PHARMACEUTICAL INDUSTRY, DRUG QUALITY AND REGULATION: EVIDENCE FROM UK AND FRANCE

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Foreward:

This thesis examines the relationship between drug price and drug quality and how it varies across two regulatory regimes in the pharmaceutical market: Rate of return regulation (RORR) in the UK and Maximum Price regulation in France. We used drug quality data from Tufts-New England Medical Center-Cost Effectiveness Analysis Registry which was then merged with data from the respective countries price databases. The theoretical analysis provides two main results. First, an RORR offer more incentives to the firm to produce higher quality drugs. Second, MPR reduce the price variance between the high and the low quality of drug, and reduces the average price.

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Research question: What are the effects of different extents of price controls in France and the UK and drug quality on prices of drugs?"

INTRODUCTION

As late as the 1930s, the remit for a doctor was limited to palliative care, setting bones and delivering babies (Coben, 1991). The few pharmaceutical drugs that were around back then had little to no impact on curing the diseases that they were designed for (ibid, 1991). This was suddenly changed in 1940s with the emergence and proliferation of Alexander Fleming's discovery of the antibiotic, Penicillin (Fleming, 1950). It's impossible to exactly pinpoint how many lives have been saved from this drug however experts have estimated it to be in the region of 80-200 million. Whilst this is arguably the greatest breakthrough in modern modern medicine, since then some other notable feats have been drug related improvements to cancer treatment resulting in 23 millions lifes years accrued between the years of 1988-2000 (Lakdawalla et al., 2010). Clearly, with figures such as these, the importance of the availability of drugs for human welfare is unparalleled to almost any other product invented.

This high value unfortunately does not come without its cost. Consequently most drugs, just like Penicillin, enter the market at an incredibly inordinate price. These high prices ultimately result in the majority of people being priced out of the market. In most other markets, this is fine, however given the implications of these people not receiving these pharmaceutical products, there is a difference. The reason for this is that the implications are directly related to health. According to the World Health Organisation, two billion people were at risk of death or severe health related issues as a result of not having access to essential medicines due to their prices (World Health Organisation, 2015)

Mass production of Penicillin meant that its price dropped from a priceless amount in 1940 to 20 dollars around 1943, and then as little as 55 cents in 1946 (Shaffer, 1959). Whilst for some drugs a similar price path has been followed, we have recently been seeing drastic and permanent price hikes. For example, Doxycyclin is a hugely popular drug that helps cure numerous infections such as pneumonia, acne, and chlamydia. It was marketed in 1967, yet between 2013 and 2014 however, its price rose by more than

8,281% (Palmer, 2014). In that same time frame another drug Captopril, an important drug that helps blood pressure rose 3900 percentage points in price from 1 cent to 40 cents a pill. These stories are not in isolation. Infact, over 500 drugs have seen 1000% price rises between 2008-15 (Lapook, 2014).

These prices reflect to some extent the feasibility of the research into finding these drugs that leads to these improvements. This interdependence dynamic is often not explored, yet arguably this system critically depends on this. This is supported by not only the fact that those companies with highest profit margins also have the highest amount R&D investment (in percentage terms) but also the fact the companies which are allowed to have the most flexibility to price have also produced an overwhelmingly high proportion of the best/most innovative drugs (Keyhani et al., 2010). Therefor, it's unclear to what extent exactly the proliferation of drugs that we see today would be without this structure.

They are also reflecting the asymmetries that often occurs in a universal or insurance ran market such as pharmaceuticals, which hinders normal market functions, giving firms an inordinate amount of power. For a market to run efficiently, Arrow (1963) argues, utility has to be maximised and ultimately this depends on the ability for consumers to be able to properly evaluate the utility of the products that are on offer; in others words, to be able to distinguish the good products from the bad. What is clear with the insurance/universal market structure that health often exists in however, is that this is almost impossible to produce. This is evidenced by the abnormally long chain that forms in this market from seller to consumer, which goes from firm to physicians, to the pharmacists/hospital, which is first paid by the government and then finally by the consumer (the patient) in the form of tax (Berman, 2017) . The extra steps involved mean prices signals are distorted and consumer choice is observed indirectly, both of which convolute utility maximisation. Additionally, costs are also indirectly observed since rises in premiums may result in less wage rises or higher taxes. All in all this creates ideal conditions for an asymmetrical market that obstructs value based decision making in the pharmaceutical market.

Furthermore, they are also reflecting market forces at play too. For example, Hikma Pharmaceuticals had to shut down in production Doxycycline in 2011 because of issues over quality checks. (Sarpatwari, 2015). This undoubtedly factored into its price rises that we saw previously. Captopril was found to be a cure for another disease around the time of its price rise. Again, this unexpected demand surge this would have factored into its price rises (ibid, 2015).

Consequently, the true picture is convoluted. Therefore the ability to assess these markets failures in order to reduce their external cost has meant an increased demand and importance of health economics in order to cultivate an environment that produces the best results for society. This is reinforced by the fact that in the wake of austerity budgets, low growth and performance across western economies, increased cost to most effective drugs and increased demand from an increasingly elderly demographic, we are looking at a future which is being shaped by radically increased cost of healthcare in the marketplace whilst also seeing dwindling amount of resources into health care budgets that are able to cover it (The Economist Intelligence Unit, 2016). This has led creation of various agencies and institutions and the profliciaiton of cost-effectiveness measures which have been set up to determine how best to harness true value in this market for society. The disparaging ideas on how these bodies choose to regulate the market is where this thesis enters the discussion. More specifically, this thesis will look into a range of different quality of drugs across two forms of regulatory options, a less direct form of regulation called Rate of Return Regulation (RORR) and a more direct form of price regulation, Maximum Price Regulation (MPR) and its effect on drug prices.

Therefor, the crux of the argumentation of this thesis essentially comes down to ability to facilitate access to the most high quality and most innovative drugs with the demand to improve access for the majority of society, which are given as diametrically opposed choices (Carbonari, Bhattacharya and Atella, 2012) . The choices made from this dichotomous relationship will create a trade offs and this thesis looks to the trade offs that emerge from price regulatory strategies that are positioned on this. On the benefit side of the trade off to direct price regulation is a reduced prices and also a lower overall variance to the drugs on offer in the market (ibid, 2012). Given that people prefer less financial risk when they are in need, direct forms price controls will achieve that dimension which will also increase the access for those who usually would not be able to afford. On the cost side however, arguments have been made that direct price regulation will distort the market away from the highest priced (and therefor highest quality drugs), by obscuring price signals which particularly impact higher quality drugs (Danzon, 2001). And therefore, this thesis will explore the argument held by Spencer (1975) that, to the extent that a regulatory regime would like pursue a pharmaceutical market that inhibits and thus highest quality of drugs, the extensive use of more stringent and direct price controls will hinder this. Given the reluctance of politicians to even admit a trade off is occuring (Maynard and Bloor, 2003) let alone discuss the ramifications of such action, the goal of this paper is to investigate the role that different regulatory schemes and drug quality can have on on drug price in the pharmaceutical market.

To look into these tradeoffs this thesis will use the work Besanko, Donnenfeld, and White (1988) and Spencer (1975). To forward their claims I will be looking at data sets that detail different qualities of drug and looking to see whether the prices of these drugs differ between the markets of France; characterised by MPR ; and the UK, characterised by RORR. More specifically, my hypothesis and methodological goals will centre around whether I can find a tighter correlation between drug price and quality in the UK as compared to France.

2 LITERATURE REVIEW

In order to gauge a more nuanced perspective for the complexities of the pharmaceutical market, one must have a fundamental understanding for the way price interacts with the market itself. Given these complexities, I have incrementally separated the literature review into 3 parts; starting with a more general broad scope of price regulation and then gradually increasing the narrowness of the lens of examination.

1.2.1 PRICE CONTROL REGULATIONS

World War II increased fiscal intervention into the economy to unprecedented levels (Higgs, 2005). Consequently, this facilitated the ideas emerging around the 19th century of equality and with it, came the proliferation of the welfare state. The welfare state's goal of equality was achieved in many ways, such as income redistribution, predistribution (education) or by intervention into specific markets. The last category consisted of subsidies, but also price ceilings and controls.

Scholars such as Galbraith (1953) rose to prominence off the back of their seminal pieces which promulgated the use price controls holistically. Their main assumptions were that regulators had full information, perfect enforcement and were benevolent. Galbraith (1953) examined industry relations and was concerned with the profit incentives from a continued reciprocity between a wage raise and price rises, which he argued was the root cause of the levels of inflation. Thus, he called for industry price control enforcement in order instill what he called a 'fair' interaction of price and wages to mediate this hazardous relationship and stabilise the economy.

Unfortunately, this was just a short-term solution that did not get at the main reason for price inflation. In the long term, sellers would become less inclined to produce and thus the market would collapse. Its outcome for the housing market in the UK for example, was that private rented sector fell from three quarters to one tenth of the total housing stock (Coyne and Coyne, 2015). This not only reduced supply but also kept prices high. Because of this, their proflication in the western world has steadily declined.

