Market Size and Pharmaceutical Innovation

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Abstract

This paper quantifies the relationship between market size and innovation in the pharmaceutical industry. We estimate the elasticity of innovation, as measured by the number of new chemical entities appearing on the market for a given disease class, to the potential market size represented by the willingness of sufferers of diseases in that class (and others acting on their behalf such as insurers and governments) to spend on their treatment during the patent lifetime. We find positive significant elasticities with a point estimate under our preferred specification of 25.2%. This suggests that at the mean market size an additional $1.8 billion is required in additional patent life revenue to induce the invention of one additional new chemical entity. An elasticity substantially and significantly below one-half is also a plausible implication of the hypothesis that innovation in pharmaceuticals is becoming more difficult and expensive over time, as costs of regulatory approval rise and as the industry runs out of "low hanging fruit".

Key words: Innovation, Market Size, Elasticity, Pharmaceuticals.

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1 Introduction

This paper quantifies the relationship between financial returns and innovation in the pharmaceutical industry. More precisely we shall estimate the elasticity of innovation (as measured by the number of new chemical entities appearing on the market for a given disease class) to the expected potential market size represented by the willingness of sufferers of diseases in that class (and others acting on their behalf such as insurers and governments) to spend on their treatment. This potential market size is influenced by broadly three types of factor, and in order to understand how to interpret our results it is necessary to distinguish these factors carefully.

First there are factors such as demographic and socio-economic change, which affect the numbers of people who are likely to suffer from a particular medical condition and the resources they are likely to have available to spend on alleviating their condition. A motivating example concerning research on gout from the New York Times illustrates the incentives for R&D. "Often called the "disease of kings" because of its association with the rich foods and copious alcohol once available only to aristocrats, gout is staging a middle-class comeback as American society grows older and heavier. ...Companies are now racing to improve upon decades-old generic drugs that do not work well for everyone. Already this year the Food and Drug Administration has approved the first new gout drug in more than 40 years...".[1] Many other examples evidently spring to mind of research motivated primarily by changing demographic and socio-economic factors, such as research into cardiovascular disease and Alzheimer's disease.

Secondly, there are factors particular to the pharmaceutical and health-care industries, such as the degree of competition among firms and the strategies that firms use to innovate, cut costs, and

[1] "Disease of Rich Extends Its Pain to Middle class", New York Times, June 12, 2009 . The story continued:
"...a product called Uloric from Takeda Pharmaceutical. Another new drug, Krystexxa, made by Savient Pharmaceuticals of East Brunswick, N.J., will be reviewed for possible approval by an F.D.A. advisory committee on Tuesday. And several other companies are testing drugs in clinical trials. "It's kind of like the forgotten disease," said Barry D. Quart, chief executive of one of those companies, Ardea Biosciences of San Diego. Ardea discovered accidentally that an AIDS drug it was developing might work against gout. Now the company has shifted its focus to gout, envisioning annual sales of $1 billion if its drug is successful. That would mean a huge increase in spending on gout medicines, which had sales of only $53.4 million last year, according to IMS Health, a health care information company. Uloric, the drug from Takeda, sells a daily pill for at least $4.50 compared with 10 to 50 cents for the most commonly used generic, allopurinol. It is estimated that two million to six million Americans have gout... Various studies suggest that the number of cases in this country has as much as doubled in the last three decades".

win customers, that affect the profitability of innovation. For example, intensified competition from generics for branded products occurs not only as a response to patent expiry but also in response to the purchasing environments. Cost-control pressures from managed care create incentives for generic use and reduce the expected market size of an innovation. The response of firms to a given potential market size may also depend on such considerations as their degree of symmetry in competence: the competition between two firms of similar size and employing similar talent pools may be quite different from competition between a leader and a follower firm.

Thirdly, there are public policies, including policies towards intellectual property protection, drug safety and testing, pricing and reimbursement, and public funding of research. As a matter of comparison, in 2004, research spending by NIH reached $28.5 billion while the members of the Pharmaceutical Research and Manufacturers of America report R&D spending of about $40 billion - see CBO 2006. Policy innovations such as the introduction of Medicare in the 1960s have had a large impact on potential market size, and various researchers have noted the consequences for research and innovation in drugs for the elderly that were the probable consequence (Acemoglu et al., 2006).

In principle it might be thought that, from a policy point of view, the only really interesting factors affecting potential market size are those in the third category, and that therefore any study such as ours should focus on the elasticity of innovation with respect to these factors only. Such estimates could be used, for instance, to calculate the social cost of a particular drug pricing regime or of a proposed change in the length or breadth of patent protection, or the social returns to additional spending by the NIH. However, this argument is flawed, even if one ignores the possibility that the influence of the other types of factor may be of independent interest (such as for predicting future trends in research and innovation). Estimating the elasticity of innovation with respect to past changes in policy would be possible only if we could observe genuine policy experiments, conducted without reference to the many factors, unobserved to the econometrician, that might influence the potential rate of innovation. But most policy changes are not like that, and arguably most of them should not be. They are typically endogenous to the rate of innovation itself, either because public policy may feel it does not need to intervene to favor areas where innovation is already coming along nicely, or

because public policy likes to bask in the glow of supporting visibly successful areas, or because once key drugs have been developed it is tempting to lower their prices to users, or for any number of other reasons. This makes the observed elasticity of innovation with respect to past policy changes unreliable as a guide to the elasticity of innovation with respect to future policy changes.

Factors of the first type, by contrast, are rarely under the influence of either government or industry participants, at least not in the short- to medium-term. Far from making them less interesting from a public policy point of view, this makes them worthwhile studying, because they represent a way of estimating the impact of genuinely exogenous changes of potential market size, and therefore of representing the potential impact of a change in public policy that otherwise holds all factors constant. In essence, using the exogenous demographic and health changes to estimate the elasticities, freed of the confusing interference on market size of the two other types of factor, allows us to simulate the effect of future policy changes.

While existing studies of these issues have focused on US data, we use both US and international data to reflect the fact that all markets, including those outside the US, constitute an important incentive for innovation. There is an older literature relating market size in a country to the R&D undertaken in that country. Because there are unobserved factors such as the level of education in a country that might affect both R&D and health spending, we do not use this source of variation. The variation we exploit in estimating the responsiveness of innovation to market size is across therapeutic classes and over time, rather than across geography. Additionally, biopharmaceutical research is carried out all across the globe by both local and international firms. The products invented by these firms might treat local healthcare needs or global ones. Therefore, a product generated by research from one country is likely to be useful, and therefore commercialized, in many countries. The appropriate level of analysis for a study of the determinants of innovation – both in terms of which products to include and which markets to count - is global.

Our identification strategy is as follows. If the cardiovascular market is expected to grow due to an aging population, there will be an increase in cardiovascular R&D and we will see the release of new cardiovascular products on the market at the time of the demand increase. Different therapeutic

markets that grow differently over time due to demographic and income differences drive changes in innovative activity. We can measure the elasticity of new products to market size using this variation.

The relatively recent literature on the topic of the elasticity of pharmaceutical innovation to market size contains two broad approaches. The older of the two uses accounting data to estimate the determinants of R&D (see Grabowski and Vernon (2000)). In theory, under perfect capital markets R&D would be chosen only in response to expected future profitability of the project. However, if capital markets are imperfect and external funds are more expensive than internal cash flow, current revenue (market size) will have a positive impact on the amount of research funded by the firm. Of course, if current market size is a proxy for future market size, then current research may be responding to future sales opportunities also, but these two effects cannot be disentangled. Giacotto et al. (2005) regress R&D-to-sales ratio on the pharmaceutical price index from the previous year and other variables. Again, this is a model of innovation responding not to expected future market size, but to recent prices. They find a 1% increase in price leads to a 0.58% increase in R&D spending. A second stream of the literature uses alternate measures both for outcomes and market size. Innovation is measured as clinical trials (Blume-Kohout and Sood, 2009), journal articles or disease regimens (Lichtenberg, 2006), while potential market size is (negative) disability-adjusted life years (DALY) or mortality (Civan and Maloney, 2006,2009, Lichtenberg, 2005). Lichtenberg (2005) finds results of similar magnitude: a 1% increase in the number of people with cancer leads to a .58% increase in chemotherapy regimens. Civan and Maloney (2006, 2009) find that a 1% increase in expected US entry price leads to .5% increase in the number of drugs in the drug development pipeline. Lichtenberg (2005) finds that a 1% increase in DALY leads to a 1.3% increase in global drug launches.

The paper most closely related to ours is by Acemoglu and Linn (2004), hereafter AL. Using variation from 1970-2000 in what US cohorts purchase and in FDA approvals, AL find that a 1% increase in contemporaneous expenditure shares leads to a 4% increase in the number of new drugs released on the market. This is a markedly higher elasticity than found in the previous literature. We will discuss the differences between our methods and data and theirs in detail below.

We examine the response of global new drug launches to global market size measured in revenues.

Of course, a simple regression of new drugs on revenues will pick up both causal directions mentioned above: revenues attract innovation and also drug innovations generate revenue. Isolating the first causal relationship requires an instrument. We use measures of population and disease prevalence in our sample of countries as our instruments for revenue. Our strategy makes sense because, as one might expect, demographics are strongly correlated with revenue. However, the invention of a new drug does not change the contemporaneous propensity for populations of a particular country to suffer from cardiovascular disease, for example. Thus we expect demographics to be uncorrelated with the error term in our regression of new drug counts. For our assumption not to hold, it must be the case that a novel therapy generates additional measurable diagnoses in the specific area. While this makes sense for narrowly targeted treatments and diagnoses, it seems much less likely to be operating at the level of fairly coarse disease areas tracked by WHO, such as "cardiovascular disease". By utilizing this instrumental variables approach we can isolate the impact of revenue changes driven by demographics and determine their impact on innovation.

