary incentives or by advertising directly to patients. For example, Gilead strategically closed their patient assistant program in July 2015, which provided free HCV-DAAs for individuals who were denied access by their insurers, amplifying their distress to increase the pressure on the TPPs [278]. Also, the industry has strong monetary ties with patient advocacy groups (e.g., the majority of funding for the national viral hepatitis roundtable comes from the pharmaceutical industry), placing additional pressure on the TPPs [279].
3. **Overall impacts of the decisions made on the system and premiums**: The arrival of HCV-DAAs was too sudden and unexpected; therefore the TPPs did not have enough time, infrastructure and resources to prepare for an extensive provision program [280]. The state Medicaid programs discussed the need to devote more human resources to the management of such programs (Data from interviews). The VA program also performed an extensive system restructuring before deciding to lift the access restrictions to all veterans [262]. Furthermore, the decision makers had to be extra careful because providing better access also meant an increase in the insurers' premium for some of the TPPs [265]. Data has shown that the overall premium increased significantly by 45 USD, of which 29 USD was the result of HCV-DAAs [281].

Obstacles to policy implementation

There were two obstacles identified for policy implementation:

1. **Fragmented system and uncoordinated policy interpretation:** The state Medicaid programs drafted an access policy and contracted MCOs to implement and operationalise the policy. Without sufficient guidance and clarification, different MCOs tend to interpret a policy differently. For example, in the state of California, the access policy in July 2015 was "*Patients with F3/F4, anyone with the substance use disorder*

had to either demonstrate six months of abstinence or be actively engaged in a drug treatment" [282]. However, this policy lacked an explanation of how the eligibility must be assessed, and thus the 30 MCOs could interpret this statement slightly differently and come up with different PAs.

2. **Justification and accountability:** The strict access restrictions to the HCV-DAAs resulted in a public outcry. One of the possible explanations for this is that the economy of health care including premiums is often difficult for the public to understand. Medicaid did explain that the implementation of the PAs was necessary for an effective use of their resources. However, there was an inconsistency in their arguments, especially when they were not supposed to consider cost in decision-making. The public TPPs, therefore, had failed to provide a sufficient explanation for their decisions [103].

Policy changes

Since the market entry of HCV-DAAs, there has been a growing debate over the issue of pharmaceutical cost in the U.S. For example, the CMS claimed that the national spending on pharmaceutical products increased from 2.4% in 2013 to 12.4% in 2014, which was in part due to HCV-DAAs [265]. In 2015, three-quarters of Americans polled answered that the current pharmaceutical prices are unreasonable and that the government must intervene [283]. At least 11 lawsuits were filed in six states challenging the pricing and reimbursement decisions made for HCV-DAAs [243]. Various mechanisms for reducing the prices of HCV-DAAs have been discussed and proposed by an increasing number of policy experts [284][77][285].

This section discusses the observed impacts that may lead to future policy changes.

- **Public outcry led to intensive government involvement:** The public outcry and the growing media attention on the pharmaceutical pricing issues had collectively generated a movement within the federal government. Drug prices became a highly debated topic for both republicans and democrats, and even part of the presidential debate (Figure 9). The initial move came in July 2014 when the senators sent a letter to Gilead asking for more information about how Sovaldi® was priced [286]. By October 2014, the National Association of Medicaid Directors expressed their concerns to the Congress [287]. Followed by Senator Bernard Sanders calling for a charge of "death panels", and to enlist pharmaceutical companies with the U.S. patents to produce their products at much lower price for government use [262][288][289]. The presidential Advisory Council on HIV/AIDS also sent a letter to President Obama in June 2015 stating that *"Current*

restrictions on access to hepatitis treatments are unreasonable and discriminatory, and are not supported by medical evidence" [267][289]. The advisory council criticised the PA system and emphasised the importance of disclosing the negotiated prices both to the public TPPs and the industry [267]. In November 2015, the CMC informed the state Medicare programs to obey the Federal law and to loosen their access restriction [243]. They also sent a letter to Gilead and AbbVie asking for further discounts [290][291]. By December 2015, the Senate Finance Committee published a report censuring Gilead's pricing on their new HCV treatments [272]. The Obama administration announced that they will investigate the TPPs that continue to use the PA system to discriminate against the socially vulnerable populations [243][292]. He also proposed to give Medicare an authority to negotiate price [265]. Despite, the national level realisation that this is clearly not just an HCV issue, and the federal government taking some actions, their efforts were directed towards blaming the industry and the TPPs, and not on the fundamental issues of the existing system. For example, there were no comments by the advisory council on how to pay for the increased spending on HCV-DAAs if they are to ease the access restrictions [267]. Furthermore, the patient advocacy groups have been advocating for a reimbursement decision-making guideline to be issued by the state Medicaid programs, but the federal government has been noncommittal since they fear that setting a precedent may affect the other high-cost medicines in the pipeline [267].

- **Potential structural and system reforms within the TPPs:** Some changes in the structure / system of the TPPs were observed as the result of the public outcry and the growing pressure from both the government and pharmaceutical industry. For example, Medicare for the first time released a detailed breakdown of the prescription claims on their website (without the rebate information) [293]. The officials announced that the intention behind this change was to encourage experts to weigh in and to come up with solutions to the existing issues [294]. Medicare Part D has proposed to set an OPP limit [265]. Several Medicaid programs are also considering legislation or ballot initiatives to improve transparency around pricing [265]. The VA program has put in enormous efforts to redesign the care provision system by disseminating training and expert advice on HCV infection and also by introducing new systems, like telehealth and video conferences, to allow a long distance treatment provision [262]. Medicaid officials are also increasingly hearing the patient voice. In California, Medi-Cal asked for public comments when deciding eligibility and have incorporated feedback received into their report (Data from interviews). In New York City, a pharmaceutical product utilisation review board gave advocates an opportunity to raise their voice (Data from interviews).

FIGURE 9: TIMELINE OF THE MAJOR GOVERNMENT ACTIONS IN THE U.S.

July 2014:

- Senators sent a leter to Gilead asking for more information about how Sovaldi® was priced

October 2014:

- The National Association of Medicaid Directors sent a letter to the Congress expressing their concerns about the prices of Sovaldi® and Harvoni®

May 2015:

- Senator Bernie Sanders sent a letter expressing his concerns regarding the current HCV-DAAs access situation of the VA program

June 2015:

- The presidental Advisory Council on HIV/AIDS sent a letter to President Obama: Calling for elimination of the PA system

November 2015:

- The CMS sent a letter to the state Medicaid programs raising concerns about access retrictions, and encouraged them to negotiate prices

November 2015:

- The CMS sent a letter to Gilead, Johnson & Johnson, AbbVie and Merck asking for more information about their negotiation practices

December 2015:

- The Senate Finance Committee published a report censuring Gilead's pricing on their new HCV treatments

- **Growing interest in HTA:** Slowly the public TPPs are becoming more aware of the need for HTA. Despite the denial of the CMS officials, it is clear in the case of HCV-DAAs that the costs were considered to inform rather than to justify decisions [148][295]. Some even argue that the ambiguity in the wording of the CMS's definition of reimbursement decision criteria, "*reasonable and necessary*" may leave some space for cost consideration (Data from interviews). There is also some evidence that the CMS looks to the HTA agencies in other countries (such as England, Canada, Australia, Germany and France), when trying to understand the clinical evidence and cost-effectiveness for a particular product (Data from interviews). In some states such as Pennsylvania, an expert consensus panel published a treatment guideline that has more focus on determining medical necessity from an accommodation of the cost rather than just clinical merits [146]. The attendance of Medicaid representatives was seen at the Institute for Clinical and Economic Review (ICER) round table, and members of ICER were also invited to attend Medicaid meetings (Data from interviews). The Medi-Cal director is now a member of California Technology Assessment forum (CTAF), and the value of HCV-DAAs was mentioned in their first treatment utilisation policy with a reference to the CTAF [296].

3.5 Challenges and reform proposals

Often the story of HCV-DAAs is treated as a “special” case. However, with advancing technology, the challenges imposed by HCV-DAAs are likely to be repeated [297]. Therefore, this section discusses the future challenges that the U.S. health system may face with respect to high-cost medicines.

Firstly, **more formal and transparent methods to structure the decision-making process are needed to synthesise evidence, to understand the uncertainties surrounding a new technology and to determine when to postpone a decision until additional information is collected**. One of the main issues, highlighted by the case of HCV-DAAs, is the fragmentation of the U.S. health system (i.e., the existence of numerous insurance schemes without any coordination). This had led to different reimbursement policies and thus unequal access to treatment. The issue was particularly severe for the state Medicaid programs, in contrast to Medicare Part D and the VA program: there was no structured means or guidelines for MCOs to determine reimbursement policies. Decisions were made based on the recommendations from different guideline organisations and other unknown sources, without medical justification or transparency. There was also no comprehensive monitoring system to oversee the access situation such as affordability, accessibility and treatment adherence. Although it is illegal under the ACA, and a violation of the Federal Medicaid Law, to selectively deny access to high-cost conditions, the consideration and coordination of ethics and public health implications were also lacking [243]. As a result, despite the initial access policy drafted by the state Medicare programs, interpretations and implementation of such policies took various forms leading to the different PAs. This also created a great deal of administrative complexity where physicians had to deal with different forms of insurance creating inefficiency and more time and money spent on unnecessary work. This absence of coordination and fragmentation of the health system resulted in extensive confusion at all levels for the stakeholders. Especially for the public, because there was no comprehensive explanation from the TPPs about their restricted access and the potential side effects of access expansion (e.g., premium increase).

Secondly, **the importance of cost consideration in reimbursement decision-making must be formally recognised.** The U.S. holds a strong cultural anticipation that consideration of cost and cost-effectiveness would lead to rationing of care. However, some argue that there is a limit to how much prices can go down by as a result of market forces [298]. Maintaining the confidentiality of negotiated prices is not to the advantage of the public

TPPs. Moreover, the focus should shift from a subjective notion of a “high” price to an objective notion of “high value” for a curative treatment like HCV-DAAs. The majority of discussion around the pricing issue has been on how to deal with the high costs of recent pharmaceutical products (e.g., by altering the patent law, allowing Medicare Part D to negotiate prices, and the state Medicaid programs to collaborate with each other to gain more purchasing power). There has been a limited focus on the product value (e.g., at what price should the product become valuable to the society). Studies have confirmed that the high health expenditure in the U.S. is less to do with its wealth or disease profile, but more to do with the fact that the price levels of the health sector are generally higher than the other HICs [235]. If U.S. healthcare is generally more expensive than other countries, comparing the prices may not be useful. A redistribution of the budgets from ineffective to high-value and cost-effective interventions may generate more gain for the investments by the public TPPs [148]. Focusing more on product value may also be a way to gain the public support by shifting their attention from the rationing of care.

Thirdly, **the cost sharing system must be redesigned to protect patients from catastrophic payment**. The current cost-sharing mechanisms, except for the VA program, has more focus on their financial stability and sustainability, and less on of the impact on patients. For example, the special tier scheme of Medicare Part D charges a high co-insurance as it was the scheme initially developed to treat conditions that affect small numbers of the U.S. population [273]. Also, most of the public TPPs do not set an upper limit on co-insurance even though commercial plans regulated under the ACA do have an OPP maximum. Catastrophic payment in the U.S. has long been an issue, but urgent reconsideration is needed to keep a balance between the fiscal stability of TPPs and the financial protection of patients. Otherwise, the situation will continue to worsen as the prices of pharmaceutical products increase.

And lastly, **systemic issues of the U.S. health systems must be confronted and tackled before any of the above issues can be considered**. Without universal health coverage or a single payer system, there is insufficient cooperation between the government, the industry and TPPs. The issue of pharmaceutical pricing and access has created an elevated tension between the industry and the TPPs; where the industry is accusing the TPPs of restricting access to an innovative pharmaceutical product, while the TPPs are denouncing the industry for the high charges. The federal government, on the other hand, has done little to solve the real problems. Instead, they have just challenged the industry about its high cost and pressured the TPPs for better access. There is also limited coordination with the FDA, and organisations like the CDC, which has led to uncoordinated public interventions against HCV

infection. For example, strong recommendation of HCV screening, when the public TPPs had limited ability to afford the latest treatments. Therefore, no organisation currently exists in the U.S. which is accountable for the escalating spending on HCV-DAAs and the associated access issues.

Furthermore, the strong presence of the pharmaceutical industry as a stakeholder is also a barrier to the development of effective / coordinated public health policy. Under the current system, a pharmaceutical company like Gilead can freely set a price as high as the market allows. In the case of an infectious disease like HCV infection, it also implies that a pharmaceutical company can manage demand until the product patent runs out by deliberately setting a high price. This maintains a portion of individuals without access to treatments, thus allowing a continued spread of infection, and making a chronic market for a non-chronic infection (Data from interviews).

Some argue that a private sector focused health system is needed to encourage greater innovation, but the experience of HCV-DAAs shown that this may not necessarily be the case [299]. Instead, the current system is simply causing further financial damages to the public TPPs while the industry has limited incentives to change the status quo. Especially when the Federal law mandates provision of all FDA approved products regardless of benefit gained per dollar spent, the public TPPs have a limited ability to control pharmacy benefit expenditure, even with the Federally mandated rebates [271]. Furthermore, the promise of the ACA established under the Obama administration was to expand the public insurance services and to provide quality and affordable care regardless of a person's pre-existing conditions [267]. However, the reality is that many people are still being denied access to HCV-DAAs, for the condition that kept them from being insured before the ACA [267]. This is because, under the pressure from the pharmaceutical lobbyists, the ACA placed an unbalanced focus on coverage instead of cost.

Health care is still a growth sector in the U.S., and thus an attempt to intensify government control of the healthcare sector may not be favoured by the business world. However, it is questionable to what extent the experience of HCV-DAA will actually result in a change unless the systemic problems of U.S. healthcare are properly addressed as discussed above. The industry is driven by financial interests and not by the interests of public health. In order to provide appropriate access to high-cost medicines while managing the long-term fiscal sustainability, the U.S. has considerably more challenges ahead than any other HICs.

3.6 Conclusions

HCV-DAAs were withheld from millions of HCV-infected individuals in the U.S. by the access policies implemented by the TPPs [300]. One of the biggest barriers for the public TPPs was the potential budget impact and the uncertainties regarding demand, clinical evidence and cost. These have indirectly impacted policy decisions and led to strict access restrictions amplified by the systematic problems that persist in the U.S. health system. Their initial responses were to restrict the coverage only to the patients with the most advanced disease. Because of the concern over the potential budget impact, the cost and cost-effectiveness of HCV-DAAs were considered, although the law prohibits it. Especially in the Medicaid programs, strict access restrictions were introduced by setting up the PAs. Due to the fragmented health system, the reimbursement policies laid out by the CMS were not interpreted and implemented in the same way by MCOs, and thus patients were faced with different access barriers. The lack of evidence also resulted in the exclusion of socially vulnerable populations. The differences in access restrictions between Medicaid and the VA program, for example, highlighted the issue of stigmatisation in decision-making. There was also no effective communication by the public TPPs, which led to an aggressive patient outcry and eventually the involvement of the federal government. As a result, by 2016, most of the TPPs had loosened their restrictions and coverage is expected to improve over time.

Accordingly, the market entry of HCV-DAAs and associated events served as an important wake-up call and thereafter brought the issue of pharmaceutical pricing and access to the forefront [265]. However, it would be a great challenge to make any improvements in the U.S. health system unless the focus is placed on its systemic systematic problems rather than pricing. The government has a responsibility to ensure that reimbursement policies are decided based on scientific evidence and the public needs, rather than the financial interests of private organisations [243]. The current system forces people with insurance to pay the highest prices in the world, despite the fact that their access is largely limited [13]. Serious reconsideration of the meaning of social responsibility and security is required in the U.S., possibly leading to some redesign of the health systems, if the continued challenges of high-cost medicines are to be more successfully met.

