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Working paper

CESifo Working Papers

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CESIFO WORKING PAPER NO. 5190
CATEGORY 3: SOCIAL PROTECTION
JANUARY 2015

CESifo *Working Paper No. 5190*

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Abstract

In the European Union, medicines are regulated products subject to both single market (e.g., regional exhaustion of property rights) and country specific health care regulations (e.g., medicines pricing). This gives rise to parallel trade (PT), a phenomenon that takes place when a patented product is diverted from the official distribution chain of one country to another parallel one where it competes with the official distribution chain. We argue that parallel trade of heavily regulated medicines conflicts with traditional sources of arbitrage (e.g., price and income differences) and instead is a form of 'regulatory arbitrage' that does not produce equivalent welfare effects. We draw upon a unique dataset that contains records of both origin and destination flows of parallel imported medicines to the Netherlands, for one therapeutic group (statins) that accounted for 5% of the market at the time of study and faced no generic competition. Our findings suggest that after controlling for country of origin (source) effects, parallel trade flows are primarily determined by medicines distribution chain regulation, and not by price differences in line with the hypothesis of 'regulatory arbitrage'.

JEL-Code: I180, L510.

Keywords: parallel trade, regulatory arbitrage, pharmaceuticals, supply chain.

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1. Introduction

The consolidation of a single European market unveiled many opportunities for different types of arbitrage, including that of regulated markets and parallel trade. Parallel trade takes place when a patented product is diverted from the official distribution chain in one country to another parallel chain in another European country where it competes with the official distribution chain. We argue that this does not immediately result in natural effects of arbitrage (e.g., price equalisation) when prices and the distribution chain is regulated, but instead gives rise to a form of regulatory arbitrage. Medicines are products under protection of intellectual property rights (IPR) but subject to European-wide (as opposed to country wide) exhaustion of such property rights after first sale in any European member state. Hence, IPR do not confer legitimate control of the product upon sale in one country, and thus if price differences arise, a parallel distribution chain may be developed in response. A number of decisions adopted by the European Court of Justice have further encouraged distributors to engage in parallel trade (Barfield and Groombridge, 1998).

In this paper, we attempt to examine whether parallel trade (PT) flows qualifies as a common type of arbitrage (Malueg and Schwartz, 1994; Richardson 2002, Jelovac and Borodoy, 2005 and Peccorino, 2002) or instead, as regulatory arbitrage. More specifically, do arbitrageurs (parallel traders) transfer medicines from Spain to the Netherlands because Spain has a lower relative income (and hence lower prices) or, because Spain has a tighter distributor margin regulation that makes the price difference worth the risk of engaging in parallel trade? We argue that for heavily regulated products, parallel trade flows might instead be induced by cross-country regulatory differences (regulatory competition) that reflect different and unobservable institutional environments including country specific lobbying and pressure group capacities (Grossman and Lai, 2006). Alternatively, another competing explanation lies in the varying degree of competition and regulation of the supply chain which can explain the persistence of parallel trade flows over time. The latter has not received attention in the empirical literature despite parallel trade being an activity that takes place at the distribution level. Policy relevance of this phenomenon is important even outside of Europe. It was estimated that 8% of Canadian medicines sales in 2004 and 0.5% of the US market (Toumi, 2009) were parallel traded medicines.

Some prior studies on parallel trade have analysed country-specific flows, but have not taken into account the presence of generic drug penetration, origin of trade flows as well as supply chain competition and reimbursement regulation both in importing and exporting countries. Furthermore, previous literature remains inconclusive about the capacity of parallel trade to increase the country's welfare (Mauleg and Schwartz, 1994, Richardson, 2002). In other words, the normative implications for welfare of increasing parallel trade are ambiguous and extremely dependent on the benefits of a unitary price as compared to price discrimination equilibrium. However, to date existing studies have failed to take into account the *bilateral* nature of parallel trade flows.

This paper fills this gap by using a unique dataset which contains a rich set of controls for the regulation of the distribution chain. This is especially important given that identifying bilateral trade flows allows us to ascertain the magnitude of the effect of economic arbitrage (price differences between country of origin and destination) *vis a vis* distribution chain regulatory differences. Furthermore, given that changes in the regulation of supply changes in exporting countries are largely exogenous, it is possible to measure whether a change in the regulated wholesale mark up does indeed affect the development of parallel trade. The paper takes advantage of a dataset that contains records of parallel imports from several European countries to the Netherlands, the only country where the country of origin could be identified in our database. We use data on parallel trade for cholesterol drugs from the 8 countries in Europe (Belgium, France, Germany, Greece, Italy, Portugal, Spain, and the UK) which distributed 95% of all observable parallel traded statins to the Netherlands across 24 quarters (1997-2002).

To avoid limitations of previous studies we rely on data from one single therapeutic group before it exhibited generic entry and we use data for a rich set of controls that measure the competition of the distribution chain and its reimbursement. We use an augmented gravity model specification that includes information on the heterogeneity of the supply chain regulation (more specifically retail and wholesale regulation incentives the on proliferation of parallel trade). Proprietary data are used and we perform several specifications that range from pooled regression to panel data analysis to capture part of the unobserved heterogeneity in measuring specific parallel trade determinants. We estimate parallel-traded sales in the Netherlands for a given drug from a given country in a given quarter. Parallel-traded sales are a function of relative price, the exchange rate (which is a variable separate from relative price), distance, and three different transformations of GDP (difference in GDP per capita, sum of GDP, relative GDP).

Our results report evidence that medicines' parallel trade is an economic activity driven by differences in prices. However, the entry or penetration in one market is contingent on the regulation of the distribution chain, and more specifically, we find that exporting market size and the regulation in drug distribution margins triggers the development of parallel trade, consistent with the hypothesis of regulatory arbitrage.

Section 2 provides some background and the theoretical underpinnings of parallel trade and arbitrage in the context of a gravity model. Section 3 presents the methodology, data sources and the approach followed by the analysis, while section 4 presents results and discusses policy implications. Finally, section 5 outlines the main conclusions.