While we will estimate the impact of financial incentives on the launch of new products, we are cautious about drawing conclusions about the welfare benefits of those new products. There are various reasons why this is not straightforward. One is that there may be diminishing marginal benefits to be had from innovation within a disease class: the first radical innovation in a therapeutic class may produce much greater overall benefits than a drug that is just sufficiently different from it to be granted a patent (though the opposite could be true if the second drug avoids debilitating side-effects associated with the first). A second reason is that it is particularly difficult in this line of research to calculate the welfare of a new innovation in the absence of measures of consumers' valuation or willingness to pay. Most patients are insured and therefore do not face a marginal price when buying biopharmaceuticals. The buyer in most cases is either the nation in the case of national health systems, or the large PBMs, in the case of private healthcare (USA), or some national systems like Germany. This buyer, while not the patient, is the one that controls the formulary and pays at the margin, and so, from the point of view of the researcher, has revealed a valuation for the treatment. However, some of these buyers may have monopsony power and face political constraints, so using negotiated prices

may not closely reflect consumer welfare. An alternative approach to calculating welfare is to simply measure life years saved by the new innovations and multiply by QALY, though comparable data for many of these products is sparse. Our elasticities should therefore be interpreted only in terms of new product numbers and great care should be exercised before any welfare conclusions are explicitly or implicitly drawn from them.

We begin in section 2 by describing a simple model with testable implications we are investigating. Section 3 describes our data. Section 4 gives our detailed results. Section 5 concludes.

2 Theoretical Framework and Testable Implications

We are interested in the effect of expected market size on innovation. The model will consider that a market represents a set of products in a given therapeutic class (though in the empirics we shall test the robustness of our estimates to variations in the breadth of definition of such classes).

Consider the question of how firms expect the share of the potential revenues in a given market to vary according to their R&D investments. This problem has two parts: how much their investments will affect either the probability of discovering new drugs or the date at which they are discovered (or both), and how the discovery of new drugs will affect their revenues given the expected presence of other drugs on the market. Several simple models can be considered to study this relationship, and predictions differ according to the assumed exogeneity of the structure of the industry, to the number of firms, to the cost structure of R&D, and to the existence of R&D spillovers.

The model in AL describes a market in which drugs within a given therapeutic category are *only* vertically differentiated; at any one moment the best drug, and only the best, will capture the entire market. However, the top drug may not remain the best for long, and ongoing research may at any moment produce a better drug which will in turn capture the entire market, reducing the revenues of the previous best drug immediately to zero. The effort of pharmaceutical research will therefore consist in trying to produce the drugs that are better than existing drugs and hold that position for long enough to sustain their development costs before the next improved drug in the class arrives. The key point to note is that in their model firms adapt the flow rate of innovation precisely to the

market size at that period (this does not imply perfect flexibility of innovation outcomes, merely that firms have enough warning of future changes in market size - and enough foresight of the behavior of other firms - to be able to bring their innovations on stream at precisely the opportune moment). Also it is only market size at that point that matters, because a product's effective economic lifetime is essentially contained between the date of its launch and the date of the launch of a superior alternative, which in equilibrium may follow quite soon afterwards (though this short lifetime is compensated - to a degree that remains to be determined empirically - by the fact that in its short lifetime the product captures the entire market).

We do not follow AL's modeling assumptions for several reasons. First, as a practical matter, it is clear that many different treatments within the same therapeutic class have positive revenue in the same time period. This, along with the findings in the clinical literature, indicates that there is substantial horizontal differentiation in pharmaceutical markets. We want our model to reflect this feature of the industry. Secondly, we are interested in developing a model that will demonstrate a link between market size and the number of products. A model that allows the firm to choose its level of R&D will yield results that depend on the trade-off between horizontal and vertical product differentiation, issues that are not well explored in a model in which the highest quality product captures the entire market. For instance, Sutton (1991) shows that increasing market size may not alter concentration in the industry if increased quality successfully attracts consumers away from horizontally differentiated alternative products. In these circumstances a larger market size will lead the firm to invest in vertical differentiation which naturally results in higher quality products, but not in the entry of new firms. The reason is that margins must support the fixed costs desired by consumers; if they want high quality, then both market share and margins must contribute to covering those fixed costs, which means concentration must also be high. Increasing the degree of horizontal differentiation weakens the Sutton result because of the built-in incentive for a firm to serve a differentiated niche even with lower quality. Berry and Waldfogel (2010) illustrate this trade-off in their work comparing restaurants to newspapers. Because restaurants are more horizontally differentiated than newspapers and costs are mostly variable (unlike in newspapers), increasing market size does call forth new

firms and reduce concentration. By contrast, newspaper quality is improved using fixed costs and newspapers compete on vertical quality measures, so increased market size does not create new firms but rather raises the quality of incumbents. In their paper, the type of differentiation and the cost structure have the same response to increased market size and work together to create maximal difference in outcomes between the two industries. Our setting, pharmaceuticals, has significant horizontal differentiation but also significant fixed costs, thus not fitting neatly into the Berry and Waldfogel (2010) framework. We present below a model that allows for both horizontal and vertical product differentiation and where quality depends on fixed cost. We show that the number of firms increases in market size when fixed costs are exogenous. To address the Sutton point, we repeat the analysis for endogenous fixed costs and find the conditions under which we achieve the same result.

Lastly, our final concern with the AL vertical differentiation setup is that it is difficult to operationalize empirically, a point we will return to below.

2.1 A Simple Model of R&D with Horizontal Differentiation

The model is a version of the well-known circle model due to Salop (1979), extended to incorporate vertical differentiation in the manner of Armstrong and Weeds (2005). The Salop circle model is a nice choice for our problem because a natural number of firms fit round the circle in response to consumers' willingness to pay and fixed costs. In this framework, when a firm considers whether it should invest or not, it forms its expectations about revenues of the product over its lifetime, taking into account the productivity of its own research programs and those of its rivals. We assume that firms have rational expectations of the number of rivals, shares and prices.

Consider a circle of unit size, with a mass m of consumers uniformly distributed around the circle. Around this circle N firms are located at equal intervals. Firm i is located at point i/N, and incurs a fixed cost of investment to produce a drug of quality v_i which it sells at price p_i; the number of firms N will be determined by the requirement that the marginal firm makes zero profits (we shall ignore integer problems).

A consumer purchases at most one unit of the drug, and has an outside option yielding utility normalized to zero, so will purchase uniquely if doing so yields weakly positive utility. To simplify the

algebra we assume marginal costs of production are zero, though nothing in the qualitative results turns on this assumption.

Consider what happens if there is market coverage – every consumer buys from at least one firm. A consumer located at point c between firm i and firm $i+1$ and who is indifferent between the two will derive utility U_c where

$$U_c = v_i - p_i - t\left(c - \frac{i}{N}\right) = v_{i+1} - p_{i+1} - t\left(\frac{i+1}{N} - c\right)$$

from which we can define c, the location of the indifferent consumer under market coverage, as

$$c = \frac{i}{N} + \frac{1}{2N} + \frac{v_i - v_{i+1} - (p_i - p_{i+1})}{2t}$$

where t is the (linear) "transport cost", an indicator of the extent of horizontal product differentiation. In a symmetric equilibrium in which all firms' prices and qualities are identical, this means that the utility of the marginal consumer becomes

$$U_c = v_i - p_i - \frac{t}{2N} \tag{1}$$

Now, consider what happens if market coverage does not obtain. Then the indifferent consumer is defined by

$$v_i - p_i - t\left(c' - \frac{i}{N}\right) = 0$$

where c' is the marginal consumer in the absence of market coverage. This implies that

$$c' = \frac{i}{N} + \frac{(v_i - p_i)}{t}$$

In practice we shall see that it is always more interesting to look at the case of market coverage, since for a given market size m there will either be no entry or else firms will enter until the available space on the circle is entirely occupied.

Now consider the objective function Π_i of firm i. We look at two cases. First, there is the case of exogenous quality, then of endogenous quality with quadratic costs of investment in quality.

2.1.1 Exogenous quality

Let's assume that the quality of products is fixed exogenously and consider first that the market coverage is complete. Then, given the expressions for the indifferent consumers, we can derive the demand for each firm i and obtain the following objective function for the profits of firm i:

$$\Pi_i = mp_i \left(\frac{1}{N} + \frac{2v_i - v_{i-1} - v_{i+1} - \left(2p_i - p_{i-1} - p_{i+1}\right)}{2t} \right) - K$$

Taking first order conditions with respect to prices while qualities are fixed yields:

$$\frac{\partial \Pi_i}{\partial p_i} = m \left(\frac{1}{N} + \frac{2v_i - (v_{i-1} + v_{i+1}) + \left(p_{i-1} + p_{i+1}\right)}{2t} - \frac{2p_i}{t} \right) = 0$$

$$p_i = \frac{2t}{N} + \left(p_{i-1} + p_{i+1}\right) + 2v_i - (v_{i-1} + v_{i+1})$$

In a symmetric equilibrium where qualities and prices are identical among firms, this implies that

$$p_i = \frac{t}{2N} \tag{2}$$

We can now use the zero-profit condition to solve for the equilibrium value of N (ignoring integer problems). Substituting for equilibrium prices in the profit function yields

$$\Pi_i = \frac{mt}{2N^2} - K$$

which when profits are zero implies

$$N = \sqrt{\frac{mt}{2K}} \tag{3}$$

Then, industry profits are zero and industry revenue is K.

This yields a monotonic, strictly concave, relationship between market size m and the number of firms N (hence of pharmaceutical products in the market), with N proportional to the square root of m. From this we can derive

$$\frac{\partial N}{\partial m} = \frac{1}{2}\sqrt{\frac{t}{2mK}} = \frac{N}{2m} \tag{4}$$

which implies that the elasticity of N with respect to m is 0.5.