Chapter 4: Case study: England

4.1 Introduction

Across the U.K. countries, approximately 214,000 people (0.3%) are estimated to be chronically infected with HCV infection, of which 160,000 are living in England (2005, latest estimate) [151]. These figures are relatively low, especially when compared with those of Japan and the U.S. [301]. However, the disease epidemiology follows a similar pattern to other HICs: the majority of infected individuals in the U.K. are claimed to have some history of illicit drug use, and approximately half of IDUs are expected to be infected with the disease [302]. The prevalence is also relatively high among black and minority communities where people have closer links to the countries with a high HCV prevalence [151]. The disease is, therefore, disproportionately affecting the communities that are usually marginalised and underserved with poor access to health facilities [151].

To combat this situation, the U.K. aims to eliminate the disease by 2030 and the U.K. countries have independently developed a national action plan for HCV infection. This includes the Hepatitis C Action Plan for England (England), the Liver Disease Delivery Plan for NHS Wales and its Partners to 2020 (Wales), the Sexual Health and Blood Borne Virus Framework 2015- 2020 (Scotland), and the Action Plan for the Prevention, Management and Control of Hepatitis C in Northern Ireland (Northern Ireland) [303][304][305][306].

The above-concerted efforts have begun to show some positive outcomes: for example, while the world average of the proportion of IDUs who are aware of their disease status is 5%, that of the U.K. has been relatively high at 68% [151]. The number of individuals tested and diagnosed annually in England has also increased by 21% from 2010 to 2015, and the incidence rate has been steady at 25% from 2008 to 2015 [151][302]. On the contrary, the mortality rate from ESLD and HCC has been increasing over time due to the accumulated disease prevalence among the older population. Since 1970, the mortality rate has increased by fivefold from 2005 to 2015 [151][307]. This recent increase indicates that more and more infected individuals are progressing into advanced liver diseases, requiring adequate access to diagnosis and treatments, and thus effective provision of HCV-DAAs across the country has become an important milestone [151].

With the above information in mind, this chapter discusses access to HCV-DAAs in England and the potential impacts HCV-DAAs have had on pharmaceutical policy.

4.2 Health system and pharmaceutical policy

The health system in England, and specifically the pharmaceutical pricing and reimbursement decision-making processes, are described below prior to an analysis of the impact of HCV-DAAs on their system.

Health system

The National Health Service (NHS), which is funded through general taxation, provides the majority of health services in the U.K. The proportion of health services that are funded through private medical insurance and / or OPPs is limited [308]. Because the spending is strictly controlled at the national level, the U.K. health expenditure has been traditionally low: in 2000, the GDP share of health expenditure was 6.9%, but since then spending has been increasing gradually and reached a maximum at 9.8% in 2009 and dropped to 9.1% in 2014 due to the 2008 financial crisis [179]. The NHS accounts for the majority of the healthcare budget: the total spending was 113 billion GBP (165 billion USD) in 2015 to 2016 and it is scheduled to increase to 124 billion GBP (180 billion USD) from 2019 to 2020 [309].

Across the U.K. countries, almost all of the health care services are provided for free, except dental care and some of the social care services [308]. However, England is the only country that continues to require co-payment for pharmaceutical products with a prescription charge of 8.40 GBP (13.66 USD) per item [310]. A patient can also choose to purchase a three-month Prescription Prepayment Certificate (PPC) for 29.10 GBP (42.30 USD) or a 12-months PPC for 104.00 GBP (151.16 USD) [310]. Patients under 16 or over 60 years old, patients with certain medical conditions as well as those with low income are exempt from the co-payment [310].

In England, the Clinical Commissioning Groups (CCGs), which are clinically-led statutory NHS bodies established in April 2013 (under the Health and Social Care Act 2012), take responsibility for the planning and commissioning of hospital and community NHS services, as well as for ensuring appropriate delivery of care by each of the NHS trusts [311]. The budget available for the CCGs are determined using a resource allocation formula and overseen by an executive non-departmental public body called NHS England (i.e., formally known as the NHS Commissioning Board) [311].

Pharmaceutical policy

England is one of the leading countries for adopting pharmacoeconomics and HTA in its pricing and reimbursement decision-making processes. There are two main players: NHS England (a single large TPP) and the National Institute for Health and Care Excellence (NICE), another executive non-departmental public body that provides guidance to NHS England on the clinical and cost-effectiveness use of pharmaceutical products and services [74][312].

Price setting

Pharmaceutical prices in England are regulated by the Pharmaceutical Price Regulation Scheme (PPRS), a non-contractual / voluntary agreement between the Association of the British Pharmaceutical Industry (ABPI) and the Department of Health (DoH) [117]. Up until the 2014 PPRS, the emphasis was on profit control [313]. Therefore, pharmaceutical companies participating in the PPRS could set prices for their products, but they were expected to return the annual excess profits to the government or reduce list prices of one or more of their products [313]. However since the government shifted the focus to control the growth of the purchase volume of branded drugs in order to keep a good balance between affordable access to high-quality medicines and a fair return for the industry [314]. The 2014 PPRS, therefore, has a similar over-arching basis as the previous PPRS, but the pharmaceutical companies have more space for negotiation with the government with respect to the payment for profit excess. Options are 1) direct payment of the excess profit, 2) reduction of list prices in the following year; and 3) restriction or delay of agreed increase in list prices [314]. The product prices of non-PPRS participants are negotiated using the statutory scheme with a compulsory rebate of 15% [116].

Another national level risk-sharing agreement (endorsed by the 2014 PPRS) is the Patient Access Scheme (PAS), which aims to ensure access to pharmaceutical products otherwise would not be supported by NICE due to insufficient cost-effectiveness [315]. A PAS can involve risk sharing, but most are simple confidential discounts [315]. A pharmaceutical company can decide whether to offer a PAS or not, rather than following the usual PPRS scheme, but the DoH makes the final approval. Although the procedure can begin before the NICE approval, most pharmaceutical companies offer a PAS only when it looks as if they are unlikely to receive a positive recommendation at the list price. While the details of the PPRS negotiations is public information, that of the PAS is often confidential in order for the government to receive a better pricing arrangement. Whilst most of the PAS have been

simple price discounts, they can also take the form of Financially-based PAS (Discounts / rebates linked to the quantity and / or types of patients and patient responses) or Outcome-based PAS (Discounts / rebates linked to the value of a pharmaceutical product) [92]. The former type of PAS leaves the list price unchanged, whereas the latter could lead to a different list price in the future.

For the pharmaceutical products that are used nationwide, the Commercial Medicines Unit (CMU) as a part of the DoH conducts the ultimate pricing negotiation, but tendering can also happen at the local level [316].

Reimbursement decision-making

The role and responsibilities of NICE in conducting HTA are well documented and available on their website and are clearly stated in *The National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013* [317]. NICE appraises health technologies selected by the Secretary of State (i.e., medical products, medical devices, diagnostic techniques, surgical procedures, therapeutic technologies other than medicinal products, systems of care and screening tools) and makes recommendations [312][318][317]. Their recommendations are then published in the form of NICE guidance. The CCGs, NHS England and their public health functions must comply with the guidance and provide funding for ensuring access to the appraised product / service within three months of the publication date [317]. The details of how healthcare professionals should care for people with ill-health conditions are the subject of clinical guideline, again published by NICE.

The questions that NICE asks during the appraisal are fundamentally different from the other regulatory authorities in that they are interested in "*How well does a product / service of interest work compared to the existing products / services?*" rather than "*Does it work and is it safe?*" (Data from interviews). Given that the NHS resources are limited, NICE focuses on maximising the societal benefits by making sure that the selected new technologies offer the best value for money, and that those who need it the most are treated first [319]. Issues that must be considered during an appraisal are listed below and in *The Health and Social Care Act 2012* [319]:

- *the broad balance between the benefits and costs of the provision of health services or of social care in England;*
- *the degree of need of persons for health services or social care in England; and*

- *the desirability of promoting innovation in the provision of health services or of social care in England*

There are four steps to the technical appraisal process as described below (Table 15) [312][318]:

Step 1: Topic selection: Since it is not practically and financially feasible to conduct a technology appraisal for every new technology that receives a regulatory authorisation, NICE selectively conducts an appraisal based on the topics of importance and the likelihood of the technology bringing significant benefits to patients. Product selection takes place at the National Institute for Health Research Horizon Scanning Centre (the University of Birmingham), and appraisal suggestions are often made directly by the pharmaceutical companies through UKPharmaScan or others can also suggest. Of the selected products, the Secretary of State for Health further conducts prioritisation based on several factors such as population size, disease severity, resource impact and the product value. The final decision is made by the DoH, and the potential topics are then passed to NICE for scoping. Unless specified by the DoH, NICE cannot publish a guidance for products that have not yet received regulatory authorisation in the U.K. This whole process takes up to seven weeks, and it is conducted in an inclusive, open, transparent and consistent manner. In order to minimise the window of uncertainty (i.e., a period when a product is available on the market without a NICE guidance) and to ensure that a guidance is published close to a product launch date, the centre usually notifies NICE about the possibility of a new pharmaceutical product obtaining a regulatory authorisation about 20 months in advance, and 15 months in advance for a new indication.

Step 2: Scoping: Scoping is a process of selecting questions to be addressed during an appraisal, which takes place once a technology is formally referred to NICE. A draft scope is developed following the PICO format (P= Population, I=Intervention, C=Comparison, O=Outcome), and how to define C becomes particularly important later in the appraisal. Available and relevant evidence are collected by the centre as well as by the NICE's information specialists whom would conduct a literature search and interviews with pharmaceutical companies. Issues that may affect the final appraisal decision such as access equality and stigmatisation are also included as additional questions. During this process, external comments are collected within 20 working days from identified provisional consultees, commentators and others to ensure that all the relevant areas and issues are covered:

- **Consultees:** Specialised commissioning groups (NHS, two clinical commissioning groups and the manufacturer) and national level patient or professional groups.
- **Commentators:** Research organisations, organisations that cover NHS England as a whole (e.g., NHS confederation), and relevant comparator and companion diagnostic test companies.
- **Others:** Any other relevant organisations such as specific ethnic groups, people with disabilities, mental health problems and / or learning disabilities.

Towards the end of this process, a scoping workshop takes place where up to two representatives from the consultees and commentators and the Assessment Group (for MTAs only, more information below) are invited. Finally, after considering various inputs, NICE submits a summary report to the DoH (i.e., block scoping report), and the ministers make the final decision. The whole process takes approximately 18 weeks.

Step 3: Appraisal: Finally, a technology appraisal takes place to make a judgment about whether the pharmaceutical product should be recommended as clinically and cost-effective for use by NHS England, or whether the use should be restricted. Therefore, the main evidence collected for the assessment is clinical (direct health benefits and the impacts on quality of life (e.g., pain and disability)) and economical (value for money in relation to the NHS resources) evidence. With respect to the product price, NICE make a recommendation based on the list price or the PAS price if there is one. NICE publishes an approximate timeline on its website within six weeks after the formal referral for scoping. However, the timeline is often revised since the duration required for an appraisal can vary depending on a product.

The appraisal process takes one of the following two forms:

- **Single Technology Appraisal (STA):** This appraisal process is designed for a single product for a single indication, typically for new technologies that do not require a collective appraisal. Pharmaceutical companies are required to submit principle evidence, which includes economic modelling results as well as other relevant information such as their plans for approaching the disease, handling of the uncertainties, and also potential challenges in data interpretation. Consultees and selected clinical experts, NHS commissioning experts and patient experts can also submit evidence. Under STA, pharmaceutical companies often have an advantage since they conduct all the clinical trials and have access to individual patient data. During this process, they can also discuss the scoping (i.e., how they intend to approach the problem definition) and the need of PAS with the committee. The Evidence Review

Group (ERG), an external independent academic organisation, conducts a review of all the evidence submitted.

- **Multiple Technology Appraisal (MTA):** This appraisal process is designed for a single or multiple products for one or more indications. In MTA, an independent Academic Group (AG) carries out the modelling process and conducts a review of all the evidence collected. Pharmaceutical companies can submit their own modelling results if they wish. Consultees and selected clinical experts, NHS commissioning experts and patient experts can also submit evidence.

As such, the main differences between STA and MTA are the body that conducts the assessment and the timeline at which the appraisal takes place. There is a general presumption in favour of STA because it is faster and uses fewer resources, and thus can minimise the window of uncertainty.

Step 4: Decision-making: The NICE appraisal committee, an independent expert group, makes the final decision based on the modelling results and other information submitted by STA / MTA. In addition, the committee considers the equality scheme and the institute's guidance on social value judgments especially when the modelling result shows borderline cost-effectiveness and / or the disease is associated with stigmatisation [320][321].

The following groups can participate in the committee meeting:

- **Clinical experts:** Experts with in-depth knowledge in the area of interest and some familiarity with NICE. Usually, professional organisations (e.g., royal college of physicians) nominate experts and then the committee chair selects members. If NICE invites a pharmaceutical company to nominate, the chair is obligated to accept their nomination;
- **Patient experts:** Patients themselves or a representative of patient organisations;
- **Manufacturer:** Two members representing the manufacturer for answering the committee's questions. They can also submit their wishes in writing, but cannot verbally comment unless asked to do so;
- **NICE representative:** The third party that manages the appraisal process, thus has little impacts on the committee's decisions; and
- **NHS representative:** Commissioning expert, but their attendance is not required.

After the meeting, the committee submits their recommendations either as an appraisal consultation document (ACD) or as a final appraisal determination (FAD). The issuing of an ACD is fairly common when the committee's preliminary recommendations do not recommend the technology, or it is more restrictive than described in the regulatory

authorisation. Once an ACD is issued, the consultees, commentators and the general public are again invited to comment, and after considering these comments, the committee finalises its recommendations in a form of FAD. Overall, NICE keeps the appraisal process very transparent. The identity of all the participants, the evidence reviewed, the decision and the committee's reasoning are publically available online [322].

Once guidance is published, it has the same legal status regardless of its production process (i.e., STA or MTA). As mentioned, NHS England must comply with positive recommendations listed on a NICE guidance, but in the case of a negative recommendation, the CCGs can still choose to make it available. Also for the products that were not referred to an appraisal, there are systems, such as the highly specialised technologies programme and a new medicines evidence summary, to support making a purchasing decision at the local level [323][324].

TABLE 15: SUMMARY OF REIMBURSEMENT POLICY IN ENGLAND (PRIOR 2014)

	Assessment	Decision	Outputs and implementation
Constitution and governance	Assessed by STA or MTA An independent assessment group conducts the analysis (MTAs only). Various stakeholders are invited	Guidance is issued by NICE Commissioning is then determined by the CCGs	NHS England is obliged to follow the recommendations listed on a NICE guidance Patients have the right to have access to recommended products
Methods, Processes	Selection of products / services for the appraisal is determined by the DoH Once the selection is referred to NICE, HTA is conducted either by STA or MTA Negative listing	Discussion at the appraisal committee Public consultation is also sought A pharmaceutical company can appeal against a decision, which can lead to another round of appraisal Not always, but a different form of negotiation can take place such as through the CMU	Appraisal duration is difficult to estimate but often less than six months NHS England is obliged to implement the guidance within 90 days from the issued date
Use of evidence	The main consideration of evidence: ▪ Comparative clinical effectiveness ▪ Cost The best available evidence is used In the case of STA, most of the data is provided by a pharmaceutical company	The committee makes an attempt to consider all evidence available The committee tends to give a positive recommendation over social and stigma issues	A NICE internal review can take place once in 1 to 3 years
Transparency and accountability	Well documented	Well documented	Well documented

4.3 Access to HCV-DAAs

There are ten HCV-DAAs recommended for use by NHS England (as of December 2016) (Table 16). The pricing decisions made for each of the HCV-DAAs and the access situations in England are explained below.