1.2.2 THE 'NEW HAVEN' APPROACH; MONOPOLIES AND REGULATION

What came from this was a more nuanced role of regulatory approach to markets which did not necessarily assume that regulator was more efficient at dealing with market problems. This created the 'New Haven' approach (den Hertog, 2010) . This assumption was operationalised by the inclusion of transaction costs and information costs of regulation (assumed to be zero in the previous era) which meant that for the majority markets, the intervention from the state would be too costly. However, for certain markets such as public utilities, due to its ostensibly high sunk costs, it could be argued that government intervention was more efficient than the market, giving rise the idea of the natural monopoly (ibid, 2010). The main idea was that the more regulation into the market, the more costs that would arise, and it would rise in an exponential fashion. Therefore, the unregulated market must run at such a inefficient state that intervention will outweigh this. This is most resolety seen in the production of trains or electricity grids, where several market failures result from these very high sunk costs (ibid, 2010).

The new haven approach can also be characterised by the pieces of work centred around this thesis, that of Besanko, Donnenfeld, and White (1988) and Spencer (1975). As previously stated, their works starts with the premise that price is taken to be the regulatory authority's control and quality is set by the firm. Taking this as the premise, they derive mathematical models that show the most efficient quality output for each of the two regulatory regimes. Their papers have two theoretical predictions. Firstly, Spence's theory (1975) was that RORR was more price responsive to quality than MPR and thus will have a tighter correlation between the quality and price. Secondly, Besanko, Donnenfeld, and White (1988) theorised that regulatory bodies that run a Maximum Price Regulation (MPR) have a price quality nexus distorted toward toward to lower quality and RORR had a price quality nexus distorted toward higher quality. These are the theories will be expanded on in the causal mechanism section.

1.2.3 THE PHARMACEUTICAL MARKET- THE LINK BETWEEN PRICE REGULATION AND QUALITY

Focussing now more specifically on the pharmaceutical market literature, scholars have developed an extensive empirical literature that examines the links in the between regulation and its effect on levels of market performance, market entry, R&D, and discovery of new drugs. The majority of this field argues that extensive regulation hampers the market outcomes.

Opening this segment, Kyle (2007) looked into the the global diffusion of drugs of firms that are headquartered in countries with high price control and those without. Her empirical investigation found that firms that are headquartered in countries that exercise price control often enter two fewer markets in comparison to countries that don't operate extensive price controls. She also found that because of this, this could be used implicitly as a protectionist strategy toward domestic firms.

Similarly, Vernon (2003) examines the global top 20 biggest pharmaceutical firms between 94-99 and tries to test the relationship between price controls and their profit levels. His findings shows a statistically significant negative relationship between a firm's sales exposed to price controlled markets and profit levels; to the extent that a 10% exposure could garner anywhere between 2.7-3.5% decrease in profits(Vernon, 2003; cited in Kresser, 2015). His paper is remarked for its two bold implications for the pharmaceutical markets; if the US was to follow suit with price regulation (where there is very little regulation) there could lead to as much as 30% industry decline in R&D globally, and that price regulation is likely the main reason for differences in profit margins between pharmaceutical firms operating in US and non US markets (ibid, 2003). The paper concludes with an attempt to measure this impact on social welfare. Whilst he was unable to statistically prove the net effect of said policy, he is confident that economic theory supports his hypothesis.

Where Venron (2003) was unable to prove its impact on social welfare, Danzon (2001) attempts to fill this void. Danzon is arguably the most well versed in this field. Her studies centre around examining the link between regulation and market performance the incentives for R&D, concluding that these controls often distort R&D investments. More specifically, her main focus is the effect of price controls diffusion rates, price disparities and launch times of drugs into different markets. Countries with the most stringent price controls also have the least amount of drugs approved by the US (an indicator of quality) in percentage terms. This was also seen by France in 1992, where over 50% of all sales of drugs for cardiovascular intervention were not allowed to launch in the US (Danzon, 1997).

In work that is more aligned to the specific area of pharmaceutical economics that my thesis operates in, Danzon also looks at the preferences of a type of drug that regulatory regimes tends to implicitly promote. Danzon hypothesised that regulation reduces incentives for R&D by disproportionately impacting prices of more innovative drugs (Danzon 1997). Building on this, Danzon and Chao (2000a) estimate the responsiveness of prices to their measures of innovativeness, defined as the the amount of countries where a molecule has been approved and molecule age. They categorise countries based on degrees of price

control in operation between 1991-92. Their main finding supported their hypothesis; countries with higher levels of price control have categorically lower prices for molecules that are more globally approved whilst also having lower prices for molecules that are older. Furthermore, findings from Danzon and Ketcham (2003) also support this. They investigated different degree reference pricing (a form of price control) and assessed them on their impact on price of 200 new drugs. They found that more stringent reference pricing inordinately forced lower prices of more expensive drugs relative to less expensive ones, relative to less stringent countries.

Finally, in the piece that inspired the methodology for this thesis; Carbonari, Bhattacharya and Atella (2012) examine the relationship between drug price and drug quality between the US and Italy. Using Besanko, Donnenfeld, and White (1988) economic theory as a foundation for their own, they derive a few mathematical models. They argue that a country operating a Minimum Efficacy Standard (MES) (comparable to that the US) will represent the lowest costs to firms and because of this they will be more inclined to invest in more risky (but often higher quality) investment profiles in order to reap higher profits from those that can pay it . MES+PC (Minimum Efficacy Standard + Price controlled, similar to MPR) however, implies a distortion to this. Their methodology looks at price dispersion between the two regimes on a selection of different quality levels, which will expanded upon in the research design.

The distinction made between the methodology of Carbonari, Bhattacharya and Atella (2012) and this thesis is twofold. Firstly, this thesis will be looking at different set of countries, namely that of the UK and France. Secondly, the methodology in their paper uses the one country that is price controlled (MES +PC) and one that isn't (MES). In principle this thesis uses the same parameters (one country that has more stringent price controls and one that has less) but there are significant differences in the existence regulatory control between UK (what would most resemble MES) and the US. Therefore, this thesis more allings itself to the works of Besanko, Donnenfeld, and White (1988) and Spence (1975) with their distinction of RORR and MPR. In order to empirically prove this theory, this thesis will still be using alot of the methodological instruments as found in Carbonari, Bhattacharya and Atella (2012). However, due the existence of some form of regulation in the UK market, we are unlikely to see as clear disparaging results as in Carbonari, Bhattacharya and Atella(2012), but according to the theory one should nonetheless appear.

2. THEORY, CAUSAL MECHANISMS HYPOTHESES

2.1 THEORY

One of the main tenets of economic theory is that where utility is maximised, society will be performing optimally. In order to achieve this, consumers and producers must cooperate in a structure known as the market, through trading. (Gruber, 2013). In most cases the competitive market equilibrium is the most efficient outcome for society (Arrow, 1963). However, as we have seen, markets on their own may fail to assure what society perceives as a proper distribution of resources, often resulting from conflicting interest with societal equity goals that private markets simply cannot achieve. When this happens, governmental intervention is necessary. With respect to the pharmaceutical industry, the primary market failure is the ability to free ride off the back of one firm's Research and Development (R&D) costs by providing the market a product which imitates those created by the original firm (Gruber, 2013). The primary government intervention here is therefore governmental provision of patents. This gives a monopoly on that product to the patent holder for a short amount of time so that the firm can get the maximum amount of revenue from that market in order to recoup the large sunk costs that are often incurred in the Research and Development (R&D) phase of a drug.

To the extent that a society perceives this initial market failure as an inadequate distribution of resources, a spectrum of differing extents to governmental interventions will manifest. Given that medicine is one of only a handful of markets that are directly responsible for a person's life and its quality, it is here where societal objectives are most prominent and thus most likely to override market outcomes that do not seem to coincide with these.

However, irrespective of how these preference takes shape in a society, the one commonality that permeates every aspect of human choice of is the idea of scarce resources. Because of this, it is possible that source(s) of value can be derived. Some societies argue value is maximised through increased state intervention that create more affordable access to drugs, whilst others argue for less forms state intervention that encourages access to drugs that yield the most gain. Given the subjectivity of the matter, it's unclear whether these value systems can be 'valued' comparatively, however what is clear is the ramifications that come from these value choices.