2. Background

2.1. Conceptual considerations

Although parallel trade is envisioned as a specific form of arbitrage, predictions of arbitrage theory do not seem to be backed by empirical evidence (Kanavos and Costa-Font, 2005). One explanation could be the creation of some accommodative market equilibrium by drug companies (Ganslandt and Maskus, 2004), whilst alternative explanations rest on the incentives resulting from country-specific regulations affecting both the probability of undertaking parallel trade and the emergence of long-lasting price differences across countries. In pharmaceuticals, regulatory interventions at national level maintain price differences over time (Kanavos and Costa-Font, 2005). Therefore, prices do not necessarily reflect differences in purchasing power across countries as in other products. Hence, medicine flows across countries might be highly correlated with countries regulation.

Similarly, for arbitrage to take place, the market size of the source country needs to be of a certain size. The larger a particular market, the more attractive it is for both pharmaceutical manufacturers and parallel distributors to undertake production and trade respectively. Most European countries, whether parallel importing or parallel exporting, operate with a single payer (national health insurance) who negotiates rates and purchases drugs on behalf of the health care system· Assuming that payers regulate prices of pharmaceuticals (Peccorino, 2002) then, *ceteris paribus*, the larger the country market, size the higher the potential bargaining power of the payer. Manufacturers may follow a dual strategy in this case: they can either *deter* parallel trade by setting a sufficiently low (high) price in a high (low) price country such that it would make it unprofitable to perform parallel trade; or, alternatively, they can *accommodate* parallel trade simply by allowing parallel distribution to take place without necessarily taking action on prices. When arbitrage is unlimited then deterrence is more profitable than accommodation. Conversely, accommodation emerges when the potential volume of arbitrage is small and trade costs are relatively high (Ganslandt and Maskus, 2004). Nonetheless, given that the distribution of medicines is heavily regulated across European countries, parallel trade might well result from the lack of total vertical control in the pharmaceutical distribution chain by the manufacturer. The latter is not self-imposed, but rather governed by regulation and more specifically statutory margins in the distribution of medicines, so that the most widely used model of distribution has to be that the manufacturer sells to the wholesaler and the latter to a retailer (pharmacy). However, there are some exemptions only relating to the structure of the distribution chain itself, namely, some countries allow a degree of vertical integration between wholesalers and retailers, whereas others allow some horizontal integration amongst wholesalers or retailers. Maintaining vertical restraints implies substantial transaction and information costs and, as a result, weak distribution control, combined with a fragmented wholesaler structure, leads to wholesalers in low-price countries channeling part of their stocks to high-price countries.

Parallel imports have been modeled as being the result of third degree price discrimination (Mauleg and Schawartz, 1994); however, they may well be the effect of second degree price discrimination too, for example resulting from discounts given by parallel distributors to pharmacists in importing countries (Anderson and Ginsburgh, 1999). Empirically, the existence of a mechanism that allows health insurance to retain part of that discount in the UK and the Netherlands, confirms this assumption (Kanavos and Costa-Font, 2005). Indeed, the theoretical predictions of this stream of literature are that parallel trade takes place due to the lack of vertical control. Parallel distributors tend to be either distributors or agents that purchase from authorized distributors, therefore changes in the wholesale price and competitive conditions in the distribution chain are likely to determine the profitability of the parallel trade business.

2.3 An empirical gravity specification

Bilateral flows of parallel traded drugs can be specified by using a gravity model on two way trade among countries. The gravity model of international trade flows has been widely used as a baseline model for estimating the impact of a variety of policy issues related to regional trading groups, currency unions and various trade distortions (Bougheas, Demetriades and Morgenroth, 1999; De Grauwe and Skudelny 2000; Glink and Rose 2002). Following Newton's gravity law, a reduced form of spatial flows could be specified, incorporating both demand and supply factors along with trade barriers such as distance and other common preference factors. This predicts that the flow of goods between two locations is *positively* related to their size (or income levels) and *negatively* related to the distance between them, after controlling for a number of other factors which might affect trade through the gravity model (price differences, differences in the competitive pressures of certain regulatory frameworks as promoting parallel trade and the size of the market as an indication of the potential demand and thus profits from parallel trade).

Parallel distributors aim at maximising an expected profit function (Kanavos and Costa-Font, 2005; Szymanzki and Valletti, 2005), and hence they are more likely to ship products to countries that are closer, and have higher prices compared to countries of origin. Given that the relevant price for parallel traders is the wholesale price prevailing in any of the countries in question, the extent of parallel trade would depend, among other things, on a number of parameters related to drug distributors. The first is the nature of competition prevailing in the wholesale distribution business and the number of wholesalers. The second relates to the economic rents from wholesaling, in terms of margins/mark-ups accruing to each wholesale distributor as part of the product's retail price, which in most European countries, are fixed by government regulation. Therefore, our research questions are: Do spatial determinants, regulation and non-gravity related aspects, such as price differences across countries, exchange rates, etc, explain cross-border bilateral flows of pharmaceutical products? Is parallel trade different from conventional (non-regulation induced) trade? How does the model specification determine the magnitude of parallel traded flows?

The model can be specified using a cross-sectional specification. Alternatively, panel data techniques offer more robust specifications. The specification defined raises a number of econometric issues: namely, the extent of inclusion of specific fixed effects, the existence of some endogenous variables, as well as measurement problems for certain regulation effects. In this paper we explore both the pool and panel data model specification possibilities. An augmented logarithmic version of the traditional gravity equation includes geographic controls as follows:

$$\ln M_{ijt} = \beta_o + \beta_1 \ln\left(\frac{p_i}{p_j}\right)_t + \beta_2 \tau_{ij} + \beta_3 \ln(GDP_i + GDP_j)_t + \beta_4 \xi_{ijt} + \beta_5 \left| \ln\left(\frac{GDP_{it}}{N_{it}}\right) - \ln\left(\frac{GDP_{jt}}{N_{jt}}\right) \right| + \beta_6 \ln(Q_i + Q_j)_t + \beta_7 \ln\left(1 - \left(\frac{GDP_{it}}{GDP_{it}+GDP_{jt}}\right)^2 - \left(\frac{GDP_{jt}}{GDP_{it}+GDP_{jt}}\right)^2\right) + \beta_8 X_{ijt} + \varepsilon_{ijt} \quad (1)$$

where *i* and *j* denote the country of origin or export country(-ies) and destination country respectively. The error term ε_{ij} captures any other random shocks and unobserved events that may affect bilateral trade between the two countries. Gravity-specific determinants include distance (τ_{ij}), the bilateral sum of GDP $(GDP_{it} + GDP_{jt})$ of the two trading countries, the difference between GDP per capita of the two trading countries $\left[\ln\left(\frac{GDP_{it}}{N_{it}}\right) - \ln\left(\frac{GDP_{jt}}{N_{jt}}\right)\right]$, the relative country size