Note that we would obtain a similar qualitative finding with a quadratic transportation cost function $t(x) = tx^2$, as we would obtain $N = \left(\frac{mt}{2K}\right)^{\frac{1}{3}}$ with a corresponding elasticity of $\frac{1}{3}$.

To verify the conditions under which this is consistent with market coverage, note that substituting (2) into (1) implies that the indifferent consumer c has utility level

$$U_c = v_i - \frac{t}{N}$$

which for market coverage with exogenous quality implies, by substitution of (3), that

$$v_i \geq \sqrt{\frac{2tK}{m}}$$

So we can conclude that, if quality is exogenous and above some threshold ($\sqrt{\frac{2tK}{m}}$) that is increasing in the extent of product differentiation (t) and in fixed entry costs (K), and decreasing in market size (m), then the number of drugs in the market increases as the square root of market size.

In the case where the market would not be fully covered, it is straightforward to show that

$$p_i = \frac{v_i}{2}$$

Then, the profit function becomes

$$\Pi_i = \frac{m{v_i}^2}{4} = K$$

which implies that fixed costs of entry are either too high so that no entry occurs, or low enough so that entry occurs until it exhausts all available opportunities. This suggests that market coverage is the only interesting case to study.

2.1.2 Endogenous quality

In studying endogenous quality, we therefore look only at the case of full market coverage. Then, the profit function can be written as follows:

$$\Pi_i = mp_i \left(\frac{1}{N} + \frac{2v_i - v_{i-1} - v_{i+1} - \left(2p_i - p_{i-1} - p_{i+1}\right)}{2t} \right) - \left(K + \frac{\gamma(v_i - v)^2}{2} \right)$$

where $K + \frac{\gamma(v_i - v)^2}{2}$ is the cost of innovating with an innovation of quality level v_i.

This differs from the profit function when quality is exogenous only in that the fixed cost contains an element that is quadratic in the cost of increasing quality above a certain base level v.

Assume that firms first choose product quality as part of their R&D decisions, then choose prices once qualities are fixed. When choosing their R&D decisions they take the R&D decisions of other firms as fixed and therefore also their entry decisions, so N is taken as given by firms choosing quality.

In solving for prices we can no longer presume equilibrium is symmetric. We assume nevertheless that equilibrium is symmetric among firms other than firm i. Writing $p_j = p_{i+1} = p_{i-1}$ and analogously for qualities, taking first order conditions with respect to p_i and substituting in the analogous first order conditions for p_j yields

$$p_i = \frac{t}{N} + \frac{2\left(v_i - v_j\right)}{3}$$

Substituting for prices in the objective function yields

$$\Pi_i = m\left(\frac{t}{N} + \frac{\left(v_i - v_j\right)}{3}\right)\left(\frac{1}{N} + \frac{v_i - v_j}{3t}\right) - \left(K + \frac{\gamma(v_i - v)^2}{2}\right)$$

and taking first order conditions with respect to v_i yields

$$\frac{m}{N} + \frac{4m\left(v_i - v_j\right)}{9t} + \gamma v - \gamma v_i = 0$$

which, since equilibrium is symmetric, implies that

$$v_i = v + \frac{m}{\gamma N}$$

This incidentally implies that the condition for market coverage can be written as

$$v + \frac{m}{\gamma N} - \frac{t}{N} - \frac{t}{2N} \geq 0$$

which implies a threshold condition for v, namely that $v \geq \frac{3t\gamma - 2m}{2\gamma N}$.

We can now use the zero-profit condition to solve for the equilibrium value of N. Substituting for equilibrium qualities and prices in the profit function yields

$$\Pi_i = \frac{mt}{N^2} - \left(K + \frac{m^2}{2\gamma N^2}\right)$$

which when profits are zero implies

$$N = \sqrt{\frac{mt}{K}\left(1 - \frac{m}{2t\gamma}\right)}$$

A real solution for N requires that $\gamma \geq \frac{m}{2t}$, which will hold so long as the cost of improving the product is sufficiently great.

Then, we also have the equilibrium quality of products which is

$$v_i = v + \frac{1}{\gamma}\sqrt{\frac{mK}{t - \frac{m}{2\gamma}}}$$

which is increasing in K, decreasing in γ, t.

We can then differentiate N with respect to m to yield:

$$\frac{\partial N}{\partial m} = \frac{t - \frac{m}{\gamma}}{2\sqrt{mtK\left(1 - \frac{m}{2t\gamma}\right)}}$$

which is strictly positive so long as $\gamma > m/2t$.

The general conclusion about the relationship between market size and innovation derived in the model with exogenous quality therefore carries over to the model with endogenous quality, so long as the cost of improving quality is sufficiently high.

2.2 Empirical Implications

The choice made in modeling competition has an impact on the empirical work due to the need to measure potential market size. Recall that in AL, competition among pharmaceutical products is vertical; that is, consumers rank products identically and all purchase the best one. A firm's sales are thus zero in all periods in which its drug is not the highest quality. In the period when it has the best quality it has 100% market share in the category. The measure of market size that most closely fits the model is revenues in the entire class in the time period the new drug is launched. In practice, there are a number of drugs in that therapeutic class on the market earning positive revenues. All these are included in the measure of the size of the market, as a vertically superior drug could capture those revenues over a window of time.

Our model, by contrast, allows for horizontal competition. In our data, it is not typically the case that drugs take 100% market share serially upon entry. Rather, drugs are somewhat differentiated in their side effects and efficacy for different groups, and each can make positive sales over time with others in the same class. When a firm is considering investing in a horizontally-differentiated

innovation, we assume it is aware of these empirical patterns and has rational expectations about the market size of the therapeutic class and revenues a typical drug in that class might earn over its lifetime. We operationalize this as the present discounted value of sales of the average drug in that category, invented in that time period, over its lifetime (20 years).

To summarize, AL measure market size as the revenues that accrue to all drugs in a category that are available on the market in a given time window (regardless of the year of their launch), while we measure market size as the lifetime revenue accruing to the average product that is launched during a particular time window. Our approach has the advantage of taking into account horizontal competitors in the innovation process that are innovating around the same time.

Observed pharmaceutical revenues are an outcome of the equilibrium relationship resulting from competition on the basis of innovation among firms in the biopharma industry. We consider that firms take investment in research and development decisions based on rational expectations of the profitability of such innovations. Given the usual time lag between R&D and innovations, we expect firms to anticipate market size and rationally invest years in advance. For example, a firm releasing a drug at time t is supposed to have begun the research process at $t - 15$ if it expects that it will take 15 years to get approval for the new drug on a given market, taking into account the different phases of the innovation process from fundamental research through the final phase clinical trials. Thus assuming rational expectations by firms, the realization of an innovation should happen at the time it has been anticipated and be driven by the revenue finally realized by such innovation.

A virtue of our approach is that it does not require us to examine the laws and regulations of the nations in our dataset to determine the lifecycle and profitability of a new innovation in each country. Rather, we use the empirical measurement of brand revenue over time to tell us the effective patent length and market size (marginal costs are very low in the pharmaceutical industry). This allows us to abstract from the exact nature of competition among brands and how many entrants enter a market on average. Likewise, the state of generic competition when the patent does end is important in determining the effective period of brand exclusivity because differing regulations result in the brand keeping a substantial share of the market after generic entry in some countries and not in others.

Additionally, in some countries (such as the USA) the entry of the generic does not drive down brand prices, whereas in others it may. Any other aspect of the IP regime that affects the brand's ability to earn profits, such as litigation by generics to end the patent term early, compulsory licensing, etc. will appear in the data as part of the revenue lost by the brand. Alternative IP provisions such as data exclusivity will likewise lengthen the effective period of brand exclusivity by keeping the cost of generic entry high (the entrant has to perform all the clinical trials again). In summary, the revenues of the brand over time will tell us what the effective market size is. We use revenue therefore as a summary statistic for differences in IP protections, entry costs, regulations, population, and wealth across countries.

Lastly, our measure of innovation is a count of new chemical entities (NCE) by therapeutic category launched anywhere in the 14 countries from which we have revenue data. While lumpy because of their small numbers, we consider these products to be uncontroversially innovative. Drug approval agencies such as the FDA in the US will approval new varieties and forms of existing medications (e.g. extended release, injectable versus oral) and generic drugs; these do not fall into our definition of innovative.

A final important empirical issue is that of reverse causality. We are interested in the extent to which a larger potential market stimulates innovation. However, a successful product, the result of that innovation, generates revenue, and thus the innovation can also create the market. AL use expenditure in the category in one of their five year time windows (times contemporaneous population) as a measure of potential market size for a new drug. They do not directly address the issue of whether unusually successful new drugs cause expenditures in that time period and category, and therefore generate causality moving in the reverse direction. Our method, as described in detail below, instruments for market size. Population of different ages and disease incidence around the world are our instruments for current market size. These measures are likely to be correlated with market size, yet unaffected by particular pharmaceutical innovations.

3 Data description

Our data set from IMS (Intercontinental Marketing Services) Health includes all product sales in 14 countries (Australia, Brazil, Canada, China, France, Germany, Italy, Japan, Mexico, Korea, Spain, Turkey, United Kingdom, USA) between 1997 and 2007 (except for China, where 1997 and 1998 are missing). The data report sales by value and unit volume for all pharmaceutical and biologic products. All values are deflated into 2007 US$ using the US consumer price index. The database reflects sales for all compounds in all 14 countries through retail pharmacies, hospitals and HMOs, and includes characteristics of drugs like their four-digit Anatomical Therapeutic Classification (ATC4) (607 different classes are reported), the main active ingredient of the drug (6216 different active ingredients are reported), the name of the firm producing the drug, whether it has been licensed, the patent start date, and the format of the drug (471 different formats are reported). Products in the same ATC4 by definition have the same indication and mechanism of action. Some other available and interesting drug characteristics are its brand type - licensed brand, original brand, other brand, or unbranded - and (when applicable) its patent expiry date - ranging from 1966 to 2030 in the available data, and which may differ from one country to another. We consider only ethical drugs and not OTC drugs. Quantities are given in standard units, one standard unit corresponding to the smallest common dose of a product form, as defined by IMS Health.