Pricing decisions

When calculated by cost-per-day list price, there was a significant difference between the first and second generation HCV-DAAs. The average cost-per-day list price of the second generation HCV-DAAs was 410 GBP (595.93 USD) [Sovaldi® (416.45 GBP, 605.31 USD), Daklinza® (291.88 GBP, 434.24 USD), Harvoni® (464.05 GBP, 674.49 USD), Viekirax® (383.33 GBP, 577.17 USD), Viekira Pak® (416.66 GBP, 605.61 USD), Zepatier® (434.52 GBP, 631.57 USD), and Epclusa® (464.00 GBP, 674.42 USD)]. This was almost double the cost of the first generation HCV-DAAs with an average price of 211 GBP [Olysio® (266.64 GBP, 387.56 USD), Incivo® (266.64 GBP, 387.56 USD) and Victrelis® (100.00 GBP, 145.35 USD)].

However, in terms of cost-per-treatment-cycle, the difference is marginal or in some cases the first generation HCV-DAAs have a higher cost, because the first-generation HCV-DAAs often require a longer treatment duration (up to 44 weeks) with a combination regime either with INF-a or RBV or both. For example, the cost of the 12-week treatment for Epclusa®, Zepatier®, Viekirax®, Harvoni® and Sovaldi® were 38,980, 36,600, 32,200, 38,079 and 34,932 GBP, respectively (56,656.98, 52,197.67, 46,802.33, 55,347.38 and 50,773.26 USD). Whereas the cost for the same duration for Olysio® was 32,155 GBP (46,736.92 USD) and 44 weeks for Victrelis® was 30,800 GBP (44,767.44 USD), which were not exceptionally lower than the second generation HCV-DAAs. The exception was, for example, Daklinza® which costs 59,501 GBP (86,484.01 USD) for 12 weeks, but this is because it requires a combination regime with Sovaldi® which substantially increases the total cost. Alternatively, if a patient is effectively treated under the 8-week treatment with Harvoni®, the cost is only at 25,986 GBP (37,770.35 USD), which is around the same cost as Incivo® (22,398 GBP for 12 weeks, 32,555.23 USD).

With respect to HCV infection, the pharmaceutical companies that so far have marketed HCV-DAAs are participants in the PPRS, except Gilead [117]. The product prices of Gilead were, therefore, negotiated using the statutory scheme, which resulted in 353.99 GBP (514.52 USD) per day for Sovaldi®.

Note that the prices of all the other HCV-DAAs marketed after Daklinza®, except Epclusa®, were negotiated with the NHS CMU, and this includes a competitive tendering work plan [144]. Competitive tendering is a way of obtaining a lower product price by forcing manufactures to compete with each other. The effective prices of these products are, therefore, not in the public domain in order to maintain commercial confidentiality. Usually, the CMU takes over the negotiation when a product is proven not cost-effective. In the case of HCV-DAAs, there was less doubt about their clinical and cost effectiveness, however, NHS England required the CMU to secure lower product prices in order to ensure affordability.

Reimbursement decisions

Since the market entry of HCV-DAAs, the uptake of HCV treatment has increased by approximately 40% from an average of 6,400 patients per year (2009 to 2014) to 8,970 patients in 2015 [151]. However, this figure is not yet optimal considering the current annual treatment rate of 6%. The majority of the infected individuals living in England are still on a waiting list, even when the policy states that all infected individuals, meeting certain conditions, must have access to HCV-DAAs.

In the sections below, access to HCV-DAAs in England is explained from the perspective of how the appraisal process was undertaken, and decisions were made and implemented.

Appraisal process: The length of an appraisal process is difficult to predict as it varies on a case-by-case basis. However, as mentioned earlier, it is not in the interest of NICE to delay this process, as they want to minimise the window of uncertainty to control the spending, especially on high-cost medicines. Interestingly for HCV-DAAs, however, the NICE appraisal process took longer than usual: the guidance for Sovaldi® was released in February 2015, which was 13 months after the EMA's regulatory authorisation. This window of uncertainty ranged from four months for Zepatier® to 15 months for Daklinza®. This delay occurred despite these drugs being appraised using STA rather than MTA. NICE did acknowledge that they had failed to follow their normal appraisal timeline, but they also reasoned that the extension period was legitimately necessary for additional analyses and considerations [142][18]. For example, the committee claimed that they were not satisfied with the clinical and cost-effectiveness evidence submitted for Sovaldi®, in particular, the data were limited for the high-risk populations (e.g., minority ethnic groups and migrants) with a high prevalence of GT 4 to 6 [68].

Appraisal decisions: By 2016, NICE had issued guidance for nine HCV-DAAs (plus, the guidance for Epclusa® issued in January 2017) [68][69][122][123][325][326][327][328][329]. The recommendations varied slightly by genotype, the level of liver damage, the absence of previous treatment experience and the reaction to INF-a. However, they overall recommended a wide use of HCV-DAAs for all chronically infected adults, but with priority given to those with the highest unmet clinical needs [330]. The issues of prevalence concentrated among minority populations and the associated stigma were discussed by the committee, but were considered unethical to be used for rationing. Furthermore, for those whom the use of HCV-DAAs is not recommended but where treatment started prior to the publication of the guidance, the continued use of HCV-DAAs is recommended until their NHS physician considers it appropriate to stop.

Implementation: In March 2014, NHS England set up an early access programme in response to the delayed guidance release by NICE [331]: with funding of 18.7 million GBP (45.9 million USD), Sovaldi® was given to 500 patients with advanced liver disease and / or awaiting liver transplantation, those who may not survive until guidance was issued. This initial effort by NHS England, seemingly to save the lives of patients, can also be interpreted as their means to control the overall spending. By limiting the number to be treated in the first year, they could circumvent the possibility of excess usage of HCV-DAAs until the guidance is published. NICE also decided that the issuing of an HCV clinical guideline should be paused until there is a stable availability of treatments, so that there will be more time for managing the cost to NHS England [332].

Furthermore, the main cause of the delay in access to Sovaldi® was not only due to the warehousing effects[1] on patients or the prolonged appraisal by NICE, but also because NHS England had asked NICE for a three months extension for implementing the guidance in addition to the standard implementation period of 90 days [333]. No document record is available, but they had initially asked for a two-year extension period (Data from interviews). NHS England claimed that more time was needed for setting up infrastructures for expanding the HCV-DAA use (e.g., a database to audit patient's adherence to treatment) [18]. This was the first time that NHS England had failed to follow the orders by NICE [333]. As a result, Sovaldi® became available from NHS England only in August 2015, four months after the due implementation date [333]. Similarly, the implementation of Harvoni® was

[1] Warehousing effects: Delaying the use of existing treatments in anticipation of better treatments becoming available in the future.

delayed, and it became available from NHS England in February 2016. This is because NHS England had questioned NICE about the quality of the submitted evidence, appealing that the proposed recommendations were not in their best interest at the time [123]. They then requested an 18-month implementation period and an additional appraisal for comparing all the oral HCV-DAAs that were on the market at the time [123].

Meanwhile, total funding for HCV infection increased from 40 to 190 million GBP (98 to 245 million USD) from 2014 to 2015 [143]. This became the single largest investment by NHS England other than the Cancer Drugs Fund. By March 2016, NHS England had implemented the access control scheme by imposing annual quotas (i.e., the number of patients to be treated) on each clinical team across the country [18]. Under this commitment, they aim to treat 7,000 to 10,000 patients per year across the 22 operational delivery networks [18][145]. Although this scheme was also endorsed by NICE, it resulted in a large disparity in access depending on the patient's area of residence and their registered NHS network [330][334]. For example, while there are some hospitals that are given a quota of 50 patients per year, the entire region of Sussex and Brighton was given only 180 [18]. Local hospitals are also required to pay for the additional financial cost if the number of patients treated exceeds the given quota [18].

Stakeholder's reactions: Some patients were initially delaying treatment, hoping to gain access to better HCV-DAAs in the pipeline. However, not surprisingly, more patients have begun to seek treatments from overseas using a legal and online system called "buyers' clubs" [335]. This is an option for patients in England to purchase pharmaceutical products at their own expense from overseas that they do not have access to through NHS England. The patients were not the only stakeholders to be outraged by NHS England: one of the members of the NHS clinical advisory group, for example, also resigned in protest at their attempt to delay and limit the access to HCV-DAAs [18].

TABLE 16: SUMMARY OF HCV-DAAS AVAILABLE IN ENGLAND (AS OF DECEMBER 2016)

Product name (Chemical name)	EMA approval date	Issued date	Recommendation (with or without interferon, treatment duration)	List Price (per treatment cycle, GBP)	List Price (per day, GBP)	Effective Price (per day, GBP)	STA / MTA
Epclusa® **(Sofosbuvir – Velpatasvir)**	July 2016	Jan 2017	▪ GT1 ▪ GT2 (except for untreated cohort and interferon ineligible) ▪ GT3 ▪ GT4 ▪ GT5 ▪ GT6	12 weeks: 38,980 40,089 (with RBV)	464	Confidential (Simple discount agreement)	STA
Zepatier® **(Elbasvir + grazoprevir)**	July 2016	Oct 2016	▪ GT1 ▪ GT4	12 weeks: 36,500	434.52	Confidential (CMU)	STA
Viekirax® / Technivie® **(Ombitasvir + Paritaprevir + Ritonavir)** **Or** **Viekira Pak®** **(Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir)**	Jan 2015 / Nov 2014	Nov 2015	▪ GT1a ▪ GT1b ▪ GT4	12 weeks: Viekirax®: 32,200 Viekira Pak®: 35,000 24 weeks: Viekirax®: 64,400 Viekira Pak®: 70,000	Viekirax®: 383.33 Viekira Pak®: 416.66	Confidential (CMU)	STA
Harvoni® **(Sofosbuvir, Ledipasvir)**	Nov 2014	Nov 2015	Treatment-naïve: ▪ GT1 (without, 8) ▪ GT1 (with, 12/24) ▪ GT4 (with, 12) Treatment-experienced: ▪ GT1 (without, 12) ▪ GT4(without, 12) ▪ GT4(with, 12): Only if criteria is met	8 weeks: 25,986 12 weeks: 38,979	464.05	Confidential (CMU)	STA
Daklinza® **(Daclatasvir)**	Aug 2014	Nov 2015	Treatment-naïve: ▪ GT1 (without, 12): Only with severe fibrosis	12 weeks: 59,501 (With Sovaldi®)	291.88	Confidential (CMU	STA

			Treatment-experienced: ▪ GT1 (without, 12): Only with severe fibrosis ▪ GT4 (without, 12): Only with severe fibrosis Interferon-ineligible: ▪ GT1 (without, 12): Only with severe fibrosis ▪ GT4 (without, 12): Only with severe fibrosis ▪ GT3 (without, 12): Only with severe fibrosis With Interferon: ▪ GT4 (with, 24)	60,304(with RBV) 24 weeks: 119,002(With Sovaldi®) 120,608(with RBV)			
Sovaldi® (Sofosbuvir)	Jan 2014	Feb 2015	Sovaldi with INF-a and RBV ▪ GT1 ▪ GT3 (with for treatment naive) ▪ GT4,5,6 (with) Sovaldi with RBV: ▪ GT2 ▪ GT3 (with)	12 weeks: 34,982 24 weeks: 69,965	416.45	353.99	STA
Olysio® (Simeprevir)	May 2014	Feb 2015	▪ GT 1/4 (with)	12 weeks: 27,220 (With 24 weeks INF-a and RVN) 12 weeks: 32,155 (With 48 weeks INF-a and RVN)	266.64	266.64	STA
Incivo® (Telaprevir)	Sep 2011	April 2012	Treatment- naïve: ▪ GT1 (with, 12) Failed previous treatments: ▪ GT1 (with, 24 to 44)	12 weeks: 22,398	266.64	266.64	STA
Victrelis® (Boceprevir)	July 2011	April 2012	Treatment- naïve: ▪ GT1 (with, 24 to 44) Failed previous treatments: ▪ GT1 (with, 24 to 44)	44 weeks: 30,800 Recommendation is 24-32 weeks	100.00	100.00	STA

Source: NICE homepage

4.4 Impacts of HCV-DAAs

The following sections discuss obstacles to appraisal, reimbursement and policy implementation experienced with the HCV-DAAs, and consequent policy changes.

Obstacles to assessment / appraisal

There was one obstacle identified related to the appraisal process at NICE.

1. **Uncertainties in evidence:** Strong clinical and cost-effectiveness evidence are essential for an effective appraisal. However, to obtain quality data on the following two variables was exceptionally complicated with HCV-DAAs due to the characteristics of HCV infection [301]:
    - **Size of the target population:** To predict accurately overall prevalence of HCV infection and that of the target populations was a challenge for four reasons. 1) it is estimated that close to half of the 160,000 infected individuals in England are unaware of their infection [151]. 2) due to the side effects, many patients have failed to complete the treatment course [334]. 3) a high prevalence is expected among the hard-to-reach populations with complicated pathology (e.g., HIV/AIDS infected individuals and IDUs). 4) patients are usually at the late disease stage when they enter a healthcare facility for the first time. Unpredictability led to over-exaggeration of the potential size of the target populations. For example, in a letter sent to NICE in November 2014, NHS England stated that they are not yet prepared to accommodate such a large number of patients for treatment [18].
    - **Effectiveness of HCV-DAAs:** To obtain quality evidence to determine the true effectiveness of HCV-DAAs was a challenge. This is because when a potential cure is available, it is considered unethical to conduct a blinded clinical trial with a control group. Therefore, a disease model based on historical controls was used to predict the effectiveness (Data from interviews). Confounding was also an issue because the patients in a trial tend to be healthier than the actual population with the disease, and they are often not from the minority and hard-to-reach communities.

Obstacles for reimbursement decision-making

There were two obstacles identified related to the decision-making process at NICE.

1. **Prioritisation (Generalisability):** Due to the above-mentioned uncertainties in evidence, making a coverage decision was particularly challenging, especially with respect to which results can be generalised (e.g., when there is a very little evidence on how the treatments would work on individuals with HIV/AIDS). Accordingly, the issue of limited data and the stigma associated with HCV infection were discussed during the appraisal committee: from the public health perspective, which focuses more on societal benefits, it is actually more cost-effective to first treat the high-risk populations rather than the sickest as it can lead to a change in the disease pathology, preventing further new infections [336]. Especially when the U.K. taxpayer money is used to pay for the HCV-DAAs, decision makers are accountable for gaining maximum societal benefits from these treatments. However, because the appraisals did not include the prevention aspects, the prioritisation decision was made to treat the sickest first and then to gradually expand the coverage. This further led to a question of who can receive the treatment next once the most severely sick are treated. The committee confronted these questions and decided to place more emphasis on access equity over societal benefits.
2. **STA or MTA:** STA was chosen for the appraisal of HCV-DAAs, even though NHS England preferred MTA (Data from interviews). The selection of appraisal process has an important implication with respect to access and agreement over price. Under STA, for example, products potentially become available from NHS England sooner than with an MTA because the STA process is timetabled / planned to be more rapid than the MTA process (an appraisal is conducted per product rather than having to wait for a regulatory authorisation for all the products under consideration). A faster formulary decision-making process also means less time and authority for NHS England to make their own financial decisions. On the other hand, although it takes a longer time, there is a higher chance for products to receive a negative recommendation with potentially lower final price when MTA is used. As for the case of HCV-DAAs, although the government knew months before that there would be a line of similarly effective products for HCV infection entering the market, STA was chosen because they prioritised access over price. However, the use of MTA instead of STA might have led to better pricing deals considering that NHS England chose to delay the process anyway to prepare for the potential budget impact.