$\left(1 - \left(\frac{GDP_{it}}{GDP_{it}+GDP_{jt}}\right)^2 - \left(\frac{GDP_{jt}}{GDP_{it}+GDP_{jt}}\right)^2\right)$ and the exchange rate (ξ_{ij}). Given that parallel trade is

theoretically conceptualised as a specific type of arbitrage (Ganslandt and Maskus, 2004), it is arguably driven by the existence of a difference in relative prices between the two countries $\left(\frac{p_{it}}{p_{jt}}\right)$ and a volume effect in the form of total drugs from the specific therapeutic group of interest $(Q_i + Q_j)$. Finally, a number of key determinants are included in X_{ij}. These are as follows: first, the competition environment in the wholesaling sector, defined as the relative number of wholesalers in country *i* with respect to country *j* and, second, the impact of drug distribution, defined as the relative margins of wholesalers and pharmacists in country *i* with respect to country *j*. Finally, β denotes the vector of coefficients and ε_{ij} measures the set of other influences on bilateral parallel imports.

[Insert Table 2 about here]

3. Data and Empirical Strategy

We used the Intercontinental Medical Statistics (IMS) database on a quarterly basis over the 1997-2002 period for a set of products that fall in the therapeutic product category of statins and exhibit parallel trade during the study period, resulting in a total sample size of N= 768 observations. Hence, the data exhibit a three-way panel structure, 4 products 8 exporters to the Netherlands, in 24 quarters. Data for each product were made available at dispensation level. IMS collect data on prices and sales for a number of countries, including the Netherlands, and for the selected product group, statins, on a product-by-product (e.g. simvastatin, pravastatin, etc) and product presentation basis (e.g. simvastatin, 20mg, 28 tablets). The accuracy of the database's sources has been validated externally (IMS, 2002). Pricing data are available at public level, i.e. inclusive of all wholesale and retail margins as well as Value Added Tax (VAT). Through official national sources, the relevant margins for wholesalers and retailers (pharmacists), as well as the statutory VAT rates applicable for prescription-only (POM) medicines can be identified. The group selected for the analysis (statins) accounts for a significant proportion of total retail sales of prescription only medicines in European countries (5.7% in 2002) (**Figure 1**).

Table 1 provides some descriptive evidence on the differences in the regulation of prices and the wholesaling competitive conditions across European countries. We find that in France, wholesaler margins are the lowest in 2005, and other southern European countries also follow suit. Southern European countries exhibit a significantly higher fragmentation in their wholesaling and retailing practices compared to other European countries.

[Insert Table 1 about here]

Statins are drugs that lower levels of LDL ("bad") cholesterol by 30-50%, and have been popularly prescribed to (primary and secondary) prevent coronary heart disease (CHD), including myocardial infarction (MI), and their use has been increasing over time, making them, in turn, desirable targets for parallel trade (Kanavos et al, 2006). All drugs within the group were protected by a patent during the study period, therefore, the effect of parallel trade could be isolated from other effects, such as competition from generic equivalents, and studied without having to account for the competition effect due to generic penetration which may be significant (Frank and Salkever, 1991; Grabowski and Vernon, 1992; Ganslandt and Maskus, 2004).

We examined parallel import flows of statins into the Netherlands and were in a position to identify the source country. In this particular case, and for the above study period, the Netherlands parallel imported statins from Belgium, France, Germany, Greece, Italy, Portugal, Spain and the United Kingdom. We were able to identify with precision the price and quantity differences at any point in time between each exporting country and the Netherlands, and estimate the impact of arbitrage in the Dutch market for each of the products within the statins group.

In explaining trade flows, we consider the influence of price differences, given the arbitrage nature of parallel trade, the nature of competitive forces in the drug distribution system, and the cross national differences in wholesale price regulation. Recent studies (Kanavos and Costa-Font, 2005) already find that some of the gains from parallel trade are invisible because of the incentive structures of different stakeholders that play a key role in the distribution of medicines in general and parallel imported medicines in particular, most notably parallel distributors and pharmacies.

[Insert Figure 1 about here]

In estimating the gravity model we first reproduce the results of a pooled (cross-section) purely for comparative purposes which is the followed by a panel data approach to measure the impact of country-specific or time heterogeneity effects that can be modelled by including country-pair "individual" effects and, accordingly, identifying bilateral trade. Hence, the pooled (cross-section) specification contains a reduced form bases on implausible assumptions (e.g., the presence of unobserved heterogeneity resulting from unobserved characteristics related to bilateral trade relationships) , whilst the panel case refers to a random effects approach consistent with the gravity specification whereby some variables are country-specific (e.g. distance). Thus, a country would export different amounts of the same product to two other countries, even if their GDPs are identical and they are equidistant from the exporting country. This is due to potential differences in drug regulation, which are not entirely observed, along with the presence of country-specific heterogeneity. Since the cross-section OLS estimates may not be able to account for these heterogeneous factors, the results are likely to suffer from substantial heterogeneity bias. In contrast, a panel-based approach may be more desirable in order to deal with heterogeneity issues because the effects of such determinants can be modelled by including country-pair “individual” effects. In this case, a random effects approach would be more appropriate, whereas a fixed effects approach would not allow for estimating coefficients on time-invariant variables such as distance or common language, though the consistent estimation of such effects is equally important in many situations. Finally, we separate the full model from the restricted model, following a two-part approach, whereby if we group all explanatory variables in $X\beta$ then, the conditional expectation of bilateral trade is: $E(M_{ijt} / X\beta) = E(M_{ijt} / M_{ijt} > 0 / X\beta) pr(M_{ijt} > 0 / X\beta)$. We follow standard practice with modelling the ‘effect of zeros’ to avoid reducing the sample size and biasing our estimates. Hence, we can separate the entry decision into a market $E(M_{ijt} / M_{ijt} > 0 / X\beta)$ from the actual penetration of a market $pr(M_{ijt} > 0 / X\beta)$ in order to disentangle potentially different explanatory effects.