Overall, the initial dataset has 6,163,465 observations (one per drug, country, year) but only 2,972,419 have strictly positive revenues and quantities (many observations correspond to years where the drug was not yet launched, or had disappeared in a given year and country, or to missing data on revenues or quantities). As for China, all observations for 1997 and 1998 have been dropped, revenues and quantities are zero at the same time for all drugs. It is clear that China was not observed these years, for unexplained reasons. After removing observations with zero revenue or quantity, some active ingredients and ATC4 classes disappear but we still have 6091 different active ingredients and 606 ATC 4 categories. Then, only the 251,558 branded drugs were kept (i.e. those where the brand type is either a licensed brand or the original brand) in order to focus on revenues from patented pharmaceutical innovations. This leads to dropping data from one country, India,

where brand type is always unavailable in the data ('patent N/A'). In addition, this restriction leads to dropping many other active ingredients (4503), formats (217) and ATC4 (217) that appear in generic form only. Finally, since patents last 20 years, only the 68,219 observations that have their first patent date (throughout the different countries) after 1977 are kept, in order to have at least one observation (revenue & quantity) in all countries where the drug was sold. This leads to dropping 158,904 observations of old products with older first patent date, 5,568 with unknown first patent date and 18,867 with uncoded first patent date. In total, our restrictions to current branded products with complete data leads us to drop 1083 active ingredients, 151 ATC4, 109 formats and 30 patent years. We end up with a data set where 630 active ingredients are present in 238 ATC4 classes. We also categorize drugs into coarser ATC categories.

In the IMS data set, there are around 900 distinct on-patent products (that is, products which are on patent at some time during the 11 years of the data). Some of these are basically the same product in a different package.

All sales and prices are at the manufacturer levels, as reported by IMS, and thus approximate actual prices, except to the extent of off-invoice discounts. We believe these off-invoice discounts are not a very large factor in our data. For the US, Danzon and Furukawa (2006) compared the IMS prices with US average sales price (ASP), which includes all discounts, as reported by the Centers for Medicare and Medicaid Services (CMS) for the corresponding quarter, and found that on average, the IMS prices are similar to the ASPs. However, to the extent that unmeasured discounts exist, prices and revenues may be overestimated here.

We also use demographic data (population and mortality data) from the World Health Organization (WHO)[2]. Population has been extracted for the studied countries from available years since 1970. For all available country-year, population is known by sex (M/F) and by age distribution (0, 1-4, 5-9, ..., 70-74, 75+), except for Mexico in 1977, where only total population by sex is available. Missing population information is reconstructed through a regression in logs on a country specific effect and a time trend which amounts to assuming that population evolves at a country specific annual growth rate between available years of data that is allowed to change over time at the same rate across countries.

[2]See http://www.who.int/whosis/mort/download/en/index.html.

Mortality data across years and countries are available per disease category as classified using the ICD-10 classification. The International Classification of Diseases (ICD) has evolved over time and the most recent one is the ICD10 version. Of courses, disease categories and drug categories (ATC classes) are different things but one can attribute to each ATC class a "most likely" disease category in the ICD 10 classification. These are summarized in Table 13 in the Appendix.

It is important to realize that the time series dimension of the demographic data contains little "news", at least from year to year. Population projections change only slowly over time, as do mortality risks in any given demographic category.

The dependent variable is the total number of new chemical entities marketed anywhere in our 14 countries in a given disease category throughout a given time period. Only about one-third of the drugs approved annually in the United States are new compounds, or chemical entities; the rest represent modified forms or new uses of existing drugs.

These data in combination allow us to measure how the global size of the market for a drug in a particular category, for example, cardiovascular, shifts over years according to population and disease profile, and also allows us to see how many new NCEs (New Chemical Entities) pharmaceutical firms launch as the market size changes.

4 Estimation Method

4.1 Heuristic description

The first step in estimating the elasticity of innovation is the construction of an expected revenue measure. We do this by measuring market size over time for various disease categories in our set of countries. Then we measure how many new products are introduced over time, again by category. We describe our empirical procedure below.

We exploit differences across brand revenue in different therapeutic categories and different countries to estimate the potential market for an innovator in those different countries. For example, at launch the brand will have a share of revenues in the therapeutic category in the country. These revenues may change over time as the brand goes through its lifecycle, and will begin to decline when the patent expires and the brand faces significant new competition, or when the entry of substitute

drugs causes the brand's price and/or share to drop. These patterns will vary across jurisdictions.

Price levels are determined by willingness to pay and the level of competition among products. A nation's ability and willingness to pay for healthcare will depend on whether it is nationally or privately financed and on the preferences of consumers and voters. In general, prices for biopharmaceuticals are higher in richer countries compared to poorer ones. Competitive conditions also vary by country according to the conduct of buyers, and these affect the realized market size available to the innovator. The different income levels and competitive landscapes across different nations will affect the price levels observed in the data. In general, prices, market structures, entry, market exclusivity and other features vary across countries. We will not model these because we can measure the average outcome, namely revenue per drug, and we assume firms anticipate these market conditions when making R&D decisions.

Then, our data let us compute the true global revenue obtained per innovation as observed in sales revenue in the data. The advantage of such an approach is that the global revenue from an innovation depends on the population using the new drug during its life cycle (not only on a given shorter period of time) and on the willingness to pay of drug users, which is allowed to vary over time (in contrast to Acemoglu and Linn, 2004).

This approach thus takes into account the fact that each innovation has a life-cycle in the market for pharmaceutical products which is clearly anticipated and which implies that sales are not uniformly distributed during the duration of the patent life. It is expected that the diffusion of an innovation may take some time, and that consumer-prescribers may have switching costs or learning costs that delay the full adoption of an innovation. Moreover, the lifecycle of a drug is typically affected by the competing and future innovations in the same drug category.

As mentioned above, there are two possible causal relationships that can appear in the data, working in opposite directions. Market size and innovation might be positively related because a particular market is expected to grow and therefore firms invest in new products for that market. This is the relationship of interest in the paper. A second possibility is that a successful innovation generates large sales due to its quality and novelty, and this causes the market (measured in dollars)

to be large.

To deal with this second possible relationship, we employ an instrumental variables approach. We use as an instrument for each drug category a *potential* market size. We operationalize this idea by using population by age or gender by country and disease prevalence in different countries. We do not use actual expenditures in any way in our instrument. We note that AL defines "expected market size" and employs it as an explanatory variable, not an instrument. Expected market size is either the sum of expenditures on the class for all ages, or the sum of the number of drugs in the class used by different ages weighted by population. A feature of our method we want to highlight is our effort to avoid using the outcome of interest, innovation, in potential market size – either as number of drugs or dollars.

Our instruments do not include expenditure, number of patients, or number of drugs available. Our instruments are the population in different age categories by country and disease prevalence in different countries. For these to be valid instruments we must assume innovation does not affect potential market size, which requires that there are no changes in WHO-measured morbidity or mortality that are driven by the innovation in the short run. Indeed, innovation in class c at period t can affect future longevity and potential market size of later periods but not that of the current and subsequent periods corresponding to the patent life of the innovation. It seems reasonable to assume that class specific innovations cannot affect population size in the short run because of competing risks in other disease categories are likely to limit the immediate effect on mortality of an innovation.

4.2 Formal Definition of Market Size

Let d denote an active ingredient (or chemical entity) in a particular use class, hereafter known as a drug (all revenues correspond to revenues summed at the level of the chemical entity for different forms or brands with that chemical entity). We denote by R_d^t the revenue obtained for drug d at year t. Given that the IMS data are converted into current dollars taking already account of each year's exchange rate, we measure these revenues by summing all countries' sales and transform them into constant US dollars of 2007 using the Consumer Price Index for inflation. Our average drug has positive revenues for about twenty years (while the patent only last for 20 years, the brand is not

typically launched until years after filing, and brands typically earn profits after patent expiration in many markets.) This leads us to write the total revenue obtained thanks to the patent for drug d as

$$\widetilde{R}_d = \sum_{t'=t^0}^{t^0+20} \delta^{t'-t^0} R_d^{t'}$$

where δ is the discount factor. We assume that these discounted revenues per drug determine investment decisions of firms.

We denote by $\mathcal{C} = \{1, .., C\}$ a partition of the set of therapeutic classes (the 1 digit ATC classes). For a sub-set of drugs in set $c \in \mathcal{C}$ that are launched in year t, we denote by W_c^t the sum of global revenues obtained in this segment c by all innovations of period t :

$$W_c^t = \sum_{\{d \in c, t^0 = t\}} \widetilde{R}_d$$

We will call this the "period t innovation - class c" market size.

Then, we denote by N_c^t the number of new chemical entities (active ingredients) patented at t in class c. There is no revenue W_c^t ($W_c^t = 0$) when no drug was patented that year in that category.

As our model shows, we expect a positive relationship between market size and innovation. In the empirics this shows up as the relationship between the number of new chemical entities per class in period t (N_c^t) and the period t innovation size of class c (W_c^t).

The arrival of new products on the market is stochastic due to uncertainties in the research process and in regulatory approval. Our measure of innovation in a single year will be lumpy from year to year and contain zeros. However, as discussed above, because there is little new news in demographics every year, we use periods of 4 years for t, a procedure which smooths out our innovation measure N_c^t.