Two archetypes of such choices are discernible in Europe (Pantelli and Busse, 2016) as seen by A/B and illustrated figure 1:

High efficacy threshold for market entry, reimbursement at a predetermined price, prices most flexible:

- Reimbursement eligibility is set by a cost effectiveness threshold which takes into account the price of the product and the effectiveness of the drug
- High threshold for reimbursement but little or no reference pricing and thus more freedom for price
- UK, but also Denmark, Sweden

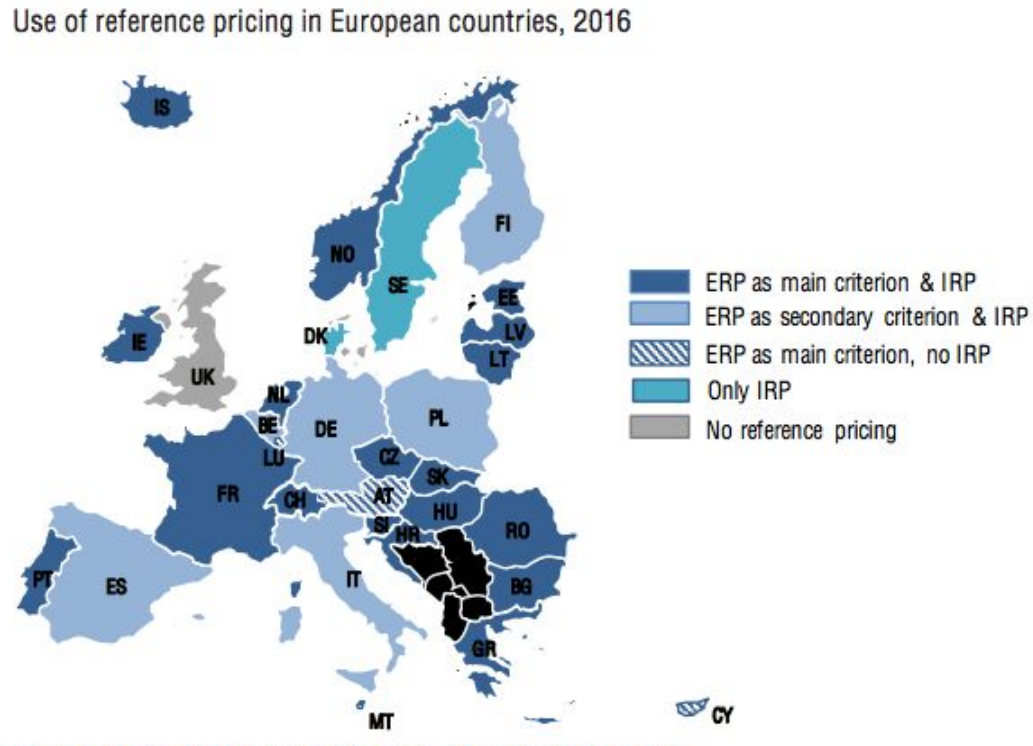
Lower threshold for market entry, reimbursement without a predetermined price, direct price controls:

- More discrepancy and discretion over evaluation, cost effectiveness factors in as small component, overall societal impact and reference price serves as the main function to decide reimbursement eligibility and price
- Lower (relative) threshold for reimbursement but prices/volume agreements is then determined by reimbursement category through external reference pricing which control price through and MPR style
- FRANCE but also Belgium Spain

The primary way this is achieved in the pharmaceutical market is through varying degrees of price controls. Price and reimbursement controls mainly occur through External and Internal Reference Pricing (ERP & IRP). Reference pricing is a way of grouping a set of drugs under a single maximum reimbursement amount, which is why it is similar to MPR. To determine the categorisation, drugs are either clustered through ERP, which is average or lowest price of a set of countries or IRP, which means drugs are clustered by their therapeutic class or similar active ingredient (Pantelli and Busse, 2016). Given that this mode of operation biases drugs towards a already predefined category, it disproportionately effects more innovative (tries to fit it into an already established drug class and reimbursement rate) and higher priced drugs (tries to set price according to countries which may have lower prices due to income levels). This has been evidenced by Bardey, Bommier and Jullien's (2010) work on reference pricing.

From the figure, we can see the extent of France's reference pricing and how it doesn't feature at all in the UK. France use Spain, UK, Greece and Germany in their ERP basket (Pantelli and Busse, 2016).

FIGURE 1



Source: Pantelli and Busse, 2016

Klesser (2014) indicates that insofar as a choice from regulator to intervene made, a tradeoff of these objectives will implicitly emerge in the form of trilemma of drug quality, patient access and expenditure control. Given that expenditure control is often a main priority throughout all countries, it often becomes a choice between drug quality and drug access. For example, extensive intervention such as a direct form of price control will likely lead to a reduction the price of drugs and as a result, which will increase the overall volume of drug consumption levels (Danzon, 2001). One could argue this achieves the access dimension of the trilemma. However, as Danzon (1997) noted, much of increased level of access were from drugs not sold in the US (a indicator of low drug quality). This is because this sort of price regulation has been seen to disproportionately effect higher priced drugs by acting as a price ceiling, since aims to control drug expenditures focus disproportionately on products that have relatively high prices or volumes. Yet these are often the drugs of higher quality.

To summarize, France's price and reimbursement are operated through MPR which directly controls price through a reference system in accordance to certain reference indexes. The UK's price and reimbursement operates no reference pricing and indirect price control through profit controlling or RORR, which does not use a reference system. Ultimately, as Spence (1975) argues, changes in price regulation will alter the incentives to a firm's most efficient position in the market for a given quality. Stringent price controls dampen the present value of the total revenue meaning that there is more risk attached to an investment into higher quality drugs. Consequently, the pursuit of more drug access will likely squander opportunities for the pursuit of higher qualities of drug, thus supporting this notion of a trilemma.

Thereofor, The theory I propose therefore is as follows; To the extent that developing high quality drugs is more expensive than developing lower quality drugs, health care regulatory systems with more direct price controlled systems will have higher levels of lower quality of drugs and health care systems with less direct forms of regulation will have higher levels of higher quality drugs in the health care system. And thus, with the implications of said quality of drugs in mainstream circulation, one could argue this gives us an indication of the efficiency of the health-care system (to be explored in the theoretical implications section).

2.2 THE CAUSAL MECHANISM:

In order to prove this, the thesis develops 4 hypotheses by using insight from two of the previously cited papers; Besanko, Donnenfeld, and White (1988) and from Spence (1975). Besanko, Donnenfeld, and White (1988) start their analysis by looking at two groups of consumers: consumers of type I and consumers of type II. This reflect different amounts willingness to pay, with group I having a higher willingness to pay than that of group II. For a fixed quality, there is a constant unit cost.

Given the existence of market failure in an unregulated market due to quality disproportionately affecting group II (as explored in their paper), the two regulatory remedies are given.

Maximum Price Regulation (MPR) (Direct price control)

This type of regulation sets a price ceiling in market that the firm cannot set above and is most accurately represented by France and by its use of external and internal reference pricing. The intuition from Besanko, Donnenfeld, and White (1988) is as follows. In the unregulated market, the monopolist reduces the quality of group II in order to increase the price it can charge and thus revenue of group I. The intervention of a maximum price through MPR will force the firm to decrease its price from group I, which consequently limits the surplus that it can obtain from this group. Therefor this implies a quality deterioration for higher type buyers. Though reference pricing (what France operates) differs slightly from the price-ceiling mechanism of MPR, this is a significant amount of evidence that supports the idea that reference pricing disproportionately impact drugs that are higher priced drugs (and thus assumed higher quality) more than lower priced and thus acts as ceiling (Carbonari, Bhattacharya and Atella, 2012).

Rate of Return Regulation (RORR) (Less direct price controls)

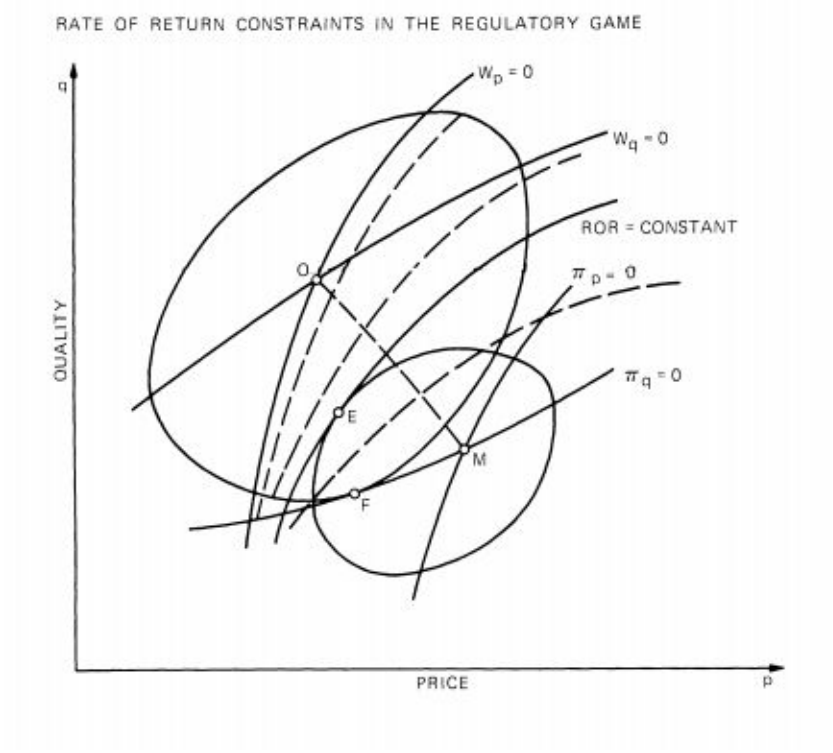
This type of regulation gives the firm the freedom to set the price however the amount of profit that can be made is controlled. This portrays the UK regulatory operation. According to Besanko, Donnenfeld, and White (1988) RORR reduces firms effective cost of capital, which induces the firm to increase its capital stock. In their workings, they are deduce that the more capital intensive the market is, the higher the quality of good offered. The pharmaceutical market is a good example of a capital intensive market due to its high sunk costs so we can assume this holds. Therefore, the increase in the capital stocks will take place by rising the prices of the high quality good. Whilst Besanko, Donnenfeld, and White (1988) also show that increases the quality of low quality too, it creates more of distortion upwards for consumers who higher priced (and thus higher quality) goods.