The dependent variable is the logarithm of real trade of statins in the Netherlands and the logarithm of total trade volume in the country of origin. First, we use the basic specification and consider the impact of core explanatory variables such as GDP, population and distance. Subsequently, in line with recent theoretical developments (Egger, 2002), we include variables measuring the size of trading countries and other barriers that might explain the development of parallel trade such as distance and exchange rates. The model described in equation (4) contains variables that are potentially endogenous, namely the price difference between the Netherlands and each $pr(M_{ijt} > 0 / X\beta)$ exporting country. We estimate two stage least squares (2SLS) and two stage generalised least squares (2SGLS) models to account for such effects. To instrument price differences - at the wholesale level given that parallel trade takes place at the distribution process- between importing and exporting country we employ the difference in pharmacy mark-ups and the relative number of wholesalers as instruments as neither variable is associated with volume, but both help explain drug prices. The latter does not conflate in any respect with direct price regulation in some countries, which continues to exist and does necessarily correlate with wholesale and retail regulation. Indeed, as discussed elsewhere (Kanavos and Costa-Font, 2005), incentives to purchase parallel traded drugs by wholesalers and pharmacies take place through unobservable discounts which, in the vast majority of cases, remain unaccounted for by health insurance. We test and confirm the existence of endogeneity in price formation.

The variables employed in the analysis are presented in **Table 2** and are as follows: (a) (M_{ijt}) is the observed volume of each statin imported into the Netherlands from another EU country; (b) (τ_{ij}), represents the distance between two areas and is defined as the Euclidean distance of latitude and longitude between country capitals; the reason for measuring distance in this way rests on the fact that kilometers are not necessarily a good approximation for distance given alternative and more direct ways of transportation (e.g. air travel); (c) exchange rate (ξ_{ijt}) is an obvious determinant of parallel trade insofar as it impacts price transparency (given that not all countries examined are in the euro area and the period examined corresponds to before the euro was introduced), especially in the context of European integration.; (d) following the predictions of a gravity model, our model includes the bilateral sum of country GDPs (in logs) $\ln(GDP_{it} + GDP_{jt})$, as it is conventional in the literature we measure relative country size (in logs) $\ln\left(1-\left(\frac{GDP_{it}}{GDP_{it}+GDP_{jt}}\right)^2-\left(\frac{GDP_{jt}}{GDP_{it}+GDP_{jt}}\right)^2\right)$, the difference of GDP per capita (in logs) $\left[\ln\left(\frac{GDP_{it}}{N_{it}}\right)-\ln\left(\frac{GDP_{jt}}{N_{jt}}\right)\right]$, and the sum of statins sales in € (in logs) $\ln(Q_{it} + Q_{jt})$ that is the specific therapeutic group in question which has been growing in size during the study period which were included after testing for colinearity in the regression; (e) furthermore, we consider the point of entry of a parallel traded drug or product presentation as a variable to select the sample under consideration. As expected from a model of arbitrage, relative prices between countries (in logs) $\ln\left(\frac{p_{it}}{p_{jt}}\right)$ should be a key determinant, with a negative expected sign. Finally, (g) a set of variables has been added to measure the aggregate number of distributors, which accounts for the degree of competition in the distribution chain in both countries proxied by the relative number of wholesalers in the Netherlands and the exporting country $\ln\left(\frac{N_{it}}{N_{jt}}\right)$ and the (h) relative wholesaler $\ln\left(\frac{\eta_i}{\eta_j}\right)_t$ and pharmacy mark-up difference $\ln\left(\frac{\rho_i}{\rho_j}\right)_t$ and account for possible economic incentives for parallel trade which are exogenous proxies for regulations.

4 Results

We begin by reporting evidence of trends and stylised facts, which appear to suggest an increase in parallel import penetration to the Netherlands post 1999 (**Figure 2**). Whilst this is initially attributable mainly to a single product (simvastatin), subsequently, other competitor statins increase their share in total statin imports. According to IMS, the market share of parallel imported statins is about 30% over the study period.

Figure 3 reports the patterns of trade from each of the potential countries of origin. The most common country of origin of parallel imported drugs in the Netherlands, at least in the earlier parts of the study period, was France. This is not totally unexpected although France does not have the lowest statin price among exporting countries. Significant exporting activity by France may be due to the fact that France is a large country with a significant capacity to parallel export (Kanavos and Costa-Font, 2005). At the same time, of all the other existing countries that can potentially export, France is, together with Belgium, closest geographically to the Netherlands. Finally, the wholesale margin in France is the lowest of the countries considered (**Table 1**), and this can be interpreted as an incentive for wholesalers to divert part of their stocks to other countries, seeking higher returns.

[Insert Figure 2 about here]

Importantly, the evidence presented in **Figure 3** suggests that although 90% of parallel imported statins into the Netherlands were sourced in France in 1997, Spain's market share has increased significantly since 2000. By 2002 Spanish exports accounted for 40% of all statins parallel imported into the Netherlands.

[Insert Figure 3 and Table 3 about here]

5.2 Econometric specifications

By undertaking the econometric estimation of the gravity equations following the premises of equation (2) we then attempt to ascertain the influence of economic versus regulatory determinants of parallel trade entry and penetration. Purely for comparative purposes, **Table 3** provides the estimates of a pooled OLS model which includes equation (2) along with regulatory variables that influence the decision by local distributors (wholesalers) to sell to parallel exporters. Accordingly, we add the wholesalers' mark-up difference to measure the effect of competitive conditions in the drug distribution system. Column (3.1) presents the determinants of total bilateral parallel trade. Column (3.2) shows the volume of parallel trade restricted to the existence of some penetration and column (3.3) shows the determinants of market entry. Our evidence suggests that total bilateral parallel trade increased the lower the relative price of the exporting country is, as expected from a specific form of arbitrage (column 3.1).