Obstacles for policy implementation

There were two obstacles identified related to the implementation of the NICE decisions.

1. **Increase in associated cost:** Another interesting obstacle identified was the additional costs claimed by NHS England for setting up an HCV-DAAS provision network (e.g., training, staffing and infrastructure for existing treatment centres to adopt the technology) [18]. Usually, such additional costs are not an issue. However, NHS England judged that it was necessary to allocate an additional budget to develop this network, although it was not featured in the appraisals. Interestingly, some TPPs in the U.S. also similarly claimed the need for an additional budget for setting up a new system [280]. Advocacy groups, however, argued that extra spending was unnecessary since HCV-DAAs are a simple technology and that NHS England was using it as a justification for delaying implementation (Data from interviews). Regardless, this opposing dialogue indicates that there were a missing conversation and unmatched expectation between NHS England and the public, whether HCV-DAAs should be considered usual or exceptional.
2. **Budgetary impacts or cost-effectiveness:** The appraisal committees were fully aware of the high cost of HCV-DAAs, as well as their high clinical effectiveness (and thus acceptable cost-effectiveness). As such, the public health benefits were undoubtedly clear, nevertheless, NHS England was hesitant to adopt HCV-DAAs due to a concern over the potential budget impact. In April 2015, NHS England estimated that 7,000 to 32,000 people would become eligible annually if access was given to all patients at all stages of the disease, which would cost 285 to 777 million GBP (699 to 1,906 million USD) per year, respectively [18]. Although 32,000 may not be realistic, NHS England claimed that they would still not be able to afford the treatment for 7,000 patients per year with the existing budget [18]. They also argued that 1,542 lives would be lost across the country if 300 million GBP (736 million USD) were diverted from the existing budget to pay for HCV-DAAs, and further 3,598 lives would be lost if 700 million GBP (1.8 billion USD) were invested [18]. Although these estimates were based on the list prices before discounts, it was enough to create a fear of budget impact, which led to numerous conflicts and damage including the delayed provision of treatment. The fact that NICE had approved the request to extend the implementation of the Sovaldi® guidance indicates that this is an example (possibly the first) where consideration of budget impact was prioritised over cost-effectiveness [334]. Furthermore, this obstacle may have

highlighted one of the core issues of the existing access scheme in England, that is the current organisational relationship between NICE and NHS England.

Policy changes

The mortality rate from ESLD and HCC in England is reported to have dropped by 11% in 2015 [151]. Although further research is needed to truly understand the positive and negative impacts of HCV-DAAs, it was evident in the case of England that the market entry of HCV-DAAs has brought about a threat to its financial sustainability at the national level [333]. Accordingly, the market entry of HCV-DAAs has resulted in a few but visible changes in the policy, as discussed below:

- **Changes in the prescription charge**[337][338][339][340][341]**:** England is the only country (in the U.K.) that still levies prescription charges. The per item cost has been increasing over time: 7.40 GBP (10.76 USD, 2011), 7.65 GBP (11.12 USD, 2012), 7.85 GBP (11.41 USD, 2013), 8.05 GBP (11.70 USD, 2014), 8.20 GBP (11.92 USD, 2015) and 8.40 GBP (12.21 USD, 2016). However, during those years, the PPC cost was kept the same at 29.10 GBP (42.30 USD) for three months and 104.00 GBP (151.16 USD) for a year to protect patients from financial constraints. Although this change is not entirely due to HCV-DAAs, it highlights the desperate need for the government to increase funding in response to the increasing cost of pharmaceutical products. The government claims that this would largely increase the NHS revenue for supporting the delivery of high-quality services.
- **HCV infection registry** [342] (Data from interviews)**:** Quality data is essential for any decision making, especially for determining treatment prioritisation from both ethical and public health perspectives. For example, having a good understanding of the length of effective treatment duration (12 or 24 weeks) based on the real-time database can be helpful for budget allocation. Accurate and trustworthy evidence is also important especially as a justification for the use of taxpayer money for purchasing high-cost medicines. NHS England has therefore implemented an HCV patient registry where in exchange for a prescription for HCV-DAAs, patients are required to provide clinical data such as their genotype and SVR. This has become the largest HCV registry worldwide.
- **Changes for HTA for highly specialised technologies** [343]**:** NICE has recently developed a few new policies to collaborate with NHS England to support the

delivery of technologies in the best interest of patients and the industry. The most important policy that resulted from the market entry of HCV-DAAs was the introduction of a budget impact threshold. Under this policy, negotiations between NHS England and the pharmaceutical companies can start while the appraisal is still ongoing for a product where its budget impact in any of the first three years of use is expected to exceed 20 million GBP (49 million USD). Significantly, NHS England will be allowed to delay, or stage, the adoption of the technology for up to three years (even if the product receives a positive NICE recommendation). The aim is to limit the chance of the introduction of a new technology disrupting the funding of the other NHS services and to strengthen NHS England's bargaining power.

The development of the new Cancer Drugs Fund is also a good example of a collaboration between NICE and NHS England for improving access to highly specialised technologies, however, this has less to do with HCV-DAAs. Another example of NHS England and NICE working together is the plan to introduce a 'fast-track' appraisal process for most promising new technologies (below 10,000 GBP per QALY), which was agreed by NHS English within 30 days of its proposal.

4.5 Challenges and reform proposals

Just like in the other HICs, the recent market entry of HCV-DAAs brought about a significant financial burden to NHS England. Although there were few immediate impacts, it created several challenges for both NICE and NHS England in terms of ensuring access to medicine in the era of accelerating innovation and rising pharmaceutical prices. Overall, four challenges were identified as discussed below:

Firstly, **for future decision-making on prioritising access and for its justification, further exploration of innovative approaches to the collection of timely and accurate data is needed:** When a country can no longer afford the rising prices of pharmaceutical products, some form of rationing is unavoidable. However, as highlighted by HCV-DAAs, such decisions must be based on solid evidence to be accountable for using taxpayers' money. In response to this challenge, NHS England has started the HCV registry. However, a similar approach will soon be required for other chronic diseases. Recent developments in IT, such as electronic medical records, will possibly become key for collecting the basic epidemiological data. In addition, there are already various technologies available where individual data are collected in a timely fashion and stored elsewhere, but are not yet linked to one another. How to enable access to and manage such abundantly available personal health data under one system and then to link it to the appraisal process will be a future challenge.

Furthermore, with respect to the cost data, there needs to be greater clarity around the actual cost of pharmaceutical products to NHS England in order to minimise avoidable confusions and public outcry. In the case of HCV-DAAs, different stakeholders had a different understanding about its potential impact on the NHS budget. Most of the budgetary complaints issued by NHS England (and in the media) were based on the list prices. Due to commercial confidentiality, it may be impossible to disclose effective prices. However, an effective and accurate communication of the budget impact of the future pharmaceutical products may improve the current situation.

Secondly, **further debate is needed regarding managing the potential budget impact on access.** The market entry of HCV-DAAs highlighted that affordability became the prominent determinant of access while the decisions on formulary listing were still based on cost-effectiveness. Some argue the limitation of cost-effectiveness as a tool for determining a product value such that when considered on a cost-effectiveness plane, a paradox of

“those highly expensive treatments being considered cost-effective when they are marginally superior to the existing treatments” is worsening [16]. However, what happened with respect to HCV-DAAs was that regardless of the result of cost-effectiveness analysis, the implementation was delayed due to the substantial budget impact. Therefore, to reflect the true health opportunity costs of high-cost medicines, the disparity between the current budget and the cost-effectiveness threshold given the ability of NHS England to produce health benefits must be revised [11][344]. In other words, if there is no limit to the healthcare budget, the cost-effective threshold can stay the same or be lowered even with the rising spending on healthcare. However, the current budget for the NHS cannot easily be increased due to political reasons. As mentioned above, with the current cost-effectiveness threshold, there is a danger that the existing evaluation methods may fail to accurately access the true value of the latest emerging technologies. The cost-effectiveness threshold should be lowered thus making positive reimbursement decisions less likely. While this has the disadvantages of limiting individual’s access, it can be justified in terms of reducing wasteful pharmaceutical spending and thus making better use of public money.

Thirdly, **decentralisation of prescription practice needs careful coordination**. NHS England has laid out a policy that it is down to each network to determine pharmaceutical product prescription based on the severity of liver disease [18]. This scheme aims to provide the local authority more autonomy and allow their decisions to reflect the local needs. On the other hand, this generates extra challenges that may lead in practice to incoherent access across the country where an extra responsibility will be placed on the local physicians. This would not become an issue at the initial phase when the access is still restricted for those who are severely sick. However, a more detailed guide for prioritisation will be needed at the later phase when most of the sickest individuals have been treated [11].

Last, but not least, **the relationship between NICE and NHS England and the healthcare resource allocation model must be reconsidered**. While NICE recommended wide access to HCV-DAAs, NHS England for the first time struggled to follow their guidance. Despite the view of NHS England that their delivery of HCV-DAAs has been successful following the NICE guidance, many clinical experts do not agree with their tactics, such as the 2016 access scheme where the annual number to be treated was determined based on their affordability and not by the need [18]. It is an impressive tactic since by setting the annual quota for each network, NHS England can effortlessly manage the budget. However,

they may have overlooked the potential impacts this may have on access equity and quality. When each facility has a limited number of HCV-DAAs that they can give away, the chance that they would come up with uncoordinated rationing schemes is high. Some argue that the intention of NHS England was to hamper NICE's ability to impose high-cost medicines on the health system by turning the organisation into a recommendatory rather than mandatory body, and chose the battleground of HCV infection because the HCV-infected populations are marginalised groups with less of a voice [18]. Another example of an on-going conflict between the two organisations is with respect to appropriate staffing levels [345]. On the other hand, an effort to improve the collaboration between NICE and NHS England is also on-going, for example, the new Cancer Drug Fund and the recent consultation and decision on the changes for HTA for highly specialised technologies [343]**.** Regardless, in England, the role of each organisation and their relationship may need an investigation and re-adjustment to fit the current status quo.

4.6 Conclusions

England is excellent at responding to issues associated with technical aspects of HTA, for example, the implementation of the HCV registry, and the budget impact threshold of 20 million GBP (49 million USD). However, the obstacles experienced and the challenges introduced by the market entry of HCV-DAAs to the English heath system became a case in point that the HTA currently in use by NICE is a potential solution, but still remains theoretical today and requires additional efforts [16].

The challenge is not only at the product level, but also at the organisational level, especially with regard to organisational management of the two institutes. The failed coordinated efforts between NICE and NHS England clearly entails that cost-effectiveness itself is no longer enough to justify access. Despite knowing that the new technology was in the pipeline, both parties failed to plan to prepare for the big budget impact of HCV-DAAs. Even with its high clinical- and cost-effectiveness, NHS England attempted to delay the appraisal procedure and when it failed, tried unprecedentedly to ration access. A further investigation may be required to explore the impacts of HCV-DAAs on the organisational structure, relationship and function of these two organisation.

Part 3: Discussion and conclusions

Finally, Part 3 as a conclusion of this thesis discusses the key findings and the main contributions of this study, which is divided into two chapters:

- Chapter 1: summarises the findings from the comparative case studies, and concludes on the similarities and differences in the approaches that worked and did not work towards better access to high-cost medicine.
- Chapter 2: discusses the main contributions of the thesis and further implications of the overall findings on policy. It also discusses future research priorities and identifies limitations of this study.

Chapter 1: Discussion

1.1 Introduction

Irrespective of the stage of economic development, countries struggled to provide access to HCV-DAAs, a struggle which made the political headlines worldwide.

The countries most affected by the market entry of HCV-DAAs were MICs with a high prevalence of HCV-infection. Due to their weak purchasing power, HCV-DAAs were simply too expensive to afford. The situation was further complicated by the availability of the manufacture-led access schemes where HCV-DAAs were made available at a substantially low cost for some of low-income countries (LICs) (e.g., Egypt), but not for MICs (e.g., China, Russia and South American countries). Countries with greater purchasing power, HICs, also struggled. Despite the proven cost-effectiveness, the total cost of HCV-DAAs was a significant short-term financial impact to their health systems, which became a threat to its financial stability. Accordingly, while the struggles for LMICs were often linked to the issues of licensing deals, IP rights and generic production, the challenges for HICs were in achieving timely and equal access to HCV-DAAs by negotiating product pricing and minimising the overall budget impact.

Three years have passed since the market entry of Sovaldi®, policy solutions were sought, product prices have gone down marginally and some improvements were made with respect to access. However, there continue to be large differences in the prices at which HCV-DAAs are available globally, and access is still far from sufficient even in HICs. Therefore, the fundamental questions that this study asked were: 1) what were the reasons for the arrival of HCV-DAAs being such a shock to health systems worldwide; and 2) what are the important implications for future pharmaceutical policymaking? To answer these questions, the findings from the case studies conducted in Japan, the U.S. and England are compared and discussed in the following sections.

Note that due to the obvious differences with respect to the pharmaceutical pricing and reimbursement decision-making processes, the study does not aim to identify the best practice. Also, for the comparison, Medicare Part D was chosen to represent the situation in the U.S., as it is responsible for the largest proportion of HCV-infected individuals.

1.2 Prices of HCV-DAAs

This section compares the list and effective prices of the second generation HCV-DAAs in the studied countries taking account of the differences in the pharmaceutical pricing policy.

Overall, the list prices of HCV-DAAs differed largely by country and by pharmaceutical company. When compared using cost-per-day, the list prices of HCV-DAAs were the highest in the U.S., followed by England and Japan (Figure 10). When compared by pharmaceutical company, the Gilead products were significantly more expensive than the non-Gilead products: also on average, non-Gilead products in the U.S. were 1.8 times more expensive than in England (range: 1.6 to 2.0), and 6.0 times more expensive than in Japan (range: 3.5 to 8.3). As for the Gilead products, the list prices in the U.S. were 1.7 times more expensive than in England, and 1.6 times more expensive than in Japan.

Interestingly, while the prices of HCV-DAAs in England were relatively constant, the prices in Japan fluctuated considerably over time. For example, prior to the 2016 price adjustment, the prices of Sovaldi® and Harvoni® were exceptionally high compared to that of Daklinza® and Olysio®. One of the possible explanations, as stated in the MHLW's official documents, is that a special premium for innovation was applied for Sovaldi® (and Sovaldi® was used as a comparative drug for Harvoni®) and thus the price went up. Another explanation is that the foreign price adjustment was not applied for Daklinza® and Olysio® as they were marketed first in Japan, therefore, the MHLW could set low prices for these products. It is also unusual that the Gilead products were priced significantly higher than non-Gilead products in Japan when the price difference between the two products in England was small. This may indicate that there was agreement on a price, which was mutually acceptable to the pharmaceutical companies and the MHLW, prior to formulary listing.