4.3 Imputation of Revenues over Drugs Life-cycle

Before going further on the empirical estimates, it is important to observe that we cannot forecast expected revenues entirely by taking means of actual revenues by therapeutic class, entry date, and year, because we do not see enough drugs nor the entire lifecycle of most drugs in the data since we observe only 11 years of data. Thus, we implement an imputation method to obtain a series of parameters for each ATC class that allows us to predict revenue for a drug over its entire lifecycle

using the average lifecycle within the class. We then use this estimate as the forecast of manufacturers making innovation decisions.

Thus, for a given drug d, the data do not allow us to observe all the R_d^t for years t^0, t^0+1, ..., t^0+19. As we want to take into account the lifecycle of drugs, we compute the average evolution of revenues of new chemical entities within a class c between patent age τ and $\tau+1$ as the ratio between patent age τ and $\tau+1$ of average revenue (across active ingredients) for all drugs of a given drug category c. Defining $\Gamma(c)$ as the set of drugs in class c, we can also use the following definition [3]:

$$\lambda_c^\tau = \frac{1}{\#\Gamma(c)} \sum_{d \in \Gamma(c)} \frac{R_d^{t^0+\tau+1}}{R_d^{t^0+\tau}}$$

Assuming that the expected revenue of a drug of class c will follow the life-cycle pattern estimated using these λ_c^τ we can estimate the revenue at a given future patent year. Then, when $R_d^{\tau+1}$ is not observed, we estimate it with $R_d^{t^0+\tau+1} = \lambda_{c(d)}^\tau R_d^{t^0+\tau}$ which allows us to reconstruct the lifecycle revenues of any drug on the market during the period of our data.

5 Empirical Results

We will consider two levels of ATC classes $\mathcal{C}$ and $\mathcal{C}'$. The finer level of classification (2 digit ATC classes) considered will be $\mathcal{C}'$. A class denoted c' will thus correspond an element of this finer classification. With the previous notations, $\frac{W_c^t}{N_c^t}$ is the revenue per new chemical entity in class c and patent period t. All revenues are expressed in thousands of 2007 US dollars and the discount factor used is $\delta = 0.95$.

5.1 Descriptive Statistics

Table 1 presents descriptive statistics by ATC class on the number of innovations and lifecycle revenues per ATC class at level 1. Table 2 shows the same statistics as Table 1 but using the 2 digit ATC classification. Tables 3 and 4 present the same data as Tables 1 and 2, but averaged not over ATC class but according to the number of new chemical entities. This shows a broad descriptive relationship between market size and the number of new chemical entities.

[3] Using a definition of λ_c^τ that gives weights to active ingredients proportional to their revenue in the class, we have $\lambda_c^\tau = \frac{\sum_{d\in\Gamma(c)} R_d^{t^0+\tau+1}}{\sum_{d\in\Gamma(c)} R_d^{t^0+\tau}}$, which leads to similar results.

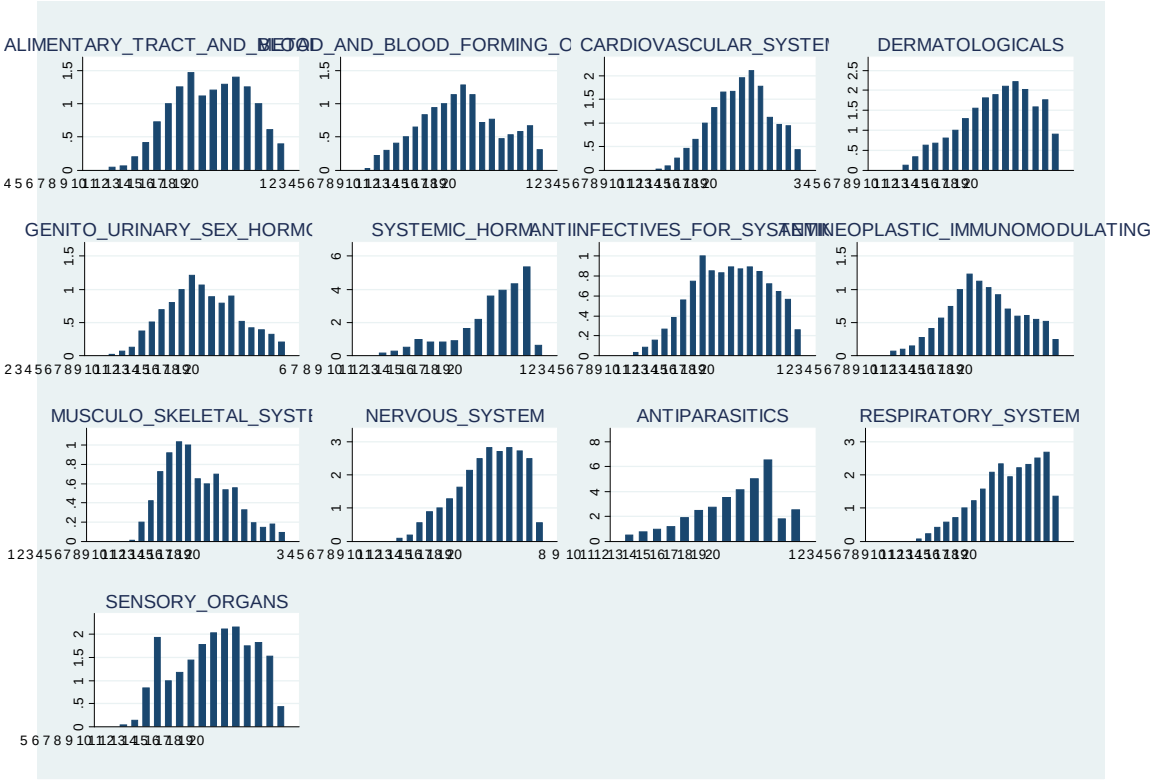

Figure 1: Means of Revenue by Patent Age for Each ATC-1

On average, the total revenue per ATC class seems to be increasing with the number of innovations except when the number of innovations is the largest. This result holds on aggregate and does not account for the heterogeneity of revenues and innovations across categories of ATC classes.

5.2 Lifecycle of drugs

In order to impute some unobserved revenues, we described above a method of imputation which consists in estimating average lifecycle of drug revenues per ATC class. The estimation of these average lifecycle of drugs is interesting and shown in next Figure 1 for all categories (digit 1 ATC classes) and patent ages. Figure 1 shows the mean revenues of drugs by class for each patent age and ATC-1. Remark that for these shapes to be seen on a same picture, we have normalized the total sales for patent year 10 for all drug classes, which implies that the height of each vertical bar should not be compared across drug categories.

We can see that the lifecycle of sales of drugs is not uniform across classes. Some classes have longer

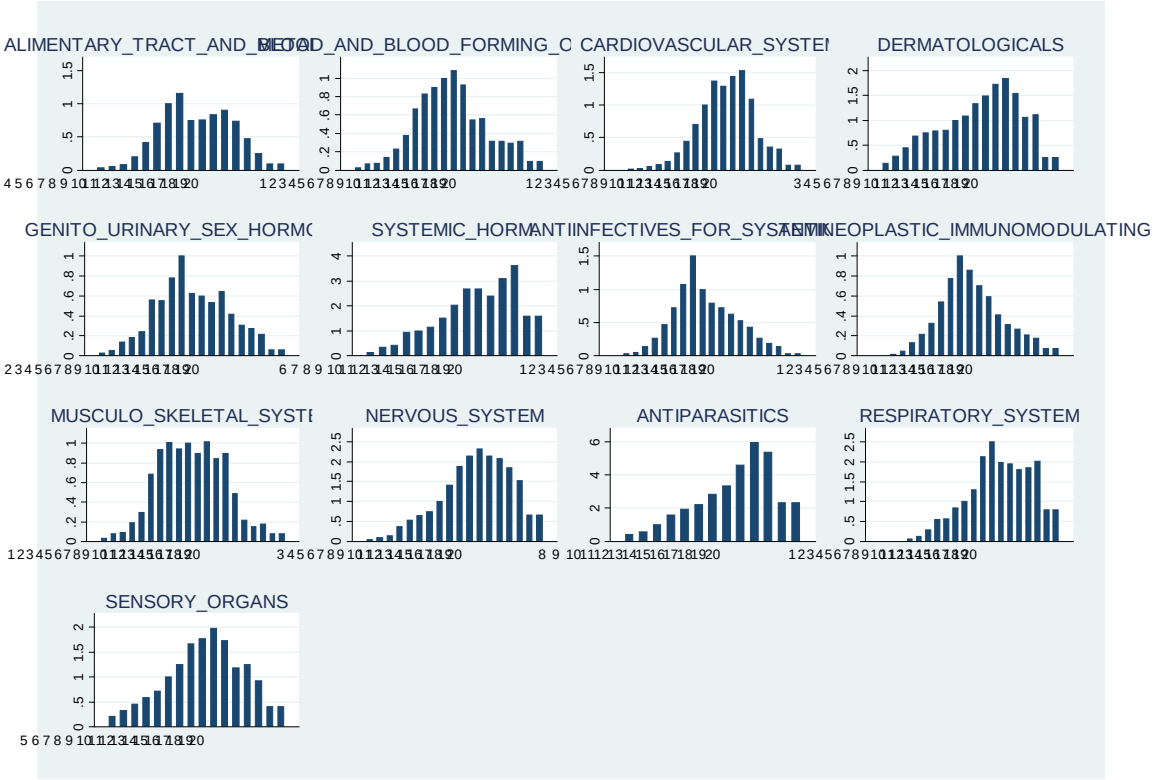

Figure 2: Estimated λ_c^τ by ATC-1 and patent age

delays of penetration, some classes have lower duration. These lifecycle shapes also show that sales are not at all uniform during the patent life and thus that it seems important to take into account the expected lifecycle of the patent revenues of drugs in the incentives to innovate for the pharmaceutical industry.