Monetary barriers to trade – such as exchange rates – are relevant in explaining parallel import penetration and reveal the expected negative effect on trade flows[1]. Similarly, transport costs – measured by distance – seem to affect parallel import penetration in a way consistent with the

[1] This has to do with the fact that in some parallel exporter countries such as Spain and France the introduction of the euro has eliminated the exchange rate variability with the Netherlands

prediction of a generalised gravity model. More specifically, the higher the distance between two countries, the lower the extent of bilateral parallel trade. Entry decisions are associated with distance. We find that the similarities of both the two countries in terms of GDP and of the countries' relative factor endowment favour intra-industry trade and therefore are significant parallel trade determinants. However, unlike in standard models of trade, we find that a higher combined income seems to influence negatively parallel trade. As expected, bilateral parallel trade flows increase with the size of the statins market. Finally, and consistent with our theoretical predictions, relative wholesaler mark-ups are associated with import penetration (column 3.2) and the entry decision to undertake parallel trade (column 3.3), although the significance level is around 10%, only.

Next, we tested for endogeneity following Wooldridge (2009) by performing a regression on the potentially endogenous variable using all exogenous variables and the instruments available, obtaining the residuals and testing the significance of those in the initial specification. We have found unambiguous evidence of endogeneity. Accordingly, we instrumented the price difference using data on relative pharmacist margins across countries $\ln\left(\frac{\rho_i}{\rho_j}\right)_t$ and the relative number of wholesalers across countries $\ln\left(\frac{\eta_i}{\eta_j}\right)_t$. The theoretical justification for including these variables as instruments lies in the fact that they are strongly associated with the formation of drug public prices given that both pharmacy margins (mark-ups) and the least competitive conditions for drug distribution are responsible for the formation of final public prices, whilst they do not appear to be associated (both in prior correlation analysis and in OLS regression models that include this variable as a covariate) with parallel trade volume, given the latter is driven by the nature of incentives at wholesale level. On the other hand, parallel trade strongly is associated with price differences. Therefore, an instrumental variables (IV) estimation should provide a consistent estimate of the coefficients of interest and could well correct for any omitted variable bias (Angrist and Krueger, 2001).

[Table 4 about here]

Table 4 reports the results of a gravity equation estimated using instrumental variables**.** When IV estimation strategy is implemented; exchange rates and distance exhibit the opposite expected effects. With regard to distance, this may be explained by the fact that within relative small areas, such as the EU, distance does not become a significant barrier and relatively distant sources geographically have incentives to become better connected. With regard to the effect of GDP, and as mentioned above, larger countries tend to be less likely to parallel export, although countries with similar relative factor endowments and countries with larger market sizes for statins are more likely to ship larger quantities to the Netherlands. Finally, the relative wholesaler's margin seems to explain rather well parallel trade, especially when the entry decision has to be made.

Nonetheless, so far, it may be the case that some country- and product-specific effects might be driving the dynamics of parallel trade flows, or more generally, some unobserved heterogeneity might be present which need to be accounted for. This could be corrected using panel data analysis and controlling for fixed effects as in **Table 5**. Two important results come out of such a strategy. First, the Hausmann test reveals that a fixed effects specification is more efficient. Second, fixed effect specification suggests that neither medicine price differences nor economic size exert an effect in explaining parallel trade unlike what one would expect had parallel trade been purely a form of economic arbitrage. In contrast, differences in wholesale mark-ups are found to increase bilateral Medicines parallel import flows in line with the regulatory arbitrage hypothesis.

[Insert Table 5 about here]

6. Conclusion

This paper is the first to examine bilateral medicine parallel imports to test whether the regulation of medicine distribution chain or differences in medicine prices drives parallel trade flows. Drawing from a unique sample of parallel imports of statins (a therapeutic group subject to patent protection during the period of analysis and not affected by generic entry) into the Netherlands, we test whether economic and regulatory determinants play a role in driving parallel trade flows. Specifically, the paper measures the impact of country-specific regulation of the distribution chain on the proliferation of parallel trade in proprietary medicines in both exporting and importing countries (The Netherlands). By focusing on in-patent medicines only, the paper examined the effect parallel trade has on the destination country. We have specified a large number of gravity specifications, controls and specification robustness checks.

Results suggest that medicines parallel trade is indeed a regulation-induced phenomenon, consistent with theoretical predictions in other similar settings (Peccorino, 2002), that mainly takes place at the distribution level, whereby changes in the regulated wholesale margin stands the main trigger of parallel trade flows. The latter has important implications for European economic policy insofar as it suggests that the traditional beneficial effects that are typically associated with market arbitrage do not hold in this case.

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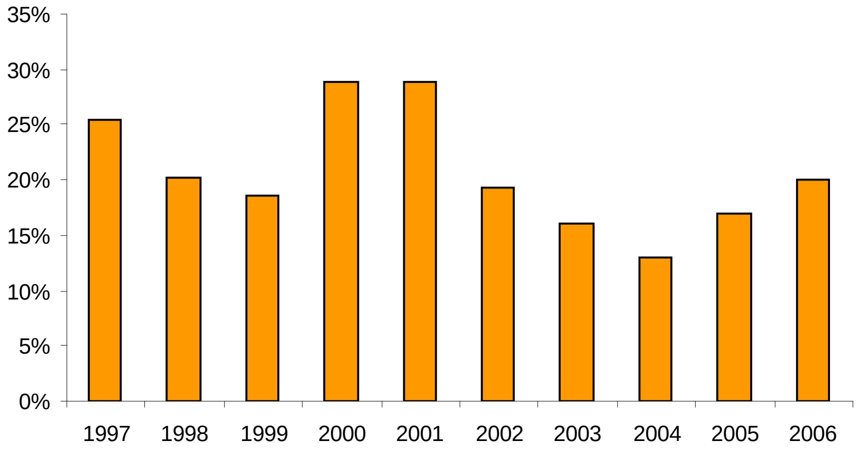
Figure 1