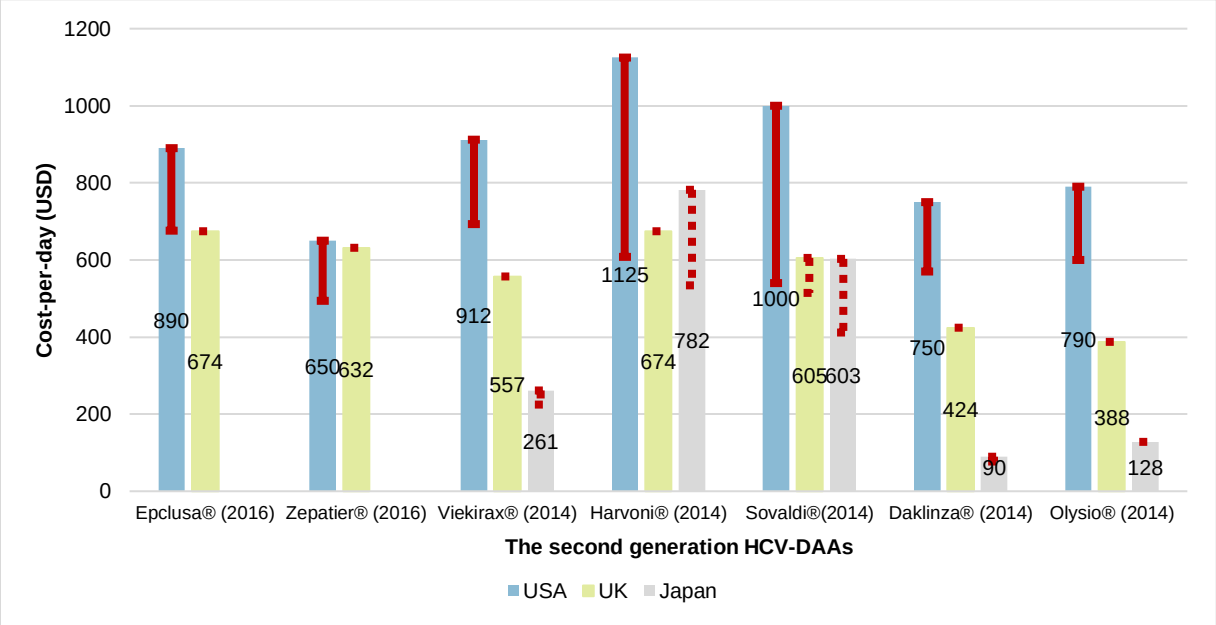
As for the products which were marketed after 2016 (Epclusa® and Zepatier®), the price differences between the U.S. and England were at 1.3 and 1.0 times, respectively (these products were not yet marketed in Japan at the time of this study). As such, the price differences between the U.S. and England for these two products were much less than for the products marketed before 2016. Reasons for this trend may require a further investigation, but it may indicate that the HCV-DAAs prices had responded to the resulting market competition after Harvoni®. The fact that Epclusa® became available in England with a simple discount agreement instead of a negotiation by the CMU may also indicate that the pricing war had properly begun by late 2016.

Overall, it can be summarized that until late 2014, Gilead was in a special position having Sovaldi® and Harvoni® as their main products for treating HCV infection. Soon enough, similar products began to enter the market, but that did not lead to a substantial drop in product prices because demand was still high so that the other companies could set their prices high to match those of Gilead (i.e., mutual forbearance). However, in 2017, the situation began to change due to the decline in patient numbers, which gave the companies an incentive to reduce prices.

Despite the challenge in estimating the effective prices, potential price ranges were calculated from the available documents (Figure 10: indicated in red). As shown, the U.S. had received the most discounts from the pharmaceutical companies, especially for the Gilead products. However, this may not reflect the reality since the evidence from the U.S. is weak and most of the rebates available for England are commercial in confidence. By 2016, Japan also reduced the price drastically by 31.7% for Sovaldi® and Harvoni®, and 14% for Viekirax® and Daklinza®. Therefore, as shown, the differences between the three countries in effective prices may have actually been less for the Gilead products compared to the other HCV-DAAs. This finding is consistent with other studies [101].

When compared using the list prices per treatment cycle, the U.S. was again ranked highest, followed by England and Japan (Figure 11). The combination therapies of the second generation HCV-DAAs were most expensive, but were considerably lower in Japan compared to the other two countries. This is because of the low cost of Daklinza® and Olysio®. Due to limited data and the complexities around the type of recommended combination therapies and their duration, the effective prices for the combination therapy were not estimated.

FIGURE 10: LIST AND EFFECTIVE PRICES OF THE SECOND GENERATION HCV-DAAS (COST-PER-DAY) BY COUNTRY

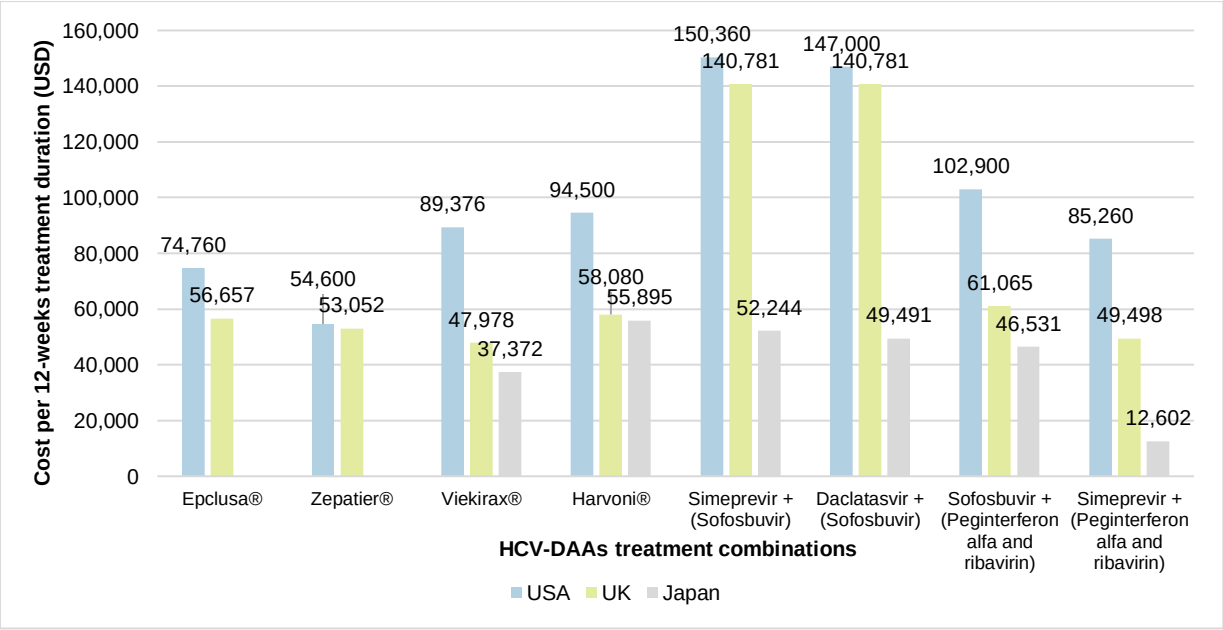


*Red solid line: indicates a possible range of effective prices.

*Red dotted line: indicates a drop in product price due to a discount

*Red dot: Some indicates a possibility of price discount (but the detail on discounts was unavailable / confidential).

FIGURE 11: LIST PRICES OF THE SECOND GENERATION HCV-DAAS (COST-PER-TREATMENT-CYCLE) BY COUNTRY



1.3 Time to formulary listing

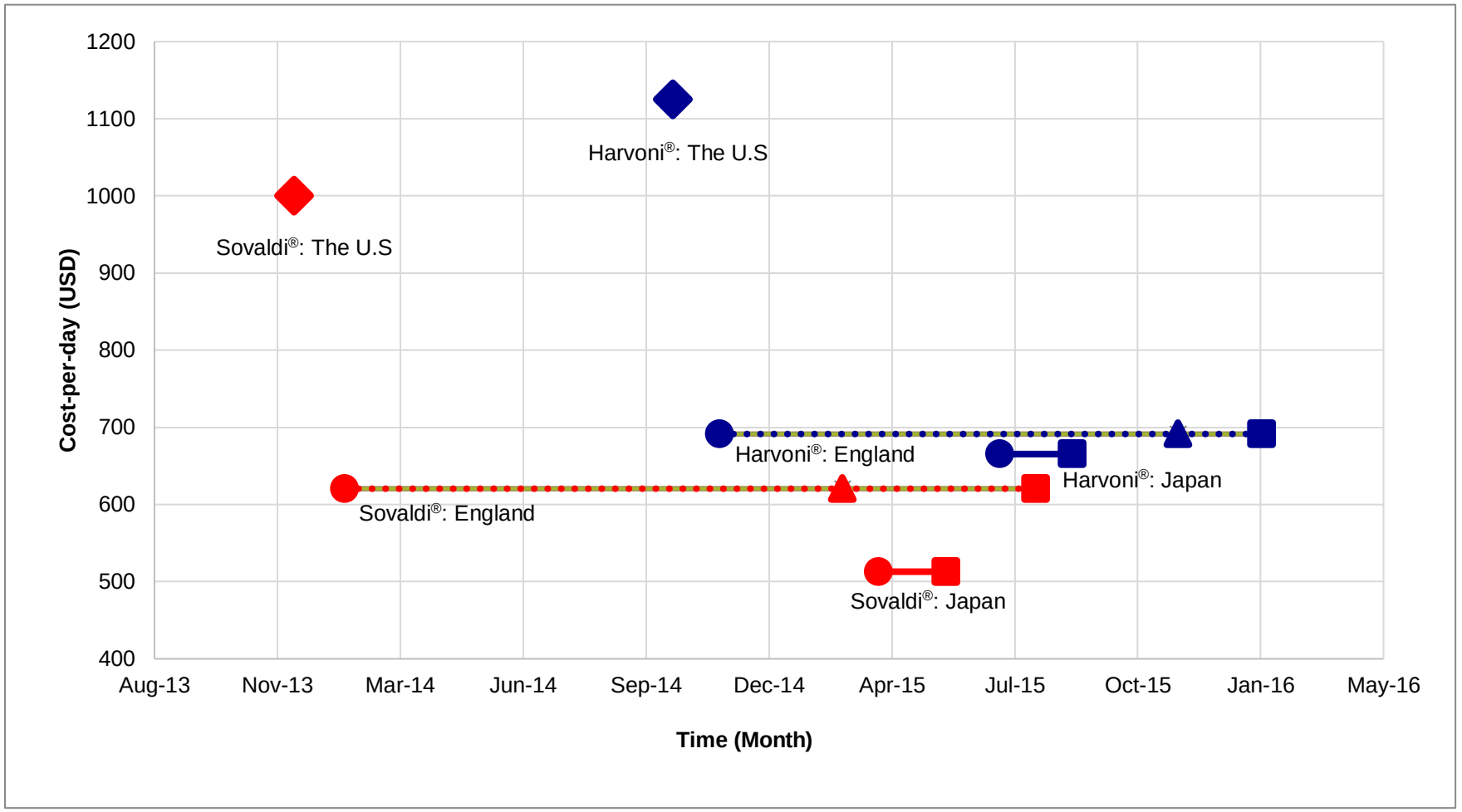
This section compares the time a product took from obtaining a regulatory authorisation to patient access. In order to simplify the comparison, Sovaldi® and Harvoni® were selected as they were the biggest financial shock to the health systems worldwide. Note that patient access in this context refers to the date of formulary listing (i.e., the date when a treatment became eligible for a full or partial subsidy by a public TPP).

As indicated, the regulatory authorisations were first issued by the FDA, followed by the EMA and the MHLW (Figure 12). This is the standard trend considering that the pharmaceutical companies are likely to make a business decision to apply for regulatory authorisation in the U.S. first. This is because without a single-payer system, and where the free market system dominates, the fourth hurdle differs by individual TPPs, and thus pharmaceutical companies will be able to set higher prices in the U.S., which in turn can influence the global pricing.

The situation is different for countries with a single-payer system, such as Japan and England. In these countries, the internal process that comes after regulatory authorisation has more implications for patient access. Although the regulatory authorisations for Sovaldi® and Harvoni® were obtained much later in Japan, both products were listed in its formulary list months before England. This is because whilst the system in Japan is designed to be less sensitive to product prices, that of England is highly sensitive as it uses HTA for assessing product value. It is not surprising that England takes a longer time for this assessment considering that an additional procedure in the decision-making process also means the need for more time for the final decision-making. However, what was special in the case of HCV-DAAs was that the differences in the level of sensitivity over product prices reflected in the design of respective pharmaceutical policies had led to different reactions by the countries: whilst the appraisal and implementation processes in England were significantly delayed, that of Japan was hardly affected.

The dates for formulary listing in the U.S. are not specified in the figure because it was difficult to map out due to the different pharmaceutical policies by state and by TPPs.

FIGURE 12: TIME TAKEN FROM OBTAINING REGULATORY AUTHORISATION TO PATIENT ACCESS BY COUNTRY



Product type: Red: Sovaldi®, and Blue: Harvoni®

Country: Spade marker: U.S., Dotted line: England, and Straight line: Japan

Decision date: Circle marker: Regulatory decision date; Triangle marker: NICE appraisal approval date; Square marker: Formulary listed date

1.4 Access situation

Of the three countries studied, Japan had achieved the highest prescription numbers per head of population just in 2014 [205]. Although the official prescription figures for 2015 and 2016 are not yet available, they are expected to be substantially higher than those for 2014, simply due to the total market sales of HCV-DAAs which spiked after the listing of Sovaldi® and Harvoni® in 2015.

The situation was different in the other two countries. The access situation in the U.S. differed by state, but generally, access was strictly restricted due to its high cost for the TPPs and individuals. The incoherent and strict access restrictions were, therefore, implemented in the form of PAs. As for England, as previously mentioned, publication and implementation of the NICE guidance for HCV-DAAs were severely delayed. Therefore, only 500 patients received HCV-DAAs in 2014 (through NHS England). Even after the guidance was published, NHS England had set up an annual quota so that only 7,000 to 10,000 patients are being treated per year since 2016.

So what policy decisions led to such differences in the access to HCV-DAAs among these three countries? In this section, the situation with respect to the cost to individuals and the access control policies are compared (Table 17).

The cost to individuals

The cost of pharmaceutical products to individual patients differed largely by the health system. In the U.S., where numerous co-payment schemes exist even under the same TPPs, there was a great variation in the cost of HCV-DAAs to individuals. For example, even for the enrollees of Medicare Part D from the low-income background, the amount of co-payment ranged from 1,080 to 1,191 USD [244]. Therefore, those from the higher-income background are expected to have paid more for the same products.

On the contrary, both England and Japan have a stronger emphasis on the protection of patients from catastrophic OPP. In England, all pharmaceutical prescription products are available at 8.20 GBP (11.92 USD) per item, and HCV-DAAs were no exception. Patients from particular age groups and socio-economic backgrounds are exempt from this payment, therefore, it is expected that for those receiving treatments in England, it is available at almost no cost. The amount of co-payment in Japan was only slightly higher than England,

supported by the special tax-funded subsidisation scheme for hepatitis patients due to the severity of the HCV epidemic and the history behind it. Under this scheme, HCV-DAAs are available twice in a patient's lifetime at the cost of 10,000 to 20,000 JPY (980 to 1,951 USD) per treatment cycle. Consequently, the cost of Sovaldi® to patients is 1% of the cost to the health service in England, and it is 16% in Japan. Note that the existing subsidisation scheme in Japan is unique to hepatitis. Therefore, for normal high-cost medicines (e.g., for cancer), the cost to individual can go up to a set monthly cap depending on a patient's socioeconomic background, which ranges from 24,600 to 140,100 JPY (240 to 1,367 USD). Therefore, the standard cost to individuals for high-cost medicines in Japan can be as high as that of the Medicare Part D enrollees from a low-income background.