This variability shows why the coefficients λ_c^τ will have some variation across patent age and across classes. Figure 2 shows the obtained coefficients for all classes and patent ages. These coefficients will be used for imputation of life-cycle revenues for future years on still young drugs. Though these life-cycle of revenue per drug are averages, our estimated revenues using expected life-cycle patterns are valid provided firms do not have better information on expected revenues during the lifecycle of new drugs.

5.3 Elasticity of Innovation to Market Size

We now look at the relationship between the number of innovations or New Chemical Entities N_c^t at period t in category c and our "market size" W_c^t. In each year we have data from 238 therapeutic classes. As noted above, we sum revenue and innovation in four year periods (which reduces the sample size but creates much more content to each observation). Our time periods t are thus 1977-80, 1981-84, 1985-88, 1989-92, 1993-96, 1997-2000, 2001-04.

We use several specifications to estimate the elasticity of innovation with respect to market size. First, we estimate the following model

$$\ln N_c^t = \alpha \ln W_c^t + \beta_c + \delta_t + \varepsilon_c^t$$

which relates the number of innovations (number of NCEs) patented in period t in each class to the total revenue provided by sales of all drugs (on patent and licensed) in the class during the duration of the patents issued at t.

In this reduced form model, α can be interpreted as the elasticity of innovation to market size, β_c is a fixed unobserved effect specific to the ATC class c, δ_t is a common unobserved period effect and ε_c^t an unobserved random shock on the innovation outcome.

Assuming all right hand side variables are exogenous means that

$$E\left(\varepsilon_c^t | \ln W_c^t, \beta_c, \delta_t\right) = 0$$

We first estimate such a model using OLS. Then we employ 2SLS because of the strong likelihood, previously discussed, that innovation drives market size. Our instrumental variables are demographic: population and disease prevalence in different countries. To be valid instruments, demographics and disease prevalence must be correlated with market size. It is intuitive that the population and the share of the population likely to use drugs in each ATC class will be correlated with the revenue in that class. Secondly, innovation, or launch of new products, must not cause changes in demographics or disease prevalence. We can imagine that at a very fine level of categorization, this could be a problem. For example, a pill for Ausberger's (mild autism) might well increase diagnoses of Auberger's and therefore autism. But the WHO data we use are much coarser: for example, how many people died of

cardiovascular diseases in period t. We do not think the therapies available for different cardiovascular diseases affect this measurement.

For this reason, we use male, female, and "more than 50 years old" population variables, as well as the number of deaths of males and females for the disease categories that each drug class (ATC class) can be considered to target. This instrument is thus varying across periods and drug classes. These set of instruments are interacted with dummy variables for 1-digit ATC classes or 2 digit ATC classes depending on the cases.

For the population measures we compute the size of the population in countries where drugs of each ATC class are sold and sum this over countries and years for the duration of the patent. This population is denoted P_t^c. This instrument is varying not only over time but also across ATC classes. We use a similar definition for male or female population, and for the "over 50 years old" population. Table 6 details the different sets of instruments used in the regressions below. As will be shown later, these sets of instruments satisfy the different usual tests of exclusion (Sargan test of overidentifying restrictions) and of significance in the first stage (F test of joint significance of excluded IVs in the first stage regression). In our empirical work, set A will be used for regressions at the ATC-1 level and B, C or D for regressions at the ATC-2 level.

Recall that the number of innovations N_c^t that can be observed on each market is censored at zero, and that W_c^t is unobserved when there are zero innovations. We have a fundamental problem of unobserved potential market size of any innovation that did not happen and therefore need a truncated regression model. In particular, it could be that ε_c^t is not mean independent of all right-hand-side variables because of the truncation of the model when $N_c^t = 0$.

With some parametric assumptions on ε_c^t, one can estimate the model taking into account the truncation[4]. For example, as we are dealing with count data, we can assume a Poisson distribution for the number of innovations, such that

$$P\left(N_c^t = n\right) = \frac{\exp\left(-\mu\right)\mu^n}{n!}$$

[4]Nonparametric estimation of such a truncated regression model is difficult and is a subject of ongoing research (Lewbel and Linton, 2002, Chen 2009). Chen (2009) and Lewbel and Linton (2002) show that if the exogeneity assumption of right hand side variables is satisfied, then with some additional technical assumptions, one can identify the non parametric conditional expectation of the truncated dependent variable conditionally on the right hand side variables.

where we specify the intensity parameter μ as $\mu = \exp\left[\alpha W_c^t + \beta_c + \delta_t\right]$. Such a model implies that

$$E\left(N_c^t | W_c^t, \beta_c, \delta_t\right) = \exp\left[\alpha W_c^t + \beta_c + \delta_t\right]$$

As the data are truncated at zero since W_c^t is unobserved when $N_c^t = 0$, we correct for the truncation using the zero-truncated Poisson maximum-likelihood regression implying that

$$P\left(N_c^t = n | N_c^t > 0\right) = \frac{\exp\left(-\mu\right)\mu^n}{n!\left(1 - \exp\left(-\mu\right)\right)} \text{ with } \mu = \exp\left[\alpha W_c^t + \beta_c + \delta_t\right]$$

In this case, we take into account the endogeneity of W_c^t using the control function approach. As suggested by Wooldridge (2002) and Blundell and Powell (2003), this technique is useful for non linear models. It amounts to perform a first stage regression of the endogenous variables on all exogenous variables and excluded instruments and then use residuals and polynomials of these residuals as additional "control" variables in the main regression (here the zero-truncated Poisson). The results of this first stage regressions are shown in Table 14 in appendix and show that excluded instruments are statistically significant (as confirmed also by the joint F test shown at the bottom of the Tables). Results show that excluded IVs from sets A, B, C or D are significant and the F test of joint significance always rejects strongly that they have no explanatory power. In the case of the control function approaches, we used sets of instruments A for analysis of N_c^t and D for $N_{c'}^t$ but results are similar with other sets of instruments. In the case of ATC-1 level regressions, instrumental variables A proved satisfactory and consist in male and female population of corresponding countries, male and female deaths of corresponding ATC-1 class and countries. In the case of ATC-2 level regressions, instrumental variables B, C or D proved satisfactory and consist different male or female demographic variables interacted with ATC-1 or ATC-2 dummies.

In all following tables, standard errors are clustered at the class level and show in parentheses. Also, dummy variables δ_t for time periods are not shown to conserve space. They are always significant. Tables 7 and 8 show the results of estimating the linear model for the 1-digit and 2-digit ATC categories respectively. Tables 9 and 10 show the corresponding results of the estimation of the count models. In each case we show results with and without instrumenting for potential market size. All standard errors are clustered at the ATC-1 level.

The specifications yield a range of elasticities between 6% and 40%, meaning that increasing market size by 1% yields an increase in the number of new products of .06 to .4%. There is no clear relationship between the elasticity and the type of specification (linear versus count, one-stage versus two-stage) or the instrument set. Overall, our preferred specification among these is Equation (13). It takes into account the truncated nature of the data and the need to use instrumental variables, and it uses the finer set of instruments in which the demographic variables are interacted with 2-digit therapeutic categories, thus taking account of the fact that different demographic profiles generate different market sizes in the various treatment categories. It uses the finer 2-digit disease classification for the dependent variable, which we prefer because we understand it is relatively rare for drugs in one ATC-2 category to be discovered while searching for therapies in a different ATC-2 category.

Equation (13) yields an elasticity of 12.3%, with a t-ratio of around 5, which gives the elasticity a confidence interval of around 8% to 17%[5] Given the assumptions of our model, this implies that entry costs must be increasing in market size (since the marginal innovation requires substantially higher revenue than the average innovation). Since we have no independent measure of quality we cannot of course rule out the possibility that this is because the quality of pharmaceutical products is increasing as market size increases. However, another interpretation is possible, which is that innovation is subject to significant decreasing returns. This may be true both with respect to number of innovations in a segment (the industry may running out of "low-hanging fruit" - see Cowen 2011), and also true over time - the costs of regulatory approval appear to have been rising in recent years. Although our results do not directly test the "low hanging fruit" hypothesis they are certainly compatible with it.

However, for this very reason the assumption that the elasticity is the same across disease categories may not be realistic, since the extent to which the industry has had low-hanging fruit may well vary for scientific reasons from one disease category to another. To investigate this possibility we estimate the count model with ATC specific market size coefficients α_c using

$$P\left(N_c^t = n | N_c^t > 0\right) = \frac{\exp\left(-\mu\right)\mu^n}{n!\left(1-\exp\left(-\mu\right)\right)} \text{ with } \mu = \exp\left[\alpha_c W_c^t + \beta_c + \delta_t\right]$$

which also implies that the elacticity to market size of the expected number of innovations is $\frac{\partial \ln EN_c^t}{\partial \ln W_c^t} =$

[5] This point estimate enables us easily to reject the hypothesis of an elasticity equal to $\frac{1}{2}$ or even to $\frac{1}{3}$ (the latter being the predicted elasticity under the hypothesis of quadratic transport costs of product differentiation).)

αW_c^t.

Given the size of the elasticity, we can also compute how much additional revenue in a given drug category is needed to obtain one additional innovation as the inverse of the elasticity times the average revenue per innovation observed on the market (because $dW_c = \left(\frac{\partial \ln N_c}{\partial \ln W_c}\right)^{-1} \frac{W_c}{N_c}$)

Table 11 reports such results and Table 12 reports then the obtained elasticities by ATC class. We find higher elasticities on average than in the model with the elasticity constrained to be constant across disease categories, though they remain within the range of elasticities found under previous specifications.

We see that the elasticities of innovation vary by ATC class, and that the average lifecycle discounted market size increase needed on average to obtain one additional NCE also varies across classes. For comparison, we estimate the log-linear model with ATC-1 specific elasticities (results not reported), and find larger absolute values than in a specification without heterogeneity. The values are a little smaller than those of this count model, varying between 8% and 30% depending on the disease class.