Market share of parallel imported statins in the Netherlands, 1997-2006

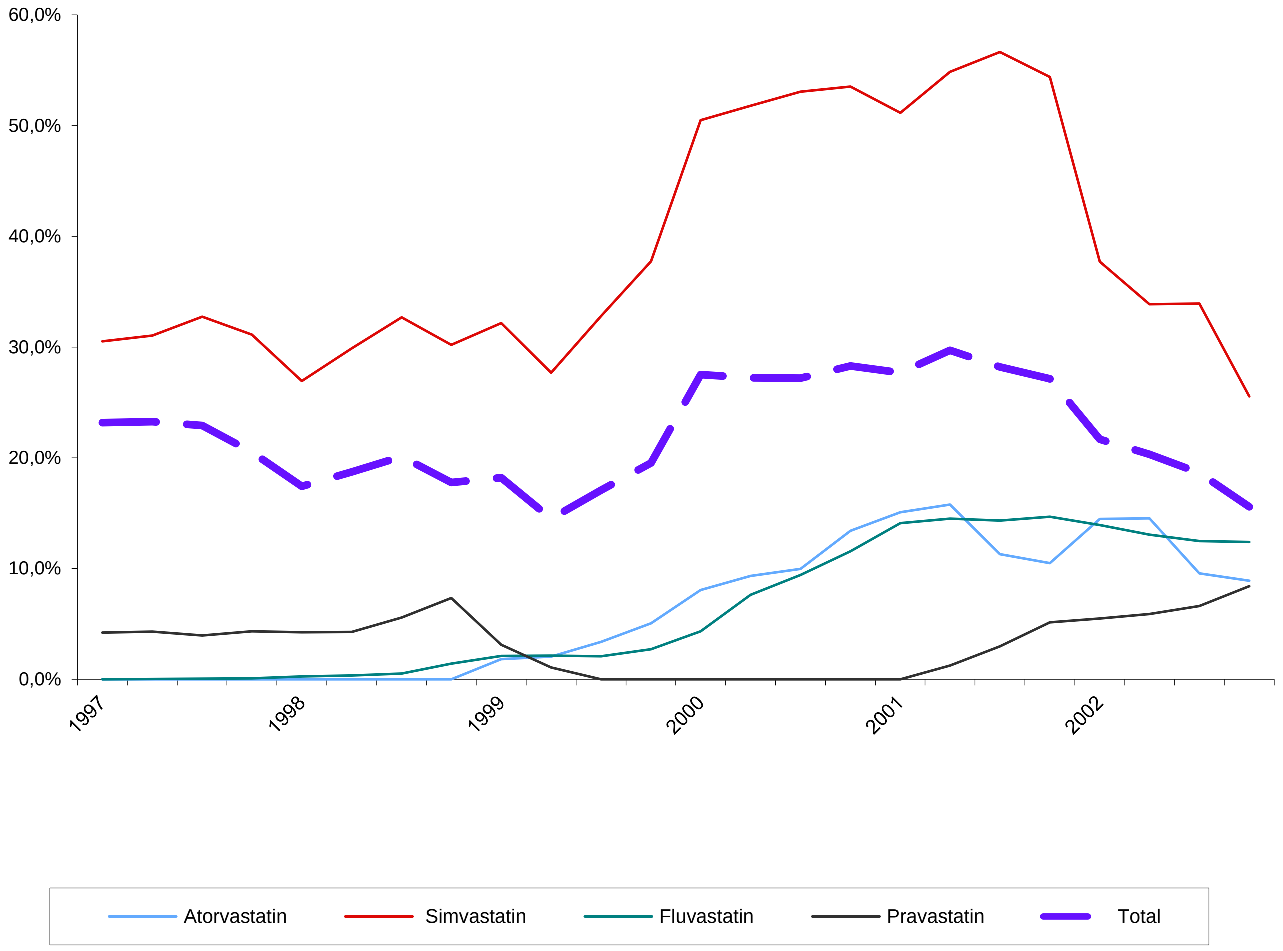


Source: The authors from IMS, 2004.

*These include United Kingdom, Germany, The Netherlands, Sweden, Denmark, Norway and Sweden.

Figure 2

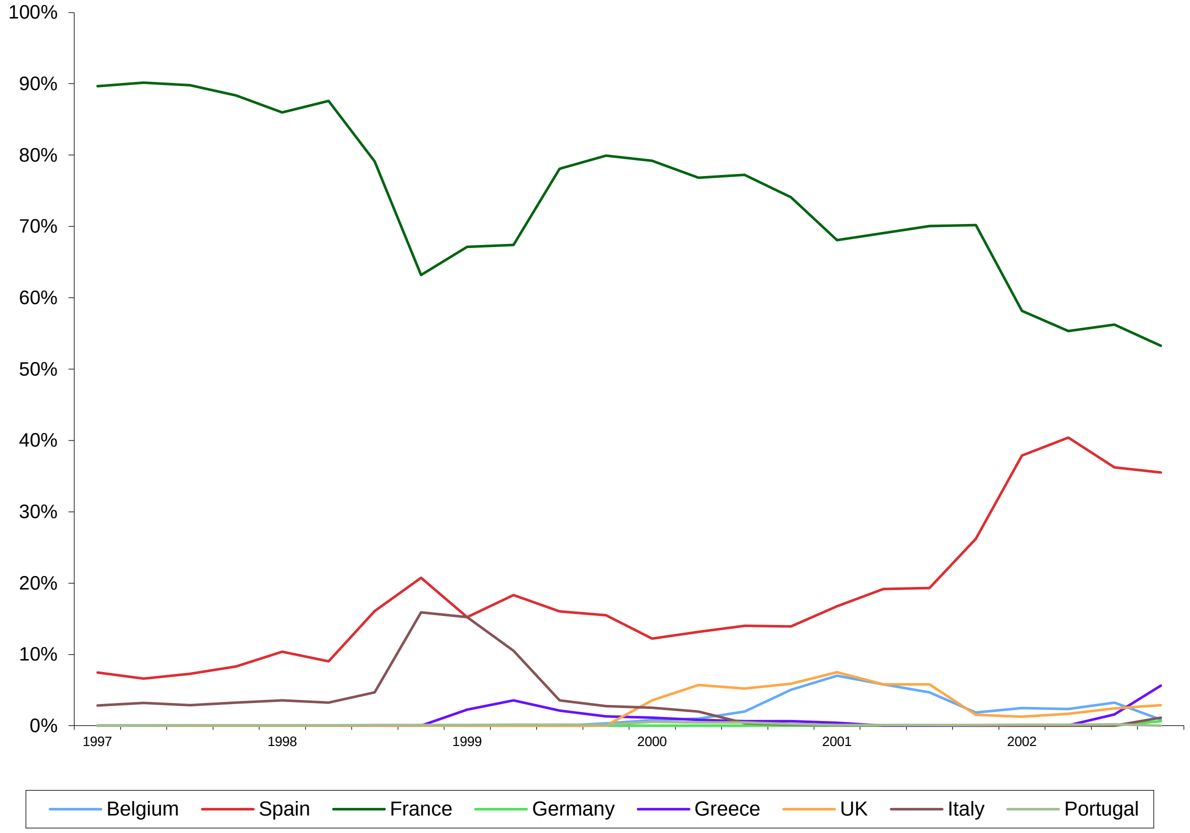
Parallel trade penetration of statins in the Netherlands (parallel imports as a % of total product market), 1997-2002