Access restriction

A specialist prescription was required to obtain HCV-DAAs in all the three countries. Although this policy limits access, it was a clinical decision rather than a financial one because there was a concern of potential development of drug resistance if prescription practice and drug adherence were not properly managed.

Apart from the above restriction, access in England and Japan were mostly controlled at the level of liver disease stage. HCV-DAAs were most easily obtainable in Japan, where there were almost no access restrictions, except that patients had to show some symptoms (F2 or above). In England, NHS England designed a system for controlling the total spending by setting an annual prescription quota for each NHS trust, with the patients with a liver stage above F3 being prioritised.

On the contrary, restrictions to access in the U.S. went beyond simple spending control. In the case of Medicare, HCV-DAAs were initially available for only the F3 and F4 patients. On top of this, additional restrictions in the form of PA were applied such that patients with HCV co-infection and / or a history of drug and alcohol use were excluded from eligibility. These strict access control policies were set up without sufficient evidence and the stigma against certain socially vulnerable populations also had a significant impact on decision-making. Accordingly, in the U.S., it was often difficult and time-consuming to be recognised as eligible for treatment, especially in the public sector, which required extensive paperwork and commitment from both patients and physicians. The incoherent exclusion of certain population groups in the U.S., as opposed to England, were evidently the result of the lack

of shared social value judgments and / or of a system to communicate these values across different TPPs. It is important to note here that some of the policies in the U.S. were revised in 2015. For example, in California, the eligibility is now F2 and above. The PAs related to stigma and the drug and alcohol use were also revised in many states. How and why these changes were implemented in some TPPs in the U.S. and not in others requires further investigation.

In conclusion, under the growing tension between the provision of health care and the continuous expansion of the pharmaceutical spending, policy makers are becoming increasingly more aware that the appropriate use of pricing and reimbursement policies is the key to cost-effective and sustainable access to high-cost medicines. While the focus with respect to the reimbursement decision-making process in Japan was “pay for all”, in England it was “how to pay”, by controlling spending with priority given to those who most needed the treatments, and in the U.S. it was “whether to pay”, limiting access based on patient characteristics.

TABLE 17: COMPARISON OF THE ACCESS SITUATION FOR HCV-DAAS

	US	England	Japan
Time to patient access	▪ Depends on TPPs	▪ Delayed appraisal by NICE ▪ Delayed guidance implementation by NHS England	▪ The procedure was not affected
Cost to patient	▪ Depends on TPPs	▪ Treated as a usual pharmaceutical product ▪ 8.20 GBP per item (11.92 USD)	▪ A special subsidisation scheme exists ▪ 10,000 JPY (98 USD) to 200,000 JPY (1,951 USD) per treatment cycle ▪ Can receive the treatment twice under this scheme
Access restriction	High ▪ F3 (F4) and above ▪ HIV co-infection ▪ Pharmaceutical product usage ▪ Alcohol usage	Medium ▪ F3 and above ▪ Set quota / year	Low ▪ Those with symptoms (F2 and above)
Coverage	Low	Low – Medium	High

1.5 Obstacles and responses

So why did these three countries react so differently to the market entry of HCV-DAAs? In this section, the conceptual framework developed for managed entry agreements (MEAs) is used to analyse their reactions as well as the obstacles and responses they experienced in decision-making. The framework assumes that there are three barriers for a TPP to achieve sufficient control over the two target variables *(improving cost-effectiveness* (micro-efficiency) and *limiting budget impact* (macro-efficiency)), which are uncertainties over *Comparative Effectiveness, Price* and *Use* [92].

When the second generation HCV-DAAs became available on the market, two things were seemingly obvious: their high clinical effectiveness and their high prices. In other words, uncertainty about *Comparative effectiveness* and *Price* for HCV-DAAs was relatively low. It is true that there were some initial doubts about clinical effectiveness especially with respect to the methodology used for clinical trials (e.g., the fast track applied by the FDA) and data generalisability (e.g., limited evidence for minority groups, hard-to-reach populations and genotypes as well as on their adherence and uptake). Likewise, there were some uncertainties over price because the list prices of pharmaceutical products are usually presented after its market entry and only then the effective prices are negotiated. Therefore, it is often a challenge for a TPP to predict the exact product cost to the system. Nonetheless, it was possible to predict the high clinical effectiveness and prices of HCV-DAAs in HICs where the systems are designed to foresee potential products in the pipeline, especially after the market entry of Sovaldi® as a blockbuster.

On the other hand, what was unknown then was the extent of *Use* (i.e., the demand) due to the lack of availability and accuracy of the HCV epidemiological data. On top of the general difficulty in obtaining data, there were several characteristics of HCV-DAAs that further complicated estimation of the potential demand for HCV-DAAs: including the warehousing effect of patients waiting for better HCV-DAAs to become available, amplified by the government's "uncoordinated" prevention efforts and the industry's marketing efforts (especially in the U.S.). Accordingly, the common obstacle for all three countries with respect to reimbursement decision-making for HCV-DAAs was the prediction of *Use*, and this finding is in consistent with other studies [11][39]

According to the framework, the reasons for countries' reaction to HCV-DAAs become clear when their sensitivity level to the above three uncertainties is analysed and compared. The

sensitivity level in this context refers to how sensitive a country is to the listed uncertainties when it comes to the reimbursement decision-making. Although there are no comprehensive measures to assess this, the findings from the case studies can be used to categorise the system into low, medium and high sensitivity levels (Table 18):

- U.S. (Medicare Part D): Highly sensitive to product prices, while the sensitivity levels for the other two categories differ largely depending on the TPP;
- England: With an HTA-specialised organisation like NICE, England is highly sensitive to *Comparative effectiveness* and *Price*, and medium sensitivity to *Use*; and
- Japan: Japan has a low sensitivity to all three categories of uncertainty since clinical effectiveness and safety are the only considerations for a formulary listing.

Note that whilst the data on *Comparative effectiveness* and *Price* are used to assess Cost-effectiveness, the data on *Price* and *Use* are used for determining the level of budget impact. In other words, when a country struggled to predict *Use*, it in turn also means that they had difficulty predicting the potential budget impact of HCV-DAAs on their health system. Accordingly, despite the common obstacle, the market entry of HCV-DAAs was different for these three countries and thus its impacts were seen at different phases of their reimbursement decision-making process.

In the case of the U.S. and England, due to the relatively high sensitivity over *Price* and *Use*, the fear for a potentially high budget impact had led to an over exaggeration of its potential impacts. The public TPPs in both countries, for example, measured the potential budget impact of HCV-DAAs simply by multiplying the list price and the total number of patients (an assumption that all patients will turn up for the treatment at once). The public TPPs in both countries also claimed that there would be a further budget impact due to an increase in the associated cost of preparing infrastructures and resources for the provision of HCV-DAAs. Such high uncertainties and the fear over budget impact, therefore, influenced the Assessment and Decision-making processes in both countries leading to some form of access prioritisation. The situation was entirely different in Japan because of its positive formulary-listing model that allows almost all pharmaceutical products for clinical use to be listed. It is important to note here that the notion of cost is different in Japan as opposed to the other two countries because the MHLW has more control over pricing and they do not view that spending on pharmaceuticals can or should be discretionary. In other words, while the spending on pharmaceutical products is “cost” to the U.S. and England, that for Japan can also be interpreted as “necessary expenditure”. Nevertheless, this does not mean that

HCV-DAAs did not have a significant budget impact in Japan. The high list prices of HCV-DAAs were equally an issue for the MHLW. Their response was, however, delayed simply because there was no mechanism to exclude HCV-DAAs from the formulary list or to respond to the per-product financial concerns.

Accordingly, how to manage effectively the rising budget impact of pharmaceutical products became the common challenge for all three countries, and they subsequently introduced various policy changes. One example is the new policy where NHS England are encouraged to start price negotiation while a drug is being assessed by NICE, if it is likely to have a budget impact of £20 million (49 million USD). NHS England has increased bargaining power with respect to such products by not having to make a product available within three months (in the event of a positive recommendation). In principle, they could delay introduction by up to three years.

This has similar characteristics to the price management rule in Japan, called "*Repricing for Market Expansion*". Although the scale of government control differs between these two policies, the need for the overall control on per product sales while respecting the need of industry growth may have become more obvious after the HCV-DAAs.

Interestingly, both the U.S. and Japan are now on a gradual move towards implementing HTA, and this movement seems to have been accelerated by the HCV-DAAs. Although U.S. law prohibits federal bodies from the consideration of cost in the formulary listing, the high prices of the HCV-DAAs were clearly the main cause of the delay in formulary listing and the subsequent access restrictions. Likewise, Japan is also at a turning point where they can no longer be blind to the effects of financial pressure from high-cost medicines like the HCV-DAAs. Despite the recognised needs, however, the two countries are at a different stage in implementing HTA. While the use of HTA is primarily down to individual TPPs in the U.S, the implementation plan is currently at a pilot stage in Japan.

TABLE 18: COMPARISON OF UNCERTAINTY AND SENSITIVITY LEVELS OVER EFFECTIVENESS, PRICE AND USE

	Uncertainty level	Sensitivity level		
	All	**US (Medicare Part D)**	**England**	**Japan**
Comparative Effectiveness	Low (Highly effective)	Depending on TPPs	High	Low
Price	Low (High list prices)	High in practice (Low in theory)	High	Low
Use	Medium - High	Depending on TPPs	Medium	Low
Uncertainty in cost-effectiveness (Comparative effectiveness + Price)		Low	Low	N/A
Uncertainty in budget impact (Price + Use)		High	High	Delayed
The level of access control		Strict (Whether to pay)	Moderate (How to pay)	N/A (Pay for all)

1.6 Generalisability of HCV-DAAs as high-cost medicines

High-cost medicines are not uncommon [346]. Many novel cancer medicines available today are somewhat clinically effective and can cost up to 100,000 USD per patient per year. It is also expected that there will be more high-cost medicines entering the market in the coming years. Can the lessons learnt from HCV-DAAs be applied to policy making for the future high-cost medicines? Before doing this, it is important to assess the generalisability of HCV-DAAs as a high-cost medicine available today and in the future. This section summarises three distinct features of HCV-DAAs:

Disease characteristic: The scale of demand is fundamentally different and much larger for HCV-DAAs than any other previous high-cost medicines. The issue of access seldom made the headlines with the conventional high-cost medicines as they were often found in oncology or in rare diseases with fewer patients. On the other hand, HCV infection is widely prevalent worldwide, and with the greatly improved prospect of cure, the demand for HCV-DAAs has grown rapidly.

Product characteristic: Unlike most of the treatments available for chronic diseases that require a prescription for a prolonged period, HCV-DAAs are unique because they provide a cure. A cure for an infectious disease also means that the size of the future demand would gradually decline as more patients receive treatment. This product characteristic had led to a strong incentive for the pharmaceutical companies to enter the market as soon as possible and to obtain a high market share, especially in countries with a high HCV prevalence. This trend may explain why the prices in the U.S. were less affected by competition than expected. The pharmaceutical companies had an incentive to set prices at a level which maintains the market.

Patient characteristic: To a certain extent, the discovery of HCV-DAAs may resemble the discovery of antiretroviral therapy (ART) for HIV-AIDS in the 1990s [347]. However, there are distinct differences with respect to patient characteristics that explain why it did not lead to a social movement similar to that for ART. Firstly, HIV-infected individuals were relatively young in their early twenties and were terrified of the disease that at the time was not yet well known. Secondly, while HIV-infected individuals came from various socioeconomic backgrounds those with HCV are often from the lower socioeconomic background. Accordingly, the HCV patient groups had a relatively weaker voice and were less likely to invest in lobbying activities because they were likely to come from a lower socioeconomic

background with some history of IDU (e.g., hesitant to join in mass demonstrations). Also, due to the slow progressive nature of the disease, most patients were likely to become aware of the infection at a relatively older age.

Accordingly, HCV-DAAs possessed unique characteristics that were somewhat different from the conventional high-cost medicines. However, when looking at the characteristics of other high-cost medicines that came into the market after HCV-DAAs, the products that were often associated with the issue of access were those with an unprecedented demand size. For example, PCSK9-inhibitors are neither affordable nor cost-effective at the launch price. However, because they have fewer side effects and work better with people with Statin intolerance, the demand increased despite insufficient data [348]. Another good example is checkpoint inhibitors (e.g., nivolumab and pembrolizumab), an innovative cancer treatment that stimulates the body's immune system to kill cancer cells. It has stimulated an unexpected increase in demand and thus increased pressure on the financial stability of the health systems [349]. Therefore, despite the above-noted differences, the future high-cost medicines with a high prevalence are likely to result in similar issues to those of HCV-DAAs.

Chapter 2: Conclusions

2.1 Introduction

As a summary of this thesis, conclusions are drawn from the findings and the implications for policy as well as for future research are elaborated in this section. In addition, the contribution of the thesis and the limitations of the study are also explained.

2.2 Implications for future policies

The rapid increase in upfront payment by the unprecedented market entry of HCV-DAAs had substantial financial impacts on the health care budget at the global and national levels. Especially Sovaldi® and Harvoni® are often cited as one of the major causes for large increases in pharmaceutical spending since 2013. Just with these two pharmaceutical products, Gilead has received approximately 25 billion USD in sales revenue and generated a net income of 12 billion USD in 2014 [350]. The IMS Institute for Healthcare Informatics estimated that the global pharmaceutical bill will reach 1.4 trillion USD by 2020, where the contribution of HCV-DAAs will be close to 48 billion USD [351]. For example in Germany, the 9.4% increase in pharmaceutical spending from January to September 2014 was due to Sovaldi® [108]. In 2015, Medicare Part D spending on HCV-DAAs had reached 9.2 billion USD, which is an increase of over 90% from 4.7 billion USD in 2014, increasing the premium by 8.6% [150].

Despite numerous policy reforms that took place in an attempt to minimise the budget impact of HCV-DAAs, the challenge worldwide is still the dilemmas caused by the market failure in the pharmaceutical sector. The situation is further complicated by the fact that the pharmaceutical market is now a global market. It is particularly true with respect to the HCV-DAAs, that the manufacturers' business decisions resulted in restricted access in many countries. For example, the lack of restrictions on marketing at the national level in the U.S. and Japan, may have delayed the introduction of innovative pricing mechanisims in other countries. Also, while some LMCs had access to HCV-DAAs through special access schemes, because the companies were unresponsive to the legal challenges to their patents, access was delayed in important emerging countries such as India and China

Nevertheless, it is also deeply interconnected with pricing and reimbursement decisions made at the national and individual levels. In other words, while the harmonisation of regulatory authorisation is reducing barriers to market entry, reimbursement decisions being made separately by country are deepening the disparities in access to novel medicines by geography and socio-economic status.

A study suggests that the transfer of pharmaceutical knowledge between nations, especially of the decisions made by the U.S., Europe and Japan, would have the spillover effects for other countries [95]. Therefore, the following section first discusses the country-specific policy implications, then the overall implications for the future policy making.

Policy implications for Japan

Although the impacts of the market entry of HCV-DAAs were delayed in Japan, they certainly served as a strong stimulus for the MHLW and TPPs to reconsider the current pricing and reimbursement systems. The sudden need for a change in its system created the illusion that the country needs to adopt cost-containment measures commonly used in other HICs (i.e., HTA). However, with respect to the implementation of cost-effectiveness analysis in decision-making, there are still limited studies on how HTA can or should be adopted by the Japanese health system. This study, therefore, suggests that more policy-focused research is needed to provide greater clarity on how the appraisal results should be reflected in the pricing and reimbursement decision-making process in Japan.