Across all ATC classes, we find that the average elasticity of innovation to market size under this specification is 25.2%, which implies that the average lifecycle discounted market size increase needed to obtain one additional NCE is around $1.8 billion. Remember that we used a discount factor of 0.95 which implies that the $1.8 billion over the lifecycle of a drug is equivalent to a constant annual revenue of $148 million per year over 20 years.

Next we consider whether this estimated $1.8 billion is reasonable. The most recent DiMasi et al. study of drug development estimates that a new drug incurs approximately $800 million in development costs (Adams, 2006, Di Masi et al. 2005 suggest 1$billion on average for one new chemical entity). Included in this calculation is the cost of capital, the cost of failed drugs, and the cost of clinical trials, so it is close to the total fixed economic cost of innovation. On top of this there will be variable costs of production, distribution and marketing. Industry sources have suggested to us that 50% of revenue is a reasonable guess at the size of these costs (though they may be higher in the case of biologics, where manufacturing costs are typically higher). This suggests that a new drug would need to cover

costs of around $1.6 billion in order to yield a return to the innovator. This is a little lower than our estimated market size increase of $1.8 billion needed to induce an additional innovation. Our elasticity estimate therefore seems broadly plausible in the light of what is known from accounting data.

Comparing our elasticities to others in the literature is difficult, if only because the dependent variable changes across research designs from new drugs, to new cancer regimens, to new clinical trials, to journal articles. However, both AL and we use new product launch as a measure of innovation. Recall that AL estimate an elasticity of 4: for each 1% increase in revenue, the number of new products increases by 4%, which is over an order of magnitude larger than our estimate (and of most others in the literature). There are significant empirical differences that underlie these two different results. For example, *all* new products including new forms, strengths, and generic versions are counted in the AL methodology. The authors include only US revenue in their measure of market size. Lastly, as noted above, the method in AL does not include an instrument for market size. Though it is hard to know the impact of these methodological differences, an elasticity as large as 4 appears to imply that marginal costs of innovation are falling as more innovation takes place, which does not seem a plausible description of the pharmaceutical industry in the early 21st century.

6 Conclusion

This paper has attempted to quantify the relationship between market size and innovation in the pharmaceutical industry. We have estimated the elasticity of innovation (as measured by the number of new chemical entities appearing on the market for a given disease class) to the potential market size represented by the willingness of sufferers of diseases in that class (and others acting on their behalf such as insurers and governments) to spend on their treatment. We have found positive significant elasticities with a point estimate under our preferred specification of 25.2%. This suggests that at the mean market size an additional $1.8 billion is required in additional revenue to induce the invention of one additional new chemical entity, which appears a reasonable order of magnitude since estimates of the true economic cost of developing a new chemical entity are around $800 million to $1 billion, and marketing and related costs represent some 50% of revenue. An elasticity substantially below

one-half is also plausible in the light of other evidence that innovation in pharmaceuticals is becoming more difficult and expensive over time, and is compatible both with the hypothesis that the costs of regulatory approval are rising and the hypothesis that the industry is running out of "low hanging fruit."

Our results are robust to a number of specification choices. However, the availability of data for more years would undoubtedly help to refine our estimates and we leave this as a subject for future research.

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7 Appendix

7.1 Analysis of Elasticity to Contemporaneous Revenue

Suppose we assume instead that $\ln N_c^t = \alpha W_c^t$. In this case we would want to know the bias that comes from using the contemporaneous revenue R rather than W.in our empirical work This amounts to study the derivative of $E\left(\ln N_c^t | R_c^t\right)$ with respect to R_c^t. Then,

$$\begin{aligned}
\ln N_c^t &= \alpha \sum_{\{d \in c, t_a^0 = t\}} \widetilde{R}_d = \alpha \sum_{\left\{d \in c, t_d^0 = t\right\}} \left(\sum_{t'=t_d^0}^{t_d^0+20} \delta^{t'-t_d^0} R_d^{t'} \right) \\
&= \alpha \left(\sum_{\left\{d \in c, t_d^0 = t\right\}} R_d^t \right) + \alpha \left(\sum_{\left\{d \in c, t_d^0 = t\right\}} \sum_{t'=t+1}^{t_d^0+20} \delta^{t'-t_d^0} R_d^{t'} \right) \\
&= \alpha R_c^t - \alpha \left(\sum_{t'<t} \sum_{\left\{d \in c, t_d^0 = t'\right\}} R_d^t \right) + \alpha \left(\sum_{\left\{d \in c, t_d^0 = t\right\}} \sum_{t'=t+1}^{t_d^0+20} \delta^{t'-t_d^0} R_d^{t'} \right)
\end{aligned}$$

because $R_c^t = \sum_{\{d \in c\}} R_d^t = \sum_{t'<t} \sum_{\left\{d \in c, t_d^0 = t'\right\}} R_d^t + \sum_{\left\{d \in c, t_d^0 = t\right\}} R_d^t$.

Then

$$E\left(\ln N_c^t | R_c^t\right) = \alpha R_c^t - \alpha E\left(\sum_{t'<t} \sum_{\left\{d \in c, t_d^0 = t'\right\}} R_d^t \middle| R_c^t \right) + \alpha E\left(\sum_{\left\{d \in c, t_d^0 = t\right\}} \sum_{t'=t+1}^{t_d^0+20} \delta^{t'-t_d^0} R_d^{t'} \middle| R_c^t \right)$$

and both $E\left(\sum_{t'<t} \sum_{\left\{d \in c, t_d^0 = t'\right\}} R_d^t \middle| R_c^t \right)$ and $E\left(\sum_{\left\{d \in c, t_d^0 = t\right\}} \sum_{t'=t+1}^{t_d^0+20} \delta^{t'-t_d^0} R_d^{t'} \middle| R_c^t \right)$ have no reason to be zero if there is some correlation between revenues for the same drug across periods (which is obviously the case). Remark that if revenues per drug are all independent and that we only have time autocorrelation of revenues then both terms should be positive and thus $E\left(\ln N_c^t | R_c^t\right)$ could be either higher or lower than αR_c^t.

If for example the revenues of a drug d in year t and t_d^0 are proportional to a scale factor depending only on the class to which it belongs to and the patent age $t - t_d^0$, then $R_d^t = \lambda_c^{t-t_d^0} R_c^{t_d^0}$ and

$$E\left(\ln N_c^t | R_c^t\right) = \alpha R_c^t \left[1 + \left(\sum_{\left\{d \in c, t_d^0 = t\right\}} \sum_{t'=t+1}^{t_d^0+20} \delta^{t'-t_d^0} \lambda_c^{t'-t_d^0} \right) \right] - \alpha E\left(\sum_{t'<t} \sum_{\left\{d \in c, t_d^0 = t'\right\}} R_d^t \middle| R_c^t \right)$$

where $\sum_{\left\{d \in c, t_d^0 = t\right\}} \sum_{t'=t+1}^{t_d^0+20} \delta^{t'-t_d^0} \lambda_c^{t'-t_d^0}$ would be equal to 20 if revenues are constant per drug during the patent life and there is no discounting. Thus, unless $E\left(\sum_{t'<t} \sum_{\left\{d \in c, t_d^0 = t'\right\}} R_d^t \middle| R_c^t \right)$ is also positive and very large, $\frac{\partial E\left(\ln N_c^t | R_c^t\right)}{\partial R_c^t}$ would be much larger than α.

7.2 Main Tables

ATC class ($\mathcal{C}$)	W_c^t	Mean $\frac{W_c^t}{N_c^t}$	N_c^t
A: ALIMENTARY TRACT AND METABOLISM	1,997,804	163,861	11.14
B: BLOOD AND BLOOD FORMING ORGANS	3,702,647	500,500	6.67
C: CARDIOVASCULAR SYSTEM	3,308,496	244,188	15.40
D: DERMATOLOGICALS	154,468	26,107	5.00
G: GENITO URINARY SYSTEM AND SEX HORMONES	766,613	186,571	5.33
H: SYSTEMIC HORM.PREP., EXCL. SEX&INSULINS	12,370	5,821	2.20
J: ANTIINFECTIVES FOR SYSTEMIC USE	5,143,922	287,501	14.86
L: ANTINEOPLASTIC&IMMUNOMODULATING AGENTS	6,186,711	356,246	12.29
M: MUSCULO-SKELETAL SYSTEM	2,535,125	435,702	6.17
N: NERVOUS SYSTEM	922,066	110,055	8.86
P: ANTIPARASITICS INSECTICIDES REPELLENTS	9,098	4,550	1.50
R: RESPIRATORY SYSTEM	817,246	106,632	7.40
S: SENSORY ORGANS	176,557	51,686	4.40
V: VARIOUS	19,844	18,984	2.00

Table 1: Total lifetime revenues per 1-digit ATC class of NCEs patented by period, number of entities per period, and revenue per entity Unweighted averages by 1-digit ATC class

ATC class ($\mathcal{C}$)	$W^t_{c'}$	Mean $\frac{W^t_{c'}}{N^t_{c'}}$	$N^t_{c'}$
A: ALIMENTARY TRACT AND METABOLISM	388,462	102,304	2.19
B: BLOOD AND BLOOD FORMING ORGANS	2,019,626	829,969	3.64
C: CARDIOVASCULAR SYSTEM	612,684	195,831	3.04
D: DERMATOLOGICALS	51,489	27,669	1.72
G: GENITO URINARY SYSTEM AND SEX HORMONES	328,549	110,245	2.29
H: SYSTEMIC HORM.PREP., EXCL. SEX&INSULINS	7,731	6,934	1.38
J: ANTIINFECTIVES FOR SYSTEMIC USE	1,895,129	426,227	5.47
L: ANTINEOPLASTIC&IMMUNOMODULATING AGENTS	1,968,499	368,424	3.91
M: MUSCULO-SKELETAL SYSTEM	845,042	265,548	2.11
N: NERVOUS SYSTEM	208,208	91,401	2.06
P: ANTIPARASITICS INSECTICIDES REPELLENTS	9,098	4,550	1.50
R: RESPIRATORY SYSTEM	240,366	63,373	2.53
S: SENSORY ORGANS	109,696	32,718	3.13
V: VARIOUS	15,875	15,249	1.60