Source: The authors from IMS, 2004.

Figure 3

Origin of parallel imported statins in the Netherlands, 1997-2002



Source: The authors from IMS, 2004.

Table 1
Pharmaceutical price structure and distribution chain market structure in selected EU countries, 2005

Country	Ex-Manufacturer[2] (% price)	Number of wholesalers	Wholesaler margin (% price)[3]	Pharmacy density (Population per pharmacy)	Pharmacy margin (% price)[3]
Belgium	56.6	13	8.5	5,200	29.2
France	64.8	12[1]	**3.8**	**2,800**	26.2
Germany	51.2	16	7.7	3,900	27.3
Greece	63.1	130	**5.5**	**1,420**	24
Italy	63.8	95[1]	**6.7**	3,700	20.4
Netherlands	63.4	4	**10.8**	6,100	20.2
Portugal	67.8	18	8.4	4,000	19
Spain	62.7	51	**6.7**	**2,000**	26.8
UK	72.4	10	10.3	4,850	17.3

Note: [1] Excluding regional offices and counting only head offices of the same wholesaler.
[2] Ex-manufacturer price as a proportion of price, assuming price=100.
[3] Margins expressed as a proportion of price, assuming price=100.

Sources: Paterson et al, 2003a; European Association of Pharmaceutical Wholesalers, 2005.

Table 2
Variables and descriptive statistics

Variable	Abbreviation	Description	Mean (s.e)
Dependent variable			
$\ln(M_{ijt})$	lquantity	Bilateral trade flow volumes of statins (logs) [a]	1.513 (2.646)
Independent variables			
$\ln(\tau_{ij})$	Ldist	Euclidean distance of latitude and longitude (in logs) of the country capitals	6.467 (0.941)
ξ_{ijt}	Ler	Exchange rates in euros (logs)[b]	0.0679 (0.102)
$\left\| \ln\left(\frac{GDP_{it}}{N_{it}}\right) - \ln\left(\frac{GDP_{jt}}{N_{jt}}\right) \right\|$	labsR	Difference of per capita GDPs (absolute terms and logs)[b] (N=population)	0.949 (0.618)
$\ln(Q_{it} + Q_{jt})$	lsumst	Sum of total sales of statins (logs)[a]	11.494 (0.608)
$\ln(GDP_{it} + GDP_{jt})$	lG	Bilateral sum of GDPs (logs)[b]	10.782 (0.107)
$\ln\left(1 - \left(\frac{GDP_{it}}{GDP_{it}+GDP_{jt}}\right)^2 - \left(\frac{GDP_{jt}}{GDP_{it}+GDP_{jt}}\right)^2\right)$ Type equation here.	lS	Relative country size (logs) [b]	-0.711 (0.247)
Entry	Entry	Dummy variable measuring the entry of a new drug in the parallel trade market[a]	0.283 (0.450)
$\ln\left(\frac{p_{it}}{p_{jt}}\right)$	lrelP	Relative price between Netherlands and source country adjusted by defined daily doses (DDD)[a]	-0.359 (0.436)
$\ln\left(\frac{\eta_i}{\eta_j}\right)_t$	lrelMWS	Relative wholesalers' drug margins (logs)[c]	-0.518 (0.296)

Note: Export Country (i), Import County (j) and time (t).
Sources: [a] IMS data 1997-2002.
[b]OECD Economic Outlook data 1997-2002.
[c] EFPIA, several years (www.efpia.org).

Table 3
Augmented Gravity Equation (OLS)
Dependent variable: bilateral parallel trade flows to the Netherlands (in M_{it})

	Total Flow (3.1)			Restricted Sample* (3.2)			Entry (Probit) (3.3)		
	coeff	s.e	t-value	coeff	s.e	t-value	coeff	s.e	z-value
ldist	1.809 [a]	0.263	6.88	-0.990 [a]	0.294	-3.37	0.999 [a]	0.148	6.75
lrelP	-0.501	0.306	-1.64	-0.878	0.494	-1.78	-0.386 [b]	0.159	-2.42
ler	-1.638	1.683	-0.97	-7.357 [a]	1.699	-4.33	-0.255	0.869	-0.29
lG	-11.90 [a]	3.384	-3.52	-7.616	4.624	-1.65	-3.663 [b]	1.856	-1.97
lS	145.798 [a]	18.978	7.68	-10.408	30.095	-0.35	74.108 [a]	12.383	5.98
labsR	-4.278 [a]	0.742	-5.76	2.255 [c]	1.209	1.89	-2.209 [a]	0.419	-5.28
lsumst	3.164 [a]	0.638	4.96	1.548 [b]	0.720	2.15	1.223 [a]	0.347	3.52
lrelMWS	-0.969	0.719	-1.35	0.754 [c]	0.416	1.81	-0.458	0.302	-1.52
Intercept	188.991	40.584	4.66	67.467	61.203	1.10	72.694	23.547	3.09
R^2 (Adjusted)	0.15			0.51					
N (No. of observations)	625			165			625		
Pseudo R^2							0.13		
Likelihood Ratio χ^2_8							91.29		

*Restricted to molecules where there is some evidence of parallel trade.
Note 1: [a] Denotes significance at 1% level, [b] denotes significance at 5% level,
Note 2: Breusch-Pagan test confirms the existence of heteroskedasticity, therefore, estimates contain robust standard errors