As such, there are wider issues that need to be addressed, or thought through, with respect to how HTA results are to be used within current pharmaceutical policy in Japan. For example, the use of HTA may be required for optimising access rather than for cost-containment. For this, a consideration of the system as a whole is required. For example, the bureaucratic culture and system of the MHLW that works against cultivating an understanding of and incentives for access optimisation among decision-makers, physicians and the public must be reconsidered. Perhaps, a bottom-up approach through education and practice coordination (via implementation of guidelines) may encourage cost-effective prescribing behaviours among physicians.

Nevertheless, in a country such as Japan, where the health system already has a strong egalitarian foundation and relatively few restrictions on access to medicines, any decisions that exclude products from the formulary list, or people from receiving a certain treatment,

will not be well received by the public. Therefore, the decision-making process within the MHLW must also be more transparent and accountable. For example, by allowing more involvement of the relevant stakeholders in decision-making, and by providing sufficient explanation of the decisions made to the public with evidence. The existing pricing methods that use formulas to determine a product price must also be redesigned to reflect the evidence and product value within the Japanese context.

Policy implications for the U.S.

In the U.S., the fear of the potential budget impact of allowing access to HCV-DAAs led most of the public TPPs to introduce strict access policies, and thus HCV-DAAs were withheld from many HCV-infected individuals. The market entry of HCV-DAAs and associated events served as an important wake-up call and thereafter brought the issue of pharmaceutical pricing and access to the forefront. However, the ultimate impacts of the increased attention on pharmaceutical prices at both federal and public levels are yet unknown. Especially under the new administration in 2017, the progress made after Obamacare and / or the lessons learnt from HCV-DAAs may not lead to obvious improvements. Regardless, it will be a great challenge to improve the U.S. health systems unless the focus is shifted to its systemic problems (i.e., fragmentation of the system) rather than product pricing. In order to minimise TPPs' scope to interpret the same policy differently, a coordinated policy on cost-sharing mechanism as well as control of access (e.g., with respect to the handling of stigmatisation) is essential. Culturally speaking, to adopt a single payer system may not be realistic in the current U.S. However, some coordination between TPPs would enhance the transparency of the system, as well as its justification and accountability, and would counter-balance the increasing pressure from the industry. Furthermore, more formal and transparent methods to structure the decision-making process are needed to synthesise evidence, to understand the uncertainties surrounding a new technology and to determine when to postpone a decision until additional information is collected. Incoherency in the law with respect to the consideration of cost and cost-effectiveness in reimbursement decision-making is also an issue, which can only be addressed by formal recognition of the importance of cost considerations.

Policy implications for England

Despite the clinical and cost-effectiveness of HCV-DAAs, NHS England failed to budget in a timely fashion for the provision of its broader access, by attempting to delay the appraisal as well as the guidance implementation procedures. Access to HCV-DAAs as of 2016 was still restricted to a set quota per year. The primary challenge ahead to improve access is to reflect the true budget impact of high-cost medicines by setting an appropriate threshold for cost-effectiveness that reflects the health opportunity cost of NHS spending. With respect to HCV-DAAs, there was the additional challenge that their cost-effectiveness is, in part, a consequence of future cost savings (in patients whose liver disease does not progress). There are simply no mechanisms to facilitate sudden increases in NHS sending, and because of this, the appropriate relationship between NICE and NHS England and its healthcare resource allocation model has been questioned with respect to future high-cost medicines [352]. Finally, although there is a debate on the confidentiality of product pricing, clear information on the actual / total cost of a product, and on its potential contribution to improving health, should be better communicated to the public in order to minimise the concerns of the public.

Overall policy implications

The overall policy implications for each of the decision-making stages are summarised as listed below:

Pricing: The pharmaceutical market model and the consideration of costs are directly linked to the health system and the cultural and political aspects of a country. International cost comparison may, therefore, be useful, but not effective. The pharmaceutical product pricing model and the level of government involvement must be designed to reflect the culture and demand of a country.

Assessment: Data is ubiquitously available in the modern world, but are not yet sufficiently utilised. For better evidence-based decision making (i.e., for access optimisation), innovative and collaborative approaches for collecting and analysing timely and accurate data are urgently needed.

Reimbursement decision-making: Product access must be approached from an access optimisation perspective rather than from a cost-containment perspective. Even when controlling access, there is a clear difference between the policies that exclude certain

individuals due to their socioeconomic background for cost-containment reasons and those that focus on prioritisation of those who need the treatments most. Therefore, it is important that there are shared social judgments across TPPs in the same country, which balance public health needs and individual needs. The use of an HTA approach in reimbursement decision-making is one way of doing this, but should reflect the culture and needs of the particular country. If a country has separate organisations that conduct HTA and commissioning, the organisational management between these two organisations should also be well thought through.

Policy implementation: One of the main arguments for being more transparent with respect to prices is that it facilitates negotiations between countries and manufacturers and thus, countries can get their own deals with better advantages. However, insufficient transparency also encourages price discrimination which transfers surplus to the manufacturers. When the total cost of pharmaceutical spending to the health systems has risen sharply in recent years, there is an increasing need for TPPs to be more accountable and to communicate the cost to the system to their beneficiaries. In order to achieve this, in addition to improved TPP accountability, bottom-up management is crucial through improved health literacy achieved by patient education, as well as control and standardisation of prescription practices by physicians.

2.3 Contributions of the thesis

Since pharmaceutical products represent a substantial cost driver in the health system, further work in this sector is central to future health system financing and improved access to medicine. This can be achieved in various ways, such as by looking at the cost-effectiveness of a product and / or controlling the product prices for example by increasing the market pressure to obtain competitive prices for generic products while keeping higher prices for branded medicines [72]. These approaches have been well discussed and implemented in most HICs. However, regardless of how well per-product price is controlled, the budget impact for a health system can be significant if the level of use is high. This study, using the example of HCV-DAAs, has demonstrated that cost-effectiveness consideration may no longer suffice in decision-making for sustaining health system financing. Accordingly, more work on a multi-dimensional approach in product pricing (i.e., accurate reflection of product values in prices) is needed, but an innovative approach in resource allocation (i.e., how-to-pay) should also be further explored. Moreover, when making a future pharmaceutical policy, it is highly important to take account of the culture and health system of the targeted country and to make adjustments accordingly. A methodological approach to enable this has been proposed elsewhere [353][354]."

There were challenges associated with documenting a short but rapidly evolving period of development of pharmaceutical policy. It is impossible in such a situation for information to be consistently up to date. However, it shows how rapidly pharmaceutical policy has changed during the past five years and the important role of high-cost medicines in the evolution of pharmaceutical policy worldwide. In addition, this thesis is timely with respect to documenting the responses of three important countries (clarifying the policies that worked and did not work under their different health systems) and making policy recommendations for other countries.

Furthermore, this study compared the impact of HCV-DAAs on three countries that have distinctly different health systems. Due to the complexities associated with conducting a comparative analysis of different health systems, such studies are limited. Especially due to the cultural and language barriers, there are a few studies on the Japanese context, despite the fact that Japan is one of the major world economies and has an important pharmaceutical industry. The comparison of the three distinctive situations allowed conclusions to be drawn despite the need for context-dependent approach, the world now faces a similar challenge with respect to the issue of high-cost medicines. It is thus

anticipated that the outcomes of this study may be a useful source for designing appropriate actions for improving access to the future high-cost medicines.

2.4 Limitations of this study

The study is subject to several limitations as summarised below:

Data collection: Firstly, the publications available on the decision-making process for HCV-DAAs were limited, particularly during the initial phase of the study. To minimise this risk, information sources other than academic journals were systematically searched and used. Secondly, since the effective prices are mostly confidential and change over time, the prices listed here are what was available from the collected documents as of December 2016. Thirdly detailed information about negotiations that took place between the pharmaceutical companies and TPPs were not easily available from the public domain. Therefore, the information summarised here is based on what was publicly available online and inevitably will have missed some information that was confidential. Lastly, some media sources were excluded from the study. For example, social media was excluded because unless an in-depth media analysis is conducted, information from social media can lead to unnecessary opinion bias, especially when the topic of interest is specific. News resources, which require subscription fees, were also excluded because funding was not available for purchasing subscriptions, and also it was assumed that public opinion is largely generated through the publically available news.

Data analysis: Firstly, the reimbursement decisions made at the regional and hospital levels and by the private TPPs were not considered. Although this limitation may lead to a weak representation of the impacts of HCV-DAAs, it made the multinational comparison possible. Secondly, the conceptual framework used in this analysis has not yet been used in a non-EU setting. However, this limitation was carefully considered during the research design stage, and it was concluded that it would not be an issue because the framework was used to explain and compare observed phenomena rather than to develop a new conceptual theory. Thirdly, there was a risk of researcher bias because the study was conducted by a single investigator and because the purposive sampling method was used. Although it was difficult to minimise this bias due to the design of this study, the findings were frequently shared and discussed with my supervisor. Lastly, the study period may have been too short to capture the complete story, and thus the full impacts of HCV-DAAs on each of the health systems.

2.5 Opportunities for future research

The issue of access to medicines has recently gained global attention, and there are many aspects in this area which would benefit from further research. For example, while this study looked at the pricing and reimbursement decision-making process at the national level, a more comprehensive understanding of the global impacts of HCV-DAAs may require further research on the impacts of regulatory harmonisation on pricing or an assessment of the budget impact of HCV-DAAs on different systems.

However, as this study has emphasised, a simple comparison of product price by country is not a good means for comparing the efficiency of pharmaceuticals spending, and also for proposing concrete policy recommendations. More in-depth analysis at the country level, reflecting the culture and organisation of the different health systems, is suggested below.

- Japan: considering that the design of health system and pharmaceutical policies are distinctively different in Japan from the other HICs, more studies are needed to investigate how pharmaceutical products should be valued in Japan and how the assessment results (from HTA) can be used to determine access. To perform such studies, a good understanding of its culture, politics and health system is essential, as it requires an approach that looks at the whole system for identifying what policies may work or not work in the Japanese context and why.
- U.S.: the next step for the U.S. requires more evidence for the need of a coordinated health system. It is, therefore, important to assess and document how and why the gradual changes in access restriction for HCV-DAAs occurred in different TPPs. Furthermore, an assessment of the impacts of the increasing domestic attention to pharmaceutical prices at both federal and state levels may benefit future policy making for upcoming high-cost medicines.
- England: Unlike the other two countries, England has taken innovative approaches to respond to the market entry of HCV-DAAs (e.g., implementing a budget impact threshold of 20 million GBP (49 million USD)). Therefore, it would be interesting to assess how these new policies could have worked with HCV-DAAs, and their implications for other high-cost medicines.

Concluding remarks

With a rapid advancement in technology, products of the modern pharmaceutical industry are improving the lives of patients with diseases and disorders that were previously incurable. Concurrently, due mainly to the increasing cost of pharmaceutical products and the declining ability of health systems to afford the cost, the gap between those who can and cannot access such products is widening. One of the challenges is to provide sufficient access to such high-cost medicines meeting the population demand while managing the budget impact.

The discovery of HCV-DAAs and their introduction stood out as an excellent example where the rapidly increasing pharmaceutical prices has overshadowed even the most exceptional advance in medical technology. Despite its cost-effectiveness, the significant budget impact led to restricted accessibility, even in HICs. The lesson learned from the experience with HCV-DAAs may be that the reimbursement decision-making should no longer be “pay for all” or “whether to pay”, but the focus should be on “how to pay”. This is because different payment schemes lead to different sharing of the risks and responsibilities. For example, reimbursement could be designed to spread the payment over time so that the risks and responsibilities of payment are equally being shared between TPPs and the manufacturers. The payment could also be linked to treatment success rates, i.e., a payment by results scheme. This was found in a few European countries for HCV-DAAs where TPPs were only responsible for the payment of successful treatments.

While the focus has long been on the correlation between product value and the way pharmaceutical products are reimbursed, it would become further complicated with better effectiveness, higher demands and prices. It is clear that the market-oriented pharmaceutical model does not guarantee access to life-saving medicines, and cost-effectiveness does not always indicate whether it is affordable for the health system.

In the view of declining birth rate coupled with the growing elderly population, increasing challenges with respect to the financing of the health system are inevitable. While it is difficult to cut down the budget for personnel payments, the pricing and coverage of pharmaceutical products is still an area to be explored. It is expected that there will be a succession of high-cost medicines entering the global market in the future. In order to confront the fiscal and demographic challenges that affect the health system today and in the future, dynamic innovation in health policy, especially technical solutions for pricing

control and reimbursement decision-making to manage sustainable pharmaceutical spending at the same time to prepare for any unprecedented financial crisis, is urgently needed. HCV-DAAs is just one example of an exciting new breakthrough in medicine, but catastrophic for finance. We are thus at a crossroad where decisions made on acceptance or refusal of access would have clear implications on our ability to provide access to medicine in the future.

List of abbreviations

AASLD	American Association for the Study of Liver Diseases
ABPI	Association of the British Pharmaceutical Industry
ACA	Affordable Care Act
ACD	Appraisal Consultation Document
AG	Academic Group
AMP	Average Manufacturer Price
ARVs	Antiretroviral Therapy
BMS	Bristol-Myers Squibb
CCGs	Clinical Commissioning Groups
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
CMU	Commercial Medicines Unit
CTAF	California Technology Assessment forum
DALYs	Disability-Adjusted Life Years
DoH	Department of Health
DPO	Drug Pricing Organisation
DrPH	Doctor of Public Health
EASL	European Association for the Study of the Liver
EMA	European Medicines Agency
ERG	Evidence Review Group
ESI	Employer-sponsored Insurance
ESLD	End-Stage Liver Disease
EU	European Union
FAD	Final Appraisal Determination
FDA	The U.S. Food and Drug Administration
FPL	Federal Poverty Line

FSS	Federal Supply Schedule
GDP	Gross Domestic Product
GHSS	Global Health Sector Strategy
GNI	Gross National Income
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HCV-DAAs	Hepatitis C Virus – Direct Acting Antivirals
HICs	High Income Countries
HIV/AIDS	Human Immunodeficiency Virus infection / Acquired Immune Deficiency Syndrome
HPV	Human Papillomavirus
HTA	Health Technology Assessments
ICER	Incremental Cost Effectiveness Ratio
ICER	Institute for Clinical and Economic Review
IDSA	Infectious Disease Society of America
IDUs	Injection Drug Users
INF-a	Interferon-alpha
IPRs	Intellectual Property Rights
IQWiG	Institute for Quality and Efficiency in Healthcare
JSH	Japan Society of Hematology
LICs	Low Income Countries
LMICs	Low and Middle-Income Countries
LSHTM	London School of Hygiene and Tropical Medicine
MAPDs	Medicare Advantage plan with Prescription Drug Coverage
MCO	Managed Care Organizations
MEA	Managed Entry Agreements
MERCORU	Mercado Comun del Cono Sur (Southern Cone Common Market)
METI	Ministry of Economy, Trade and Industry
MHLW	Ministry of Health, Labour and Welfare in Japan

MICs	Middle Income Countries
MPP	Medicines Patent Pool
MSF	Medecins Sans Frontieres
MTA	Multiple Technology Appraisal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
OPP	Out of Pocket Payment
ORF	Open Reading Frame
PA	Prior Authorisation
PAHO	Pan American Health Organization
PAS	Patient Access Scheme
PBS	Pharmaceutical Benefits Scheme
pCPA	Pan-Canadian Pharmaceutical Alliance
PDPs	Prescription Drug Plans
PEG-IFN	Pegylated interferon
PMB	Pharmacy Benefit Manager
PMDA	Pharmaceutical and Medical Devices Agency
PPC	Prescription Prepayment Certificate
PPP	Purchasing Power Parity
PPRS	Pharmaceutical Price Regulation Scheme
PVAs	Price-volume agreements
R&D	Research & Development
RBV	Ribavirin
RNA	Ribonucleic Acid
SMC	Scottish Medicines Consortium
SOC	Standard of Care
STA	Single Technology Appraisal
SVR	Sustained Virologic Response