To compare the effectiveness of each regime, we use three theories. Frisly, using arguments from Alexander and Irwin (1997) MPR is shown to incur more risk to firms. For example, RORR, if a firm's costs rise, prices can rise accordingly and profit will remain the same. However, with MPR regime that reviews its prices very infrequently (according to the International Society for Pharmacoeconomics and Outcomes Research, 2009 this happens every 5 years in France) this clearly would not be allowed to happen. And therefore, because prices are less adjusted each year in comparison constant return rate in RORR, investments are subject to more risk. Consequently, firms under price cap regulation have a greater incentive to lower their costs in order to compensate for this. Therefore, this will ultimately

increase incentives to produce more imitative drugs that have safer investment profiles, which are often those that are of lower quality.

Secondly, using Spence (1975) theory, we can explore this analysis further. Spence says that, whilst both of the regulatory interventions to regulate price will result in input distortions, he argues that RORR is better option given that the regulator has a lack of knowledge about the cost function of the firm. This is because the regulator needs to be able to have the ability to create a price-quality schedule where prices can "rise quickly enough with quality to provide the firm with an incentive to raise quality." (Spence, 1975). Consequently, this is achieved more in RORR because as Spence (1975) states, it implicitly constrains the firm with a positively sloped contract curve for prices and quantities, which is less so in MPR. To illustrate this, he depicts contract curves in a price quality graph as seen in figure 3. The model shows that whilst the RORR position on the diagram is not an optimal position (F), it is in a better position than the fixed priced MPR at E, due to the lack of responsiveness of price to quality increases that MPR implies.

FIGURE 2



Source: Spence (1975)

Finally, Besanko, Donnenfeld, and White (1988) look into the profit surplus that is attributed to each regime. They argue that rate of return constraints force the capital stock up, which will improve quality if quality is capital-intensive. They find that when comparing the profit levels between MPR and RORR on their price quality nexus, MPR profit maximisation for the highest priced goods (and thus highest quality goods) are distorted downwards and under RORR, the profit maximisation for the highest priced (and thus highest quality) goods will be distorted upwards on the price quality nexus.

2.3 HYPOTHESES

And thus, the hypotheses are:

Hypothesis 1: That will be a tighter correlation between quality and price in freer forms of price regulation such as RORR than one that is more directly price controlled such as MPR with fixed prices.

Hypothesis 2: There will be a lower variance of prices and a lower average price in MPR (France) than in RORR (UK)

Hypothesis 3: There will be an even greater disparity between correlation tightness between the regimes at higher quality levels

Consequently,

Hypothesis 4: The average drug quality delivered should be higher under the RORR regime than in the MPR

3. RESEARCH DESIGN

In this section, the thesis outlines the theoretical framework. This will begin by firstly an explanation on the research type and method and how its role as the framework for the investigation. This will then follow by a brief discussion on the dependent variable, price and the independent variables, namely the quality variable, $/QALY and the two regulatory regimes. And lastly, this section will close with the operationalisation of the quality variable along with a look at the confounders, which will then allow for a conceptual model to be introduced.

3.1 RESEARCH TYPE AND METHOD

Following the taxonomy of types of research that Toshkov (2016) depicts, this thesis is a positive, empirically based, and is the explanatory type. As Toshkov (2016) highlights, the main point of exploratory research is to 'identify causal effects and unconver causal processes'. Following from the hypotheses, the main explanatory aim of this thesis is therefore to look into the causal effect between the different price regulation and quality and its effect on prices. Therefore, the two independent variables will be the regulatory regime and quality, and the dependent variable will be the price of the drugs.

The mode of design will be a Large- N cross sectional design: a set of units compared at a single point in time (Toshkov, 2016). The main advantage of this design is that it enables one to identify and estimate weak and heterogeneous causal relations (Toshkov, 2016). This is achieved by looking at a selection of drugs which each have a corresponding quality level and prices. The causal effect can then be established by comparing the distribution of price across the units of quality, between the two regimes.

To ensure causality, this thesis uses the conditioning strategy. The idea of conditioning is premised on the understanding that causality is counterfactual (Toshkov, 2016). This means that to decide if something makes a causal impact, hypothetically we have to create a situation where everything else remains the same, other than the main explanatory variable (ibid, 2016). Whilst this will be discussed at length in the data collection and processing section, the main idea is that the two countries share commonalities in that they are of similar size and design/characteristics of drug market however they differ on the regulatory regimes and thus the pricing its produces.

3.2 KEY INDEPENDENT VARIABLE – $/QALY

The key independent variable is $/QALY. In order to determine value in health, decisions that involve how best to utilise healthcare resources will involve the evaluation costs and outcomes. Whilst there are several metrics that I have could used (survival rates, pressure ulcer incidence or pain-free days), the quality-adjusted life year (QALY) metric is the first that attempts to combine quantity and quality of life into a single measurement.

The basics for determining this value is to have incremental weighting on 'better' states of health. A year of perfect health has a weighting of 1, with death having a weight of 0, with other states somewhere in between this.

For example, suppose a 70 year old man who gets cancer at 74 and dies at 76. Neumann (2018) postulates that health utility weight for a 70 year old is 0.95 and the utility whilst living with cancer is 0.75. Then, beyond 70 years old, this man attains (4 years × 0.95) + (2 years × 0.75) = 5.3 QALYs. Say, a particular drug increases this man's life from 76 to 80, then this drug acrues 10 years × 0.95 = 9.5QALYs (Neumann, 2018).

Though this measure has some important caveats, (which will be discussed in the limitations) QALYs offers unique way to compare between the benefits associated with different drugs in a standardized way, which can be used as a 'common currency' to allow for comparisons across different disease intervention and thus different drugs, which is crucial for my study (Neumann, 2018) . This measure is then divided by its cost to get a cost/effectiveness ratio of the treatment which this study can then use.

3.3 KEY INDEPENDENT VARIABLE - REGULATORY BODIES: UK AND FRANCE

Since the main independent variable is a dummy, two regimes were compared: The RORR (UK) and MPR (France). This reasons for picking these two will be explored in the case selection.

The regulatory body for which pricing and reimbursement policy is dealt with in the UK is called The National Institute for Health and Care Excellence (NICE). As noted before, its Pharmaceutical Price Regulation Scheme (PPRS) controls the profit margins that companies can get from sales in the UK market. Reimbursement is 100%, however the judgment is either positive or negative evaluation, meaning

that if drug does not reach the positive threshold, it will not be allowed to enter the market (Pantelli and Busse, 2016).

In France, price and reimbursement decision are devoid of a QALY threshold. Guidelines are more ambiguous however they are taken from a collection of indicators, with the references system the as the main, acting as the MPR (Pantelli and Busse, 2016). This is conducted through the France's Haute Autorité de Sante (HAS). This is the split into two assessments. Firstly, The SMR (service médical rendu/actual benefit), rates the drug importance from I - III (I being of major importance). This decides justification for reimbursement. Secondly, the ASMR (*amélioration du service médical rendu*, or improvement in actual benefit), is a score from I to V. (I being of major importance) (Kyle and Williams, 2017). Given the referencing pricing structure, the main evaluation is the clinical importance and its relative therapeutic value over existing treatments. Crucially, this distinguishes assessment away from in the UK, given that it looking to categorize the drug into a reimbursement class, whereas in the UK the drug is treated more on an individual level (Pantelli and Busse, 2016)

Once this SMR and ASMR rating has been produced, reimbursement and pricing will then come after. The rates for being reimbursed range between 35-65%, while some more important drugs will be 100% covered. The majority are in 35% categorisation. Generics are usually subjected to a 40% price cap. All in all the final price will be represented by factors such as the ASMR, external and internal referencing pricing, and volume pricing (Pantelli and Busse, 2016).