Table 4
Gravity equation 2SLS
Dependent variable: bilateral parallel trade to the Netherlands (in M_{it})

	Total sample (4.1)			Restricted Sample* (4.2)			Entry (IV Probit) (4.3)		
	coeff	s.e	z-value	coeff	s.e	z-value	coeff	s.e	z-value
lrelP	5.877 [b]	2.939	2.00	4.014 [c]	2.124	1.89	2.546 [a]	0.356	7.15
ldist	4.012 [a]	1.059	3.79	0.363	0.946	0.38	1.379 [a]	0.145	9.49
ler	-7.042 [b]	3.068	-2.30	-9.301 [a]	1.969	-4.72	-2.407 [a]	0.650	-3.71
lG	-15.815 [a]	5.027	-3.15	-7.608	7.006	-1.09	-3.180 [c]	1.678	-1.9
lS	193.058 [a]	34.457	5.60	-4.647	48.167	-0.10	52.650 [a]	15.585	3.38
labsR	-5.067 [a]	1.091	-4.64	1.753	1.980	0.89	-1.301 [a]	0.508	-2.56
lsumst	3.852 [a]	0.896	4.30	0.876	0.960	0.91	0.818 [b]	0.352	2.32
lrelMWS	-1.754 [c]	0.935	-1.88	0.419	0.729	0.57	-0.536 [b]	0.242	-2.22
Intercept	245.661 [a]	62.091	3.91	73.164	95.749	0.76	55.129 [b]	22.992	2.40
R^2 (Adjusted)	-			-					
N	610			161			610		
Wald χ^2_8 $(\nabla\beta_i = 0)$	82.33			89.11			466.71		

* Restricted to the existence of some parallel trade.

Note: [a] denotes significance at 1% level, [b] denotes significance at 5% level, [c] denotes significance at 10% level.

Note 2: Breusch-Pagan test confirms the existence of heteroskedasticity, therefore, we have used robust standard errors.

Table 5
Random and Fixed Effects 2SGLS *(in M_{it})*
Dependent variable: bilateral parallel imports to the Netherlands

	Random Effects (5.1)			Fixed Effects (5.2)		
	coeff	s.e	z-value	coeff	s.e	z-value
lrelP	6.564	4.951	1.33	-1.304	3.140	-0.42
ldist	3.458	1.671	2.07			
ler	-2.225	9.129	-0.24	29.927	12.318	2.43
lG	12.690 [a]	3.580	3.55	0.145	4.611	0.03
lS	77.845 [a]	23.380	3.33	4.345	65.871	0.07
labsR	-1.176	1.255	-0.94	-2.044	11.494	-0.18
lsumst	-1.798 [b]	0.717	-2.51	1.290	1.046	1.23
lrelMWS	-1.643 [a]	0.536	-3.06	-0.025	0.577	-0.04
Intercept	-78.490	37.979	-2.07	-8.098	62.768	-0.13
N (Number of Observations)	610			610		
Wald χ^2_8 $(\nabla\beta_i = 0)$	57.38					
Wald Test χ^2_7 $(\nabla\beta_i = 0)$				835.40		
R^2 (Adjusted)	0.01			0.12		

Note: [a] denotes significance at 1% level, [b] denotes significance at 5% level, [c] denotes significance at 10% level.

Data Appendix: Variable Description

Bilateral trade flow volume **lquantity**

Exchange rate **ler**

Distance **ldist**

Entry **entry**

LabsR . Referes to thedifference of log of GDPpc between export and import country, representing a proxy for country's relative factor endowment. The smaller the difference, the more intra-industry trade and the lower inter-industry trade. Expected sign: negative

$$R_{ijt} = \left| \log\left(\frac{\text{GDP}_{it}}{N_{it}}\right) - \log\left(\frac{\text{GDP}_{jt}}{N_{jt}}\right) \right|$$

Following Egger 2000

- **lG** is the Bilateral sum of GDP: the larger the overall economic space, the larger trade between these two countries. Expected sign: positive

$$G_{ijt} = \log(\text{GDP}_{it} + \text{GDP}_{jt})$$

- **lS** is the Relative country size: the larger the measure, the more similar the two countries in terms of GDP, and therefore, the more intra-industry trade. Expected sign: positive

$$S_{ijt} = \log\left(1 - \left(\frac{\text{GDP}_{it}}{\text{GDP}_{it} + \text{GDP}_{jt}}\right)^2 - \left(\frac{\text{GDP}_{jt}}{\text{GDP}_{it} + \text{GDP}_{jt}}\right)^2\right)$$

lsumst refers to the Sum of total sales of statins (log). Expected sign: positive

$\ln(Q_i + Q_j)$

The logic of a additive specification would be that the number of sales stand out as a proxy for market size. The larger the size, the more the opportunities to trade (although this is already taken into account with bilateral sum of GDP).

lrelWS refers to the relative number of wholesalers as an IV for price difference. IV

Ln(Ni/Nj)

Expected sign: positive

- We are interested in the relative number of wholesalers between the two countries, since the higher and positive the difference, the more parallel trade will take place.

lrelP is the relative price between Netherlands and source country. *Expected sign: negative*. A high ratio between pi and pj means that pi is much larger than pj, therefore, the higher the price in export country, the lower the parallel trade.

$$\mathbf{Ln(p_i/p_j)}$$

With the price difference, there were problems when doing logs, converting negative price differences in missing values. The relative price gives same info and does not have problems in doing logs.

lrelMPH is the relative price between pharmacist margins in export and import country. *Expected sign: negative*. A high ratio between pi and pj means that pharmacist margin is much larger in export country, therefore, the higher the margin in export country, the lower the parallel trade.

$$\mathbf{ln(\rho_i/\rho_j)}$$

Same logic as price difference.

lrelMWS is the relative price between WS margins in export and import country.

Expected sign: negative. A high ratio between wholesalers margins export and import country means that wholesalers margin is much larger in export country, therefore, the higher the margin in export country, the lower the parallel trade.

$$\mathbf{ln(\eta_i/\eta_j)}$$

Same logic as price difference.