TB	Tuberculosis
TPPs	Third-Party Payers
U.K.	The United Kingdom
U.S.	The United States
UN	The United Nations
VA	The U.S. Department of Veterans Affairs
VISNs	Veteran Integrated Services Networks
WAC	Wholesale Acquisition Cost
WHA	World Health Assembly
WHO	World Health Organization

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Appendix

Appendix 1: Summary of cost-effectiveness of Sovaldi® and Harvoni®

TABLE 19: SUMMARY OF COST-EFFECTIVENESS OF SOVALDI® AND HARVONI®

	Cost effectiveness (GBP)	Comparator
Sovaldi® (GT1: RBV, PEG-INF)		
Treatment naïve	Cost effective (17,500/QALY) Cost effective (10,300/QALY) Cost effective (15,400/QALY)	PEG-INF, RBV Victrelis®, PEG-INF, RBV Incivek®, PEG-INF, RBV
Treatment-experienced	Cost effective (12,600/QALY) Cost effective (700/QALY) Cost effective (8,200/QALY)	PEG-INF, RBV Victrelis®, PEG-INF, RBV Incivek®, PEG-INF, RBV
Not eligible for PEG-INF	Not cost effective (47,600/QALY)	No treatment
Sovaldi® (GT2: RBV)		
Treatment naïve	Not cost effective (46,300/QALY)	PEG-INF, RBV
Treatment-experienced	Cost effective (12,500/QALY)	PEG-INF, RBV
Not eligible for PEG-INF	Cost effective (8,200/QALY) Cost effective (8,600/QALY)	No treatment
Sovaldi® (GT3: RBV, PEG-INF)		
Treatment naïve (with cirrhosis)	Cost effective (6,600/QALY)	PEG-INF, RBV
Treatment naïve (without cirrhosis)	Not cost effective (40,600/QALY)	PEG-INF, RBV
Treatment-experienced	Cost effective (19,000/QALY)	PEG-INF, RBV
Not eligible for PEG-INF Treatment naïve (with cirrhosis,)	Cost effective (10,500/QALY)	PEG-INF, RBV
Not eligible for PEG-INF Treatment naïve (without cirrhosis)	Not cost effective (28,000/QALY)	PEG-INF, RBV
Not eligible for PEG-INF Treatment-experienced (with cirrhosis,)	Cost effective (19,200/QALY)	PEG-INF, RBV
Not eligible for PEG-INF Treatment-experienced (without cirrhosis,)	Not cost effective (31,400/QALY)	PEG-INF, RBV
Sovaldi® (GT4, 5 and 6: RBV, with or without PEG-INF)		
Treatment naïve and experienced (with cirrhosis)	Cost effective (Between 20,000 to 30,000/QALY)	
Treatment naïve and experienced (without cirrhosis)	Not cost effective (39,100/QALY)	PEG-INF, RBV
Not eligible for PEG-INF	Not considered	
Harvoni® (GT1)		
Treatment naïve (without cirrhosis)	8 weeks: Cost effective (9,000/QALY) 12 weeks: Not cost effective (23,000/QALY)	PEG-INF, RBV Olysio®, PEG-INF, RBV
Harvoni® (GT4)		
Treatment naïve (without cirrhosis)	8 week: N/A 12 week: Not cost effective	-
Harvoni® (GT1, 4)		
Treatment naïve (with cirrhosis)	12 week: Cost effective (5,000 / QALY) 24 week: Not cost effective (45,000/QALY)	No treatment Sovaldi®, PEG-INF, RBV
Treatment-experienced (with cirrhosis)	12 week: Cost effective (4,500 / QALY) 24 week: Not cost effective (32,500/QALY)	No treatment Sovaldi®, PEG-INF, RBV
Treatment-experienced (without cirrhosis)	12 week: Cost effective (17,000 / QALY) 24 week: Not cost effective (77,500/QALY)	No treatment Sovaldi®, PEG-INF, RBV
Harvoni® (GT3)		
All type	Not cost effective	-
Harvoni® (People co-infected with HIV)		
All type	The same recommendations apply as the mono-infected group	-
Harvoni® (People with advanced liver disease and after liver transplant)		
All type	Limited data: Unable to make a recommendation.	-

Source: NICE Homepag

Appendix 2: List of general and industry-focused news websites

In order to collect data systematically within the scope of the DrPH research project, the following list of general and industry-focused news websites were checked during the data collection phase as a potential source of information (Table 20). On top of this, the snowball technique was used to collect additional sources from websites that are not listed here.

TABLE 20: LIST OF INFORMATION SOURCE

Type	Name	Website
General news website	ABC news	http://abcnews.go.com/
	BBC news	http://www.bbc.co.uk/news
	CNN news	http://edition.cnn.com/
	Economic times	http://economictimes.indiatimes.com/
	Military times	http://www.militarytimes.com/
	New your times	http://www.nytimes.com/
	Reuters	http://uk.reuters.com/
	The guardian	http://www.theguardian.com/uk
	Wall street journal	http://www.wsj.com/europe
	Bloomberg	http://topics.bloomberg.com
	Business standard	http://www.business-standard.com/
	Financial times	https://www.ft.com/
	Washington post	http://www.washingtonpost.com/
	Asahi shinbun	http://www.asahi.com/
	Yomiuri shinbun	http://www.yomiuri.co.jp/
Industry-focused website	Pharmaceutical industry	http://www.pmlive.com/ http://www.phrma.org/ http://www.fiercepharma.com/
	Medical marketing and media	http://www.mmm-online.com/
	Modern healthcare	http://www.modernhealthcare.com/

Appendix 3: List of web pages of stakeholder organisations

The analytical framework (*Part 1, Chapter 2.5*) was used to identify stakeholders who are directly or indirectly involved in the pharmaceutical product reimbursement decision-making process of the selected countries. Potential organisations to collect data from are indicated in the following (Table 21 to 24).

TABLE 21: KEY STAKEHOLDER ORGANISATIONS (INTERNATIONAL LEVEL)

Institutional stakeholders	Identified organisations
International organization (Public)	World Health Organization
	World Trade Organization
	United Nations
International organization (Private: non-profit)	Medecins Sans Frontieres
	Medicines du Monde
	International Pharmaceutical product Policy Consortium
	World Hepatitis Alliance
	Hepatitis B and C Public Policy Association
	World Cancer Research Fund International
	Hepatitis C trust
Pharmaceutical companies	Gilead Sciences, Inc
	Bristol-Myers Squibb Company
	AbbVie
	Merck & Co.
	Johnson & Johnson (Janssen)
	Vertex pharmaceuticals
	Medivir

TABLE 22: KEY STAKEHOLDER ORGANISATIONS (JAPAN)

Institutional stakeholders	Identified organisations
Regulatory authority	Pharmaceuticals and Medical Devices Agency
	Ministry of Health, Labour and Welfare
Third party payer	Ministry of Health, Labour and Welfare
Private sector	Japan Pharmaceutical Association
Professional Association	The Japan Society of Herpetology
	Asian Pacific Association for the Study of the Liver
Civil Society / Patients Group	Japan Hepatitis Council
	Viral Hepatitis Research Foundation

TABLE 23: KEY STAKEHOLDER ORGANISATIONS (THE U.S.)

Institutional stakeholders	Identified organisations
Regulatory authority	Food and Pharmaceutical product Administration
	Department of Health and Human Services
Third party payer	Medicaid
	Medicare
	Department of Veterans Affairs
Professional Association	American Association for the study of liver diseases
	Patient Centred Outcomes Research Institute
	The Institute for Clinical and Economic Review
Civil Society / Patients Group	Hepatitis C Association
	Hepatitis C Support Project
	Hep C Connection
	Hepatitis Foundation International
	National Association of Hepatitis Task Forces
	Pharmacists Planning Services Inc,- National Pharmacists Council on Hepatitis and Liver Disease
	American Liver Foundation

TABLE 24: KEY STAKEHOLDER ORGANISATIONS (ENGLAND)

Institutional stakeholders	Identified organisations
Regulatory authority	Department of Health
	The National Institute of Health and Care Excellence
	Medicines and Healthcare products Regulatory Agency
	European Medicines Agency
Third party payer	The National Health Services
Private sector	Association of the British Pharmaceutical Industry
Professional Association	European Liver Patients Association
	European Association for the Study of the Liver
Civil Society / Patients Group	The Hepatitis C Trust
	British Liver Trust
	European Coalition of Positive People

Appendix 4: Summary of the type of interviewees

The type of professions interviewed for additional data collection is summarised.

TABLE 25: THE TYPE OF INTERVIEWEES BY PROFESSION

	The U.S.	Japan	England
Public TPPs	0	2	2
Pharmaceutical industry	0	2	1
Academia	3	4	2
Professional associations	2	2	1

Appendix 5: Interview guide

The following interview guide was developed for ensuring consistency between interviews and for increasing the reliability of the findings.

TABLE 26: INTERVIEW GUIDE

Introduction (10 mins)	**Self-introduction** - I want to thank you for taking the time to meet with me today. - My name is Amina Sugimoto, and I am a Doctor of Public Health Student at London School of Hygiene and Tropical Medicine.
	Purpose of the study - For my research thesis, I would like to talk to you about your experience with the pharmaceutical product reimbursement decision-making process in your country with respect to high-cost medicines. Especially on Direct-Acting Antivirals (DAAs), a promising but highly priced set of interferon-free pharmaceutical products for Hepatitis C virus (HCV) infection. - As you know, the current market prices of HCV-DAAs are high, and this has surfaced the access issues of the forthcoming generation of high-cost medicines for both LMICs and HICs. - Therefore, the aim of this study to is to contribute to the understanding of the emerging challenges of high-cost medicines by conducing a comparative analysis on the current progress and obstacles for countries to ensure the access to HCV-DAAs and their responses to the challenges. - Despite the public outcry globally on restricted access to HCV-DAAs, a little is known about how the governments responded to this challenge. Therefore, although the reimbursement mechanism differs from country by country, it is important to capture how countries are facilitating the decision-making process and responding to the challenge. - A detailed comparison of countries will provide an overview of similarities and differences in their responses, which will be useful information for decision makers to identify priorities for strengthening their national reimbursement mechanism as well as for designing appropriate actions for improving the access to high-cost medicines. - Therefore your input is important since you have been (directly/indirectly) involved in the process, and has substantial knowledge on this topic.

	Informed consent - The interview should take less than an hour. I will be taking some notes during the session, but I will also be recording the session because I do not want to miss any of your comments. Because we are being recorded, please be sure to speak up so that I do not miss your comments. - All responses will be kept confidential. This means that your interview response would not be shared with anyone except myself that any information included in my thesis would be anonymised. Also, you do not have to talk about anything that you do not want to, and you may end the interview at any time. - Are there any questions about what I have just explained? - Are you willing to participate in this interview? - If so, please do sign the informed consent form.
Questions (30-45 minutes)	**About yourself and your organization (5 minutes)** 1. Could you describe your role in your organization?
	HCV endemic (10 minutes) 2. Please describe the severity of HCV transmission in your country, and the affordability and availability of the interferon and interferon-free HCV treatments? 3. How important do you/your organization think for your country to improve the access to the HCV treatments?
	Decision-making for DAAs: (20 minutes) 4. Please describe the reimbursement decision made for interferon-free HCV treatments (Hereafter DAAs)? 5. Do you/your organization support the decisions made? 6. Please explain the reimbursement decision-making progress for DAAs. a. When did your country begin to conceive a reimbursement plan for DAAs? b. Which evidence were collected and how? c. How the collected evidence were used for the assessment? d. Which organization(s)/individual(s) made the final decision? e. Which individuals/organizations that have the most and least influence over the final decision-making process f. How are you/your organization involved in the process? g. To what degree do you/your organization have an influence over the decision-making process? h. What is your relationship with other stakeholders involved in the process? i. How the decision made are being communicated and implemented? 7. Please describe the key obstacles experienced during the reimbursement decision-making process?

	a. What were key obstacles for making the reimbursement decision for DAAs? b. How is your country responding to such obstacles? c. How much of the approved DAAs will be accessible to the public? What system have your country applied to optimize its access (e.g., prioritisation)?
	Future (10 minutes) 8. Do you/your organization think the nature of public debate on the pricing and availability of HCV treatments has changed since the discovery of DAAs? If so, how? 9. To what extent the decision-making process for DAAs was different from ARVs or other high-cost medicines? 10. Do you/your organization think the experiences of DAAs can be generalized with the other high-cost medicines, and if so: a. What lessons should be drawn from the experiences of DAAs? b. What policy would you recommend for improving access to the forthcoming generation of high-cost medicines?
Closing (5 minutes)	- Is there anything more you would like to add? - I will be the one who will be analysing the information you have given to me. I am hoping to submit a draft thesis by September 2016. I will be happy to send you a copy to review at that time if you are interested. - Thank you for your time.

Appendix 6: Informed consent form

INFORMED CONSENT FORM

01/June/2016

Where are we at the emerging challenges of high cost medicines?

Multinational comparison of the pricing and reimbursement decision-making processes for the new Hepatitis C treatments

Investigator: Amina Sugimoto, Doctoral Researcher (DrPH)

You are being cordially invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask the researcher if there is anything that is not clear or if you would like more information.

- **What is the purpose of the study?**

The overarching aim of this thesis is to contribute to the understanding of the emerging challenges of high-cost medicines by conducing a comparative analysis on the current progress and obstacles for countries to ensure the access to HCV-DAAs and their responses to the challenges.

- **Do I have to take part?**

It is up to you to decide to join the study. If you agree to take part, we will then ask you to sign this consent form. You are free to withdraw at any time, without giving a reason.

- **What will happen to me if I take part?**

If you agree to participate, this will involve an interview with the researcher (Amina Sugimoto). The interview will last less than one hour and will be undertaken at your usual place of work where a private room will be booked for this purpose or through a Skype/phone. Collected information will be anonymised, and will only be identified by your organizational role to maintain confidentiality. Following analysis quotes from the data may be used, as appropriate, in publications or reports. In this case, you will be informed about the quotation prior to the publication and you will be asked to sign another informed consent form. You can also request to use the quote anonymously or refuse without giving a reason.

- **What do I have to do?**

As a participant, you will be asked to answer numerous questions during the interview. Please answer the questions based on your personal perception and experience.

- **What will happen to the results of the research study?**

The data collected during the interview will be analysed and used to inform the overall conclusions as a DrPH thesis submitted to the LSHTM. The final thesis will be submitted by March 2017.

- **Who is organising and funding the research?**

There is no sponsor for this study

- **Who has reviewed the study?**

This study was given a favourable ethical opinion by the LSHTM Research Ethics Committee.

- **Contact Details**

Amina Sugimoto MHS
Department of Health Services Research and Policy
London School of Hygiene & Tropical Medicine
Phone: +44 (0)2076364757 / Email: amina.sugimoto@lshtm.ac.uk

Thank you for taking the time to read this sheet.

Please sign your name below only if you agree to participate in this study.

1. I confirm that I have read and understood the participant information sheet dated 01/June/2016 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered fully.
2. I understand that my participation is voluntary, and I am free to withdraw at any time, without giving any reasons.
3. I agree for my photo/quote/recording/other to be used in the publication or report related to the study.
4. I agree to take part in the study.

Name of Participant	
Signature	
Date	
Principal Investigator	Amina Sugimoto
Signature	
Date	

1 copy for participant, 1 copy for Principal investigator