3.4 KEY DEPENDENT VARIABLE: PRICE

Price of drugs will be taken as the dependent variable. This is because we are looking at the extent to which price is affected by quality and regulatory body. The suspected differing levels in correlation tightness when using the regulatory dummy variable will help establish this. One established, this will help to give us an indication of whether there is a difference in price responsiveness between each market, as theorised by Spence (1975).

This data was collected from price databases from each countries public data sources. UK price data was obtained from the NICE economic evaluations website and French price data was obtained from the Base Donnees Publique Medicaments website (Their government's public data access portal). These track prices on a monthly basis. Price was changed to price per milligram per tablet, in order to control for

difference in units and and concentration of tabet. Price was also changed into log format. The reason for the natural logarithm is to increase validity of the results by reducing the influence of extreme data points. This is due to the fact that this method will reduce absolute rates of price change to relative rates of change. For example, the distance between 10 and 20 will be treated the same as 20 to 40. This is necessary for my study given the fact that my price range is 0.0002 to 273.

3.5 CONFOUNDERS AND COVARIATES

As Toshkov (2016) states, A confounder is is a 'lurking' variable which interacts and influences both the dependent and independent variable and thus ultimately reduces the validity of the studys. Given the dependent variable is a dummy variable and also the dominance of the regulator in price setting, there seems to be few other factors that could influence different price (other than quality). Other factors include the level of competition of that a particular drug has and the longevity of a drugs existence in the market. These will addressed in the validity section.

Covariates may affect the outcome in a study (Toschov, 2016**)**. For example, the level of quality in the independent variable is inferred by the cost effectiveness investigations that are produced for the drugs. However, this is a simple metric and it isn't the only way to measure drug quality. Consequently, there may be other measures may that look at other factors not accounted for by this metric, thus obvescuting the true quality value of the drug and the outcome. In addition, if investigated improperly the metric may convolute the quality true once more. Both of these issues will be addressed in the validity section.

3.6 OPERATIONALISATION

Operationalisation means transforming abstract concepts into practical indicators that can be identified, compared and contrasted (Toshkov, 2016). Given the simplicity of operationalisation of regulatory body (a dummy variable) and price is (prices of the drugs simply taking from the government databases), an overview how this thesis operationalised quality is shown below.

3.6.1 OPERATIONALIZING QUALITY

The source of drug quality data for these two groups comes from the Cost Effectiveness Analysis Registry found on Tufts Medical Centre website. This is a service funded by Bill and Melinda Gates foundation that operates as a database for papers that investigate cost effectiveness of active ingredients using keywords related to to cost-effectiveness. The active ingredient is the chemical compound that makes up a

drug's molecular base. Searching for these papers by keywords related to to cost-effectiveness across numerous other sites, TUFTS staff then manually adds papers that are relevant to the database, whilst also taking note of the population that it was tested on, the drug name, any comparator drugs used in the investigation he QALYs gained through the treatment, and finally an a cost-effectiveness ratio value ($/QALY). Each study in the dataset computes the cost-effectiveness of one or more active ingredient and its effect on a certain medical intervention in incremental costs (converted to 2015 US$) divided by the incremental health benefits quantified in terms of QALYs to create a $/QALY measure that I use. When multiple investigations were carried out on a certain active ingredient, this thesis uses the average of the $/QALY outcomes. The Tufts database has the widest coverage for drug cost effectiveness investigations that I was able to access, with data as far stretched back as to 1976.

The way to understand the $/QALY metric is as follows; the lower the $/QALY measure, the more QALY years can be obtained. And therefore the way this thesis has interpreted this is that the lower the $/QALY measure, the better the quality. Whilst there has been some criticism using the QALY design (discussed in internal validity) it is the only method of its kind that allows the researcher to measure a very detailed indicator of effectiveness which can be compared. This thesis argues that it therefore the most accurate way of assessing its quality from a societal perspective. Using a similar technique to Carbonari, Bhattacharya and Atella's we will invert the $/QALY measure in the regression for simplicity's sake and call it Quality Indicator (QI). An example of how this database works is shown below.

TABLE 1:

Article ID	Publication Year	US$/QALY *	Ratio Description	Impact
2017-01-23201	2017	25000	Lenvatinib VERSUS Sorafenib IN Specific disease- Thyroid cancer; Age- Adult; Gender- Both; Country- United States; Other- Radioiodine refractory differentiated thyroid cancer progressed within the last 14 months..	NE
2017-01-23201	2017	41000	Lenvatinib VERSUS Placebo IN	NE

			Specific disease- Thyroid cancer; Age- Adult; Gender- Both; Country- United States; Other- Radioiodine refractory differentiated thyroid cancer progressed within the last 14 months..	

Source: Cost Effectiveness Analysis Registry found on Tufts Medical Centre website.

Unfortunately, the majority of these investigations were conducted with the comparison being another active ingredient, as we can see with the first row of Table 1. Clearly, for validity reasons, the $/QALY result from Lenvatinib (an active ingredient) versus Sorafenib (an active ingredient) cannot be used to compare across another set of drugs. However, a small amount of the investigations are conducted with a placebo or without a comparator, as portrayed by the second row in 'Lenvatinib VERSUS Placebo'. This can therefore act as a control throughout all the investigations, and thus allows for its use. For every one that had this in their investigation that was possible to find, this thesis then compiled an excel sheet with its $/QALY. Once this was gathered, a search was conducted to find whether the active ingredient was present in either market. Once it be could identified whether it was in one or both of the markets, a second excel sheet was made that detailed the active ingredients and its corresponding brand drugs, with its price per milligram in the french market and the UK market (and then converted to US$). A small section of the sheet can be seen here.

TABLE 2

ACTIVE INGREDIENT - Drug	$/QALY	UK Price per mg	French Price per mg
ETANERCEPT Enbrel	33500	4.8	4.4
ETANERCEPT Erelzie	33500	4.34	3.5
ETANERCEPT Benepali	33500	4.43	3.47
ADALIMUMAB Humira	28000	11.91	11.32
DULOXETINE Krka	46000	0.0091	N/A
AFLIBERCEPT Zaltrap	190000	13.77	20.46

DULOXETINE Aspire	46000	N/A	0.045
ERLONITIB Tarceva	72000	0.48	0.58
RANIBIZUMAB Lucentis	133500	74.36	88.6
GEFITINIB Iressa	22000	0.315	0.3901
SERTRALINE Zoloft	460000	0.0069	N/A

3.7 CONCEPTUAL MODEL

A model can therefore be constructed from the theoretical framework as already described:

$$Price = \beta ETA0 + \beta ETA1Quality + \beta 2UKi + \beta ETA3Interaction\ Effect\ of\ quality\ on\ UKi + \beta ETA4Genericsi + \beta ETA5Orphani + \beta ETA6Orhpan\ generic + \varepsilon i$$

As stated before, the dependant variable is price and this will be in log format. QI (Quality indicator) is one of the independent variable. This is the inverse $/QALY data. UKi is a dummy variable which equals to 1 if the price is referring to an UK brand name and 0 if its French brand name in order to capture the effect of second independent variable, the regulatory regime. $\beta 3Interaction\ Effect\ of\ quality\ on\ UK$ is a dummy 'treatment' variable (again UK being 1 if its a UK brand and 0 if its French) which is interaction term that is used in order tests for difference in correlation across the two countries. εi is an iid zero-mean error term. In order for to achieve robustness, this thesis controlled for the existence of generics and how this may affect price distributions, which is a dummy. However, they are excluded from the conceptual model for the following two reasons. First, other than my own speculation, there is no theoretically grounded reason to expect that, at a given quality, there would be independent effects from generics. Second, the degrees of freedom decrease when including more variables to the model. The association between the two main variables of interest ($\beta 1Quality$ and $\beta 3Interaction\ Effect\ of\ quality\ on\ UKi$) will therefore be used when this model is modified for regression analysis in order to more accurately determine the true causal strength and path.

4. DATA COLLECTION AND PROCESSING

Now that the model had been established and how its fits in the context of research design, what follows is the way in which the data was collected and processed. This will begin with the reasoning for the relevant population and how they were selected it, along with a check for validity of the data collection. Finally, an examination of the descriptive statistics will end this section.

4.1 RELEVANT POPULATION AND UNIT OF ANALYSIS

The relevant population was a regime under RORR (UK) and a regime under MPR (France). Why this thesis chose just the UK and France were twofold. Firstly, in order to attempt to prove the theories posisted by Spence (1975) and Besanko, Donnenfeld, and White (1988), countries had to a operate free price RORR regulation and fixed price MPR regulation. Most of western world operated a variant of MPR, with the UK the only in europe operating RORR (Pantelli and Busse, 2016). This therefor narrowed down my options to just to the UK on the RORR side. I could have looked at more fixed price MPR countries however I feared this would jeopardize my conditioning of confounders. Therefor, the UK became my unit of analysis for RORR and for MPR was France.

Secondly, there were data issues. Most of the papers published that looked at the similar areas the economics pharmaceutical price regulation used the MIDAS dataset which was not possible to get a hold of as, after emailing them, they said that the datasets cost around $10,000 dollars per data set. Because of the fact that this MIDAS was frequently used, it therefore became unclear what data was and wasn't available to me. After continuously searching and sending off numerous emails what was clear was this sort of data were either not published by governmental agencies at all, had strict access to which I wasn't allowed, or was very hard to find. In the end, data availability for european countries amounted to around 4 or 5 countries, with the UK and France being apart of that. The unit of analysis are the drugs

themselves. The reason being is that they are the main explanatory variable and at an individual level it is here where the disparities between price lay.

4.2 CASE SELECTION

Case selection for the individual drugs was from the TUFTs Cost effectiveness website. Toshkov (2016) distinguishes large -N as a case selection defined by a number of observations on one unit of interest. Given that case selection is the fundamental blueprint for the methodology, its has heavy weighting on the validity of the results and thus the implications derived. Therefor, Toschov outlines key points in order to maintain a high level validity when selecting cases. One of points is that cases must be selected at random. Unfortunately, there were a few reasons why this could not be held up in this study. Firstly, as stated previously, the main independent variable ($/QALY) was often produced as a result as comparison between two active ingredients, which meant a large of investigations search for could not be used. Secondly, there was incomplete coverage of all drugs. Thirdly, often the active ingredient $QALY could be found however drugs which corresponded to that active ingredient were not in operation either the French or UK market. Consequently, as a result of these factors it was impossible to retain a sample large enough with whilst also using random sampling. This meant that case selection had to be conducted with using sample of convenience. Nevertheless, the sample distribution was very heterogeneous with a $/QALY range from 10,000 to 460,000 sampled.

Secondly, Toshkov (2016) goes on to say another way to maintain a high level validity is by having at least 26 observation on the main explanatory variable. This thesis meets and exceed this criteria by having 256 observations in the overall sample.

4.3 VALIDITY

Since it is expected that the price regulatory regimes explains to a large degree the price, validity and remains intact so long as a large number of observation prove a statistical significance. However, this does not necessarily provide for certain causal inference. Toshkov (2016) explains that internal validity is related to how many confounding variables you have in your experiment. The idea of confounding variables are that they interfere with the causal mechanism that is trying to be established and thus obfuscate the true strength of its relationship. Therefore, if one is trying to establish a causal impact, hypothetically we have to create a situation where everything else remains the same, other than the main

explanatory variable (Toshkov 2016). Whilst this is hard to create in an absolute sense, my conditioning process in my case selection has arguably got me as close as possible to this. Conditioning is a process of blocking the effect of a possible confounding variable by having it constant between all variables other than the explanatory one. Therefore in choosing my cases to represent the regulatory regimes, one of my justifications was that they share commonalities in many more ways than others countries. The main and arguably the most important examples of this are that they are very similar in terms of population sizes and GDP per capita. (Data.worldbank.org, 2018). Consequently, they have similar size of drug market. This is vital because drug companies can be incentivised to lower price if they feel that the population size/incomes levels will sufficiently raise demand in order to maintain the same absolute profit level. Having these factors as similar as possible between the countries will increase the chances of eradicating this confounder.

The other examples of similarities between France and the UK are at they both operated a tax funded healthcare system and each have had an early advice program on HTA with pertinent guidance published (The Economist Intelligence Unit, 2016) Whilst these last two examples may have less magnitude as a confounder, the combination of this on top of the first two should ensure a internally causal inference in the observational large N-design.

4.4 EXTERNAL VALIDITY

As stated in the covariate section, the way the quality indicator ($/QALY) is conducted is crucial to the external validity of study. This study holds little credibility if the measurements are imprecise and lacking methodological rigour. Therefor, the standard of the investigation must be kept high in order for this to remain in tact. Each investigation has a rating by experts in the field rating from 1 (lowest quality) to 7 (highest quality). As it states on the TUFTS website for its database, scores will reflect whether authors have achieved the following (in order of importance): i) have calculated the $/QALY the correct way, ii) whether the authors have correctly characterised the uncertainty of their results, iii) whether the authors have detailed what health economics assumptions they are using when conducting their investigations (discount rate and time horizon for example) iv) whether the authors have used the right utility weights (Healtheconomics.tuftsmedicalcenter.org, 2018). Therefore, in order to remain externally valid, scores with a 3.5 or above were included in the $/QALY data for this study.

4.5 DESCRIPTIVE STATISTICS

Table 1 details the descriptive statistics. The first set of rows details the amount of drugs in operating in each market and in total, along with prices and the quality indicators. In total the size of the dataset has 258 observations, with 136 operating in the UK market and 122 in the French market. The UK has more variation in drugs, hence why they have populate the dataset more.

TABLE 3:

Variable	**Mean**	**SD**	**Min**	**Max**
p	6.48	26.52	0.0002	274
log(p)	−2.084	3.194	−7.824	5.613
$/QALY	56,586	90,993	9850	460,000
QI	0.000204	0.0000279	2.17E-06	0.0001015

5. DATA ANALYSIS AND EMPIRICAL RESULTS

According to our theoretical model outlined by Spence (1975), under a price setting MPR regime such as France we would expect a lower price to quality responsiveness compared to a RORR as in the UK. In addition, according to Besanko, Donnenfeld, and White's (1988) theory at the upper echelons of the quality spectrum, the price qualtiy correlation should be distorted downwards for MPR and distorted upwards for RORR. We test these predictions by processing the data into models outlined previously and conducting a multivariate regression analysis on these.

Regression analysis is a powerful statistical tool that attempts the estimate the effect of unit of change in the dependent variable on units of change in the independent variable (Angrist and Pischke, 2015). If found, this therefore implies a relationship between the two which thus offers ways to interpret in detail causal mechanisms. This thesis uses the Ordinary Least Squares (OLS) variant of regression analysis. The reasons for this are because the main aim of OLS is get as close an line to fits the data, which is clearly ideal for the hypothesis that we are trying to prove. This is achieved through minimizing the total squared residuals of the data (ibid, 2015)

5.1 MAIN REGRESSION ANALYSIS: TESTING CORRELATION BETWEEN QUALITY AND PRICE

To do this we use the following OLS regression in order to establish and identify the coefficients from the model.

$$log(pi) = \gamma 0 + \gamma 1QIi + \gamma 2UKi + \gamma 3UKQIi + \varepsilon i$$

Where:
$\gamma 0$ is the constant/residual.

$\gamma 1$ measures the coefficient for quality.

$\gamma 2$ is a dummy variable which distinguishes the UK price variable from the French price variable.

$\gamma 3$ indicates the interaction between UK and its effect on quality.

εi is the error term.

The logic of this equation in determining its role in proving the hypothesis can be easily explained. Using the interpretation of results as described by Carbonari, Bhattacharya and Atella (2012), the ($\gamma 1 + \gamma 3$) value measures influence of that quality will have on drug price in the UK. If the ($\gamma 1 + \gamma 3$) parameter is greater than 0 then this will confirm that there is a positive correlation between price and quality existing in the UK. The $\gamma 3$ parameter says whether there will be a difference in the effect that quality has on drug prices between the UK and France. Therefor, if $\gamma 3$ parameter is greater than 0 then this will indicate that there is a stronger correlation in the UK than in France. (Carbonari, Bhattacharya and Atella, 2012) And thus, if both of these indicators are greater than 0 we can confirm hypothesis 1.

Results are shown in table 1. In the regression using the whole sample we can see numerous results. Firstly, a positive relationship between quality and price emerges for UK (($\gamma 1+\gamma 3$) > 0 and statistically significant at 0.05). Seconly, $\gamma 3$ parameter confirms that UK has more of a tighter correlation than France ($\gamma 3 > 0$ and significant at 0.05). This consequently confirms hypothesis 1, that there is a higher correlation between quality and price in RORR than one than in MPR.

TABLE 4

Variable	**Overall Sample**	**High Quality (Under the Median)**	**Low Quality (Over the Median)**
QI	-24281.61*	−9646.377	124434.8
US	−0.207	−2.05	0.017
USQI	32644.28**	40391.97*	33548.8**
Test H0: QI + USQI= 0	F = 4.35 p = .051	F = 2.35p = .082	F = 4.37p = .05
N	254	141	121
Hypothesis 1	Corroborated	Corroborated	Partially Corroborated

(a QI of 31000 was included in both high and low quality)

*$p < .1$,

**$p < .05$.

5.2 SECONDARY REGRESSION ANALYSIS: TESTING HIGH AND LOW QUALITY LEVELS

In order to look more specifically at the different quality levels, this thesis will separate the drugs into a quality categorization of low and high. This is achieved by including intro a split in the $/QALY sample above and below the median which is 31,000. This is primarily done in order to look into Besanko, Donnenfeld, and White (1988) hypothesis but this will also give us a further indication into the type of relationship that may exist within these categories, ie; whether the correlation signs change when there is this separation.

From the results, we can see that at higher quality levels, there are the same sign directions as before but also an even larger value for $\gamma 3$ showing that the correlation disparity is even higher when isolating higher quality. This therefore confirms hypothesis 3 in regard to Besanko, Donnenfeld, and White's (1988) theory arguing that at higher levels of quality, there exists a greater disparity in quality distortion offered.

5.3 THIRD REGRESSION ANALYSIS: ROBUSTNESS CHECKS

A check robustness was undertaken so that one may test the validity and reliability of the coefficient of the interacted term $\gamma 3$ and the quality term $\gamma 1$. The idea of doing this is to test to see whether generics are obfuscating the true result. It could be possible that results already found are a facade masking the differences between the UK and France in sales of lower priced generic versions. If the results do not change after conducting these, the robustness test will have been passed and it is therefore arguably a stronger and more valid relationship and thus will confirm whether the causal relationship has predictive power or not.

However, this is more than just a robustness test. Countries has different viewpoints when it comes to policy of pricing different drug types. Given that generics are created as a cheaper alternative to the brand, the policy choices that result often vary significantly and may give a more deeper insight into the regulatory decisions

Looking at table 3, we can observe that the generics dummy does not change the results of our estimates since the ($\gamma 1+\gamma 3$) > 0 and it is statistically significant at 0.05), thus confirming the good predictive power of the theoretical model.

TABLE 5

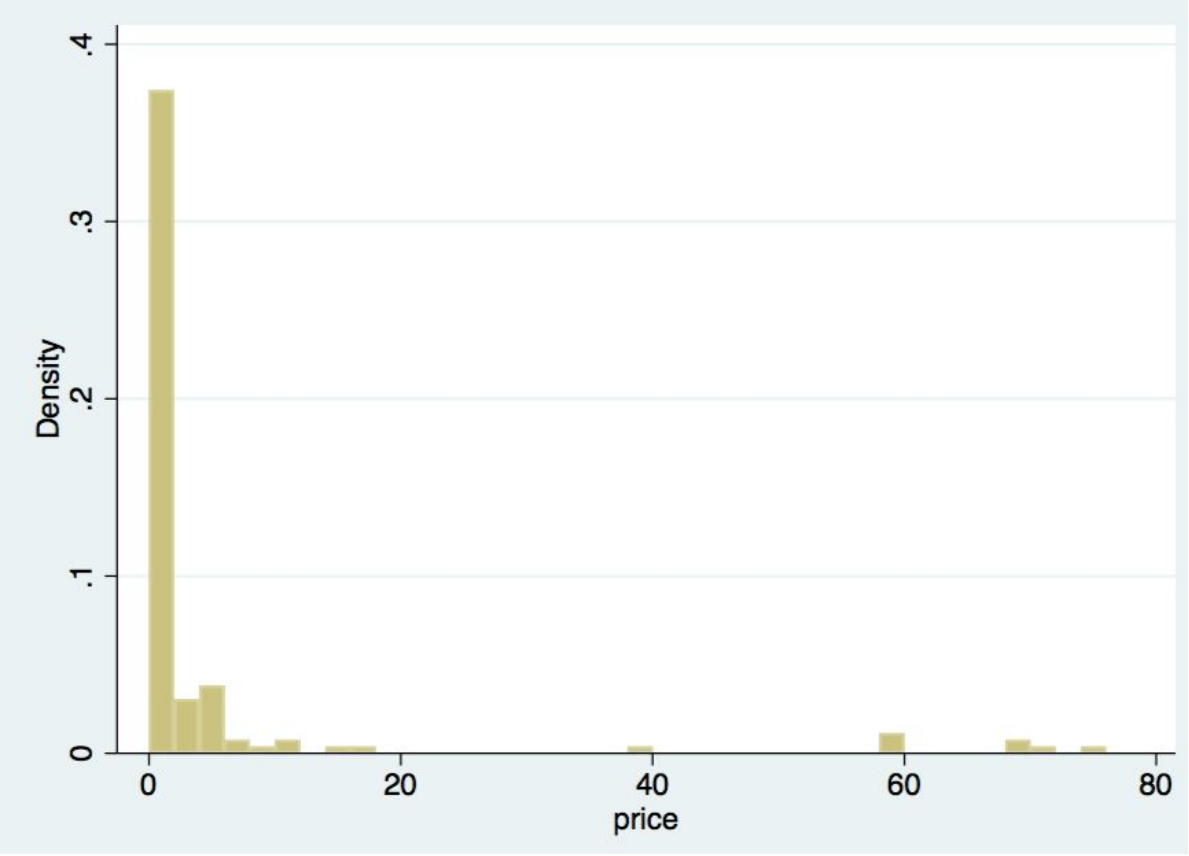
Variable	**Generic**
QI	-63256*
US	−0.47
USQI	78207*
Test H0: QI + USQI= 0	F = 3.71 p = .092
N	92

5.4 TESTING PRICE VARIABILITY AND AVERAGE PRICE

According to our theoretical model and hypothesis, we should expect a lower price variability in MPR than in RORR. This thesis conducts this prediction by compiling the two data sets and looking at the density plots of the two price distributions per mg. The results shown below in figure 3 and 4

FIGURE 3: Densities Plots of the Price Distributions: Tufts Sample (i)

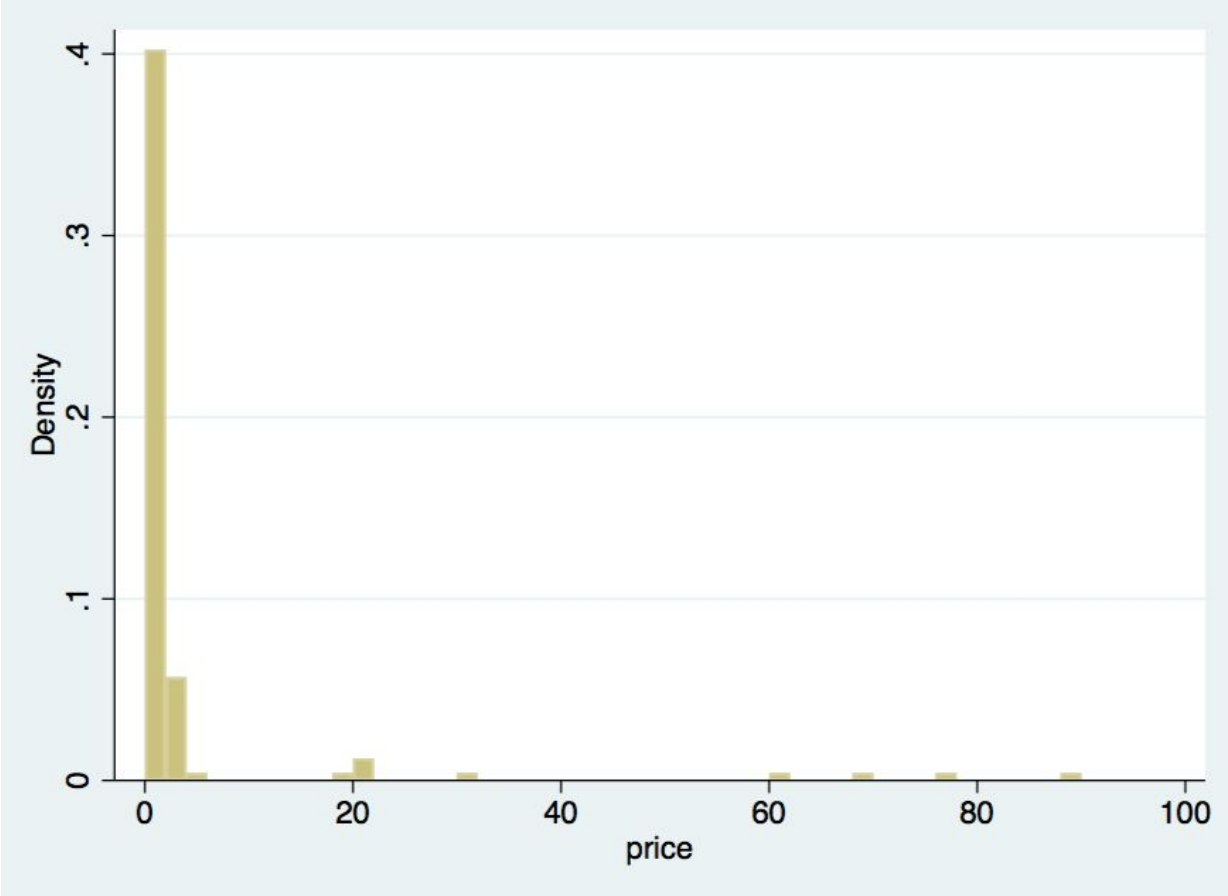
UK



Source: Stata graph from price data collection from the French and UK government websites

FIGURE 4

ii) France



Source: Stata graph from price data collection from the French and UK government websites

As predicted, the density plots show that MPR prices (France) have a lower price variability than RORR (UK) price per milligram. Whilst its only slight, it's enough to confirm hypothesis 2. The slightness also implicitly supports the arguments made by Carbonari, Bhattacharya and Atella (2012) given that RORR is

a price regulation that is not as extensive as what is used US (what they examined), thus less of a disparity between the two regimes investigated in this study is expected. Furthermore, the UK also had a higher average price per milligram, with the UK's RORR price average being 7.20 as compared to French average price being 5.40. This therefor also can confirm hypothesis 3; that there exists higher average prices in the UK as compared to France.

6. DISCUSSIONS AND CONCLUSION

The purpose of this study is to gain more insight into the interaction between of price controlled regimes its effect on drug quality. In this part this thesis presents an interpretation on the results and discuss the implications and limiting of the findings.

6.1 THEORETICAL IMPLICATIONS

With respect the confirming hypothesis 1, 2 and 3, the implication of this are as follows. Vogel (2004) explains that the firm's choice over whether to target research and development into higher quality, more innovative drugs rather than imitative products will involve a calculation of expected revenues and costs. This is broken down by on the one hand, the fact that higher quality of drugs will likely garner higher prices than less quality drugs and thus ultimately more revenue, at a given quantity. At the same time, investing in higher quality product will likely mean more risks and cost attached to that investment due the hat safety profile that these drugs being subject, meaning longer and larger clinical trials in order to ensure effectiveness of the drug (Kessler, 2014)

Ultimately, the firm will target higher quality drugs that inevitably mean increase risk of unsuccessful R&D if the calculated revenues are enough to outweigh this (Vogel, 2004). Therefor, to the degree that producing a higher quality of drug will cost more and thus will be priced higher than that of a lower quality counterpart, this reduced correlation and less price dispersion that is witnessed in MPR as compared to RORR essentially decreases and potentially outweighs the incentives to create a higher quality of drug and increases their risk profiles, implying that diversion into production of lower quality will arise (Carbonari, Bhattacharya and Atella, 2012).

The implications if this is found can be severe. To put into perspective the humanitarian impact of less circulation drugs of higher quality, Lichtenberg (2004) establishes a causal link between the launch of NCE (New Chemical Entities) and the rates of mortality, due to benefit that these drugs often can hold for

human health and life. NCE are often the most innovative and highest quality of drug. His results prove not only there there is indeed a link and that between launches of NCEs and probability of survival, but also he was to calculate the cost to life from launch delays of said drugs, to which he estimated that a launch lag of 5 years could cost as much as a 15 week reduction in life expectancy. Clearly this will have huge ramifications on social welfare.

6.2 LIMITATIONS AND FURTHER RESEARCH

The current study has a number of limitations that also point toward directions for future research. One of the most important limitations stems from infallibility of quality measurement, the QALY. Firstly, the main criticism against this measurement is over the inherent subjectivity and thus bias of the utility weights that factor into the QALY calculation. In order to calculate this utility weight, experts will often ask questions which are formulated in a way that Ubel (2000) argues tends be biased toward interventions that help individuals most in need of care, irrespective of the efficiency of the drug. Secondly, concerns have been raised over the idea that QALYs also discriminate on grounds of how old you are and if you are disabled. The intuition behind this is that the metrics for QALY calculation favours those who are younger and more healthy since that have more potential QALYs to gain. Thirdly, this not only creates disputes in how to conduct the research but also who to ask. In relation to this point, concerns have been raised over the fact that it is often those who are sick that are interviewed. Some argue these interviews should reflect the preferences of whole of society, as the cost to these reimbursing these drugs are impacted by everyone (Neumann and Cohen, 2018).

Using a more objective methodology by combining other drug quality metrics and creating an index may strengthen this area, however, it's unclear to what degree this will benefit the research. Since one must appreciate is that without QALYs, the valuation of drugs will still have difficult trade-offs (Neumann and Cohen, 2018). Clearly, the preferences of all of society should be equally weighted given that it is designed in that way to benefit all. And yet, finite resources will also mean that that this is underachieved. In addition, there are those would are either too young, too old or too impaired to understand or be able to answer the questions. In that case should we used proxies? And if so, what proxies? The point here is that these trade off will inevitably emerge regardless of which was these investigation are conducted (ibid 2018).

Another limitation was to do with the restriction of what this studyhad to use form the TUFTS database. Unfortunately, there were quite a few active ingredients for which had not been investigated at all. Often these was new drugs, however there were some very high priced prolific drugs which were missing. The other problem was a substantial amount of the data was an investigation vs another active ingredient and had not been investigated with ‘no comparator’ or ‘placebo’. Given my external validity fulfilments, I was only going to look at those ‘no comparator’ or ‘placebo’ in order to control for confounders. Consequently, there are many other important drugs missing. Certainly, this data would have enriched my regression analysis but I do not believe this would have altered the results in a profound way, given the extent of what a could find was was many times larger than what I couldn't find.

Furthermore, another limitation was the averaging of $/QALY data. As stated previously, when an active ingredient had more than one investigation on the database, I averaged the outcome. Whilst this may seem like a practical idea, questions could be raised over the validity of using this method when the $/QALYs investigations have a have a large range.

Going forward for future research, using a more objective methodology by combining other drug quality metrics and creating an index in order to reduce both the averaging and QALY issues may strengthen this for future research. However, one could argue it's unclear to what degree this will benefit the research given the inherent trade-offs that comes with attempting to value health.

There a number of possible future research suggestions outside of my direct limitation. Other scholars could build on this study by looking into the market diffusion (sales revenue over 6 years from market inception say) of certain qualities of drugs and looking to see if this has an effect between regulatory regimes. Furthermore, a look into whether the structure of the HTA (whether it be centralised or decentralised) and to see whether this had an impact on the uptake of higher/lower drugs could be further explored with future research

6.3 CONCLUSIONS

In this study, this thesis have developed a theoretical framework and methodology to evaluate the impact of two different types of drug regulation, namely that of RORR and MPR and drug quality on drug prices. From this two theoretical predictions stem. The first is that in the MPR regime, there should a lower

average quality of drug. The second is that under a MPR regime, there is a decrease in the disparity in prices between the low and high quality drug.

From this, we find that firstly, there is a tighter correlation between prices of pharmaceuticals in quality in the UK as compared to France. Secondly, we find that price variability is less under MPR in France. Thirdly, find that at the highest quality of drug, the disparity in correlation levels is even greater. This confirms hypothesis 1, 2 3 stemming from the works of Besanko, Donnenfeld, and White, and distortion theory)

In conclusion therefore, there are a few points to be raised. Clearly from the theory side, what we have seen from the theoretical implications is that there is incentive structure to make the firm more inclined to produce a lower quality of drug. In reality however, we can only that prove this correlation and incentive structure exists. This theoretical argument is underplayed by the fact that a considerable amount of the drugs that I studied that were produced under British regulation by an British company ended up in the French market and also in other markets around the world. This is mainly due to Ramsey pricing, where, in the presence of high fixed costs and international markets that act together as opposed to being isolated, firms will engage in price discrimination and accept lower prices in the stringent markets in order to reduce the risk of not recovering the fixed costs (Bishop and Walker, 2010). Because countries such as the US are almost entirely free price based, and because the US represents an overwhelming percentage of total global pharmaceutical sales at 49% ((EFPIA, 2017), they can easily recoup this lost revenue charging higher prices in. Therefor, whilst the theory is sound, it is clear that given these factors, the level of drug efficacy is equalized between the two regimes

Whilst we are unable test this prediction with our data, there is reason to believe that other papers support it. Carbonari, Bhattacharya and Atella (2012) note that european market diffusion for drugs first enters markets where price regulation is less stringent (UK) than in countries with more stringent price regulation (France, Italy and Spain). This lag isnt due to bureaucratic red tape, but instead due to the pharmaceutical company choosing to do so (ibid, 2012). This is also evidenced by an interview with the ex chairman of Pfizer when discussing the French price regulatory system who stated ‘if the government continues to put pressure on prices, there will be no more [new drugs]’ (Danzon, 1997).

The irony here is that US are often criticized for their inordinately high prices, which many have chastised as a broken system that undermines the needs of its people, yet it undoubtedly it this system that is holding other countries pharmaceutical policy afloat too. However, just last month, the Trump

administration detailed a 50 point plan for a reform in what, if passed through congress, has been described as the “most sweeping action in history to lower the price of prescription drugs for the American people.’’(Colvin and Perrone, 2018). What the future holds is anyone's guess, however if the administration that was to follow on the repercussions on this market, on the policy that deal with this market, and effect on patients will be severe.

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