Table 2: Total lifetime revenues per 2-digit ATC class of NCEs patented by period, number of entities per year, and revenue per entity Unweighted averages by 1-digit ATC class

	Revenue W_c^t			Revenue per NCE $\frac{W_c^t}{N_c^t}$		
N_c^t	Mean	Min	Max	Mean	Min	Max
1	44,201	3	372,409	44,201	3	372,409
2	173,872	13,027	727,520	86,936	6,513	363,760
3	195,064	235	779,383	65,021	78	259,794
4	443,281	6,070	880,492	110,820	1,518	220,123
5	3,381,172	409,923	9,158,344	676,234	81,985	1,831,669
6	746,740	38,124	1,808,956	124,457	6,354	301,493
7	4,157,717	8,753	17,409,894	593,960	1,250	2,487,128
8	1,157,414	54,902	2,212,882	144,677	6,863	276,610
9	1,266,605	208,775	3,891,499	140,734	23,197	432,389
10	971,439	672,811	1,344,233	97,144	67,281	134,423
11	2,089,586	118,487	5,354,649	189,962	10,772	486,786
12	901,498	901,498	901,498	75,125	75,125	75,125
13	4,552,097	1,309,560	7,794,634	350,161	100,735	599,587
14	2,670,899	1,908,117	3,433,681	190,778	136,294	245,263
15	2,510,007	1,005,747	3,344,799	167,334	67,050	222,987
16	2,124,496	2,124,496	2,124,496	132,781	132,781	132,781
18	6,913,570	2,370,214	12,676,093	384,087	131,679	704,227
19	12,188,488	12,188,488	12,188,488	641,499	641,499	641,499
20	1,038,019	126,984	1,949,054	51,901	6,349	97,453
21	13,795,792	13,795,792	13,795,792	656,943	656,943	656,943
22	18,427,938	18,427,938	18,427,938	837,634	837,634	837,634
23	5,039,901	3,835,333	6,244,468	219,126	166,754	271,499
24	3,958,308	3,958,308	3,958,308	164,929	164,929	164,929

Table 3: Total lifetime revenues per 1-digit ATC class of NCEs patented by period, and revenue per entity Unweighted averages by 1-digit ATC class. Global revenue W_c^t and the number of innovations N_c^t

	Revenue $W^t_{c'}$			Revenue per NCE $\frac{W^t_{c'}}{N^t_{c'}}$		
$N^t_{c'}$	Mean	Min	Max	Mean	Min	Max
1	81,850	0	3,659,126	81,850	0	3,659,126
2	636,227	119	14,847,439	318,113	60	7,423,720
3	947,625	52	9,146,061	315,875	17	3,048,687
4	665,355	111	2,880,434	166,339	28	720,108
5	657,552	11	3,170,524	131,510	2	634,105
6	1,285,697	29,206	4,605,718	214,283	4,868	767,620
7	1,733,441	7,723	3,284,163	247,634	1,103	469,166
8	6,358,466	1,096,551	16,636,591	794,808	137,069	2,079,574
9	998,505	998,505	998,505	110,945	110,945	110,945
10	5,381,413	117,730	10,645,097	538,141	11,773	1,064,510
11	2,939,500	2,403,055	3,475,944	267,227	218,460	315,995
12	10,976,667	10,976,667	10,976,667	914,722	914,722	914,722
13	9,739,879	9,739,879	9,739,879	749,221	749,221	749,221
16	1,242,968	1,242,968	1,242,968	77,685	77,685	77,685
19	1,909,830	1,909,830	1,909,830	100,517	100,517	100,517

Table 4: Total lifetime revenues per 2-digit ATC class of NCEs patented by period, and revenue per entity Unweighted averages by 1-digit ATC class

ATC Class ($\mathcal{C}$)	Mean Price
A: ALIMENTARY TRACT AND METABOLISM	111
B: BLOOD AND BLOOD FORMING ORGANS	544
C: CARDIOVASCULAR SYSTEM	10
D: DERMATOLOGICALS	22
G: GENITO URINARY SYSTEM AND SEX HORMONES	23
H: SYSTEMIC HORM.PREP., EXCL. SEX&INSULINS	266
J: ANTIINFECTIVES FOR SYSTEMIC USE	67
L: ANTINEOPLASTIC&IMMUNOMODULATING AGENTS	382
M: MUSCULO-SKELETAL SYSTEM	95
N: NERVOUS SYSTEM	6
P: ANTIPARASITICS INSECTICIDES REPELLENTS	8
R: RESPIRATORY SYSTEM	13
S: SENSORY ORGANS	187
V: VARIOUS	636

Table 5: Descriptive statistics on Average Price of Drugs (across countries)

Set	Instruments
A	· Male and Female Population of corresponding countries
	· Male and Female Deaths of corresponding ATC-1 class and countries
B	· Population aged 50 and over of corresponding countries, interacted with ATC-1
C	· Male Population aged 50 and over of corresponding countries, interacted with ATC-1
D	· Male Population aged 50 and over of corresponding countries, interacted with ATC-2
	· Female Population aged 50 and over of corresponding countries, interacted with ATC-2

Table 6: Definition of Instrument Sets

Linear Model	(1)	(2)
	OLS	2SLS
VARIABLES	$\ln N_c^t$	$\ln N_c^t$
$\ln W_c^t$	0.216***	0.291***
	(0.0289)	(0.0465)
ALIMENTARY_TRACT_AND_METABOLISM	0.291***	0.147
	(0.0572)	(0.0907)
ANTIINFECTIVES_FOR_SYSTEMIC_USE	0.549***	0.318**
	(0.0903)	(0.144)
ANTINEOPLASTIC_IMMUNOMODULATING	0.527***	0.366***
	(0.0888)	(0.139)
ANTIPARASITICS	-0.133	0.282
	(0.170)	(0.280)
BLOOD_AND_BLOOD_FORMING_ORGANS	0.325***	0.348***
	(0.0314)	(0.0401)
CARDIOVASCULAR_SYSTEM	0.681***	0.465***
	(0.112)	(0.165)
DERMATOLOGICALS	0.245***	0.330***
	(0.0411)	(0.0443)
GENITO_URINARY_SEX_HORMONES	-0.128*	-0.223**
	(0.0659)	(0.0964)
MUSCULO_SKELETAL_SYSTEM	0.166**	0.0564
	(0.0674)	(0.0949)
NERVOUS_SYSTEM	0.192**	0.0738
	(0.0788)	(0.121)
RESPIRATORY_SYSTEM	0.407***	0.367***
	(0.0525)	(0.0686)
SYSTEMIC_HORM	0.248**	0.567***
	(0.107)	(0.158)
Observations	74	74
R-squared	0.832	
Instruments		A
Sargan Test		2.776
Degree freedom		3
P-value		0.428

Note: All standard errors are clustered at the ATC-1 level.

*** means significance at 1% level, ** at 5 % level and * at 10% level. Year dummies included are not shown.

Table 7: Determinants of the number of NCEs per therapeutic class Linear model, 1-digit ATC categories

Linear Model	(3)	(4)	(5)	(6)
	OLS	2SLS	2SLS	2SLS
VARIABLES	$\ln N^t_{c'}$	$\ln N^t_{c'}$	$\ln N^t_{c'}$	$\ln N^t_{c'}$
$\ln W^t_{c'}$	0.0962***	0.0870***	0.0873***	0.111***
	(0.0106)	(0.0207)	(0.0206)	(0.0174)
ALIMENTARY_TRACT_AND_METABOLISM	-0.577***	-0.208***	-0.208***	-0.193***
	(0.124)	(0.0244)	(0.0243)	(0.0230)
ANTIINFECTIVES_FOR_SYSTEMIC_USE	-0.162	0.251***	0.250***	0.184***
	(0.147)	(0.0582)	(0.0583)	(0.0456)
ANTINEOPLASTIC_IMMUNOMODULATING	-0.245	0.149***	0.149***	0.109***
	(0.140)	(0.0372)	(0.0373)	(0.0306)
ANTIPARASITICS	-0.685***	-0.350***	-0.349***	-0.285***
	(0.145)	(0.0545)	(0.0544)	(0.0542)
BLOOD_AND_BLOOD_FORMING_ORGANS	-0.352**	0.0381	0.0377	0.00788
	(0.141)	(0.0390)	(0.0392)	(0.0379)
CARDIOVASCULAR_SYSTEM	-0.347**	0.0306	0.0305	0.0235
	(0.147)	(0.0267)	(0.0267)	(0.0309)
DERMATOLOGICALS	-0.698***	-0.340***	-0.340***	-0.309***
	(0.119)	(0.0450)	(0.0448)	(0.0419)
GENITO_URINARY_SEX_HORMONES	-0.493***	-0.129***	-0.129***	-0.111***
	(0.132)	(0.0346)	(0.0345)	(0.0351)
MUSCULO_SKELETAL_SYSTEM	-0.567***	-0.197***	-0.196***	-0.174***
	(0.121)	(0.0380)	(0.0379)	(0.0367)
NERVOUS_SYSTEM	-0.654***	-0.284***	-0.284***	-0.272***
	(0.122)	(0.0330)	(0.0329)	(0.0324)
RESPIRATORY_SYSTEM	-0.356**	0.00362	0.00395	0.0349
	(0.128)	(0.0318)	(0.0316)	(0.0299)
SYSTEMIC_HORM	-0.559***	-0.205**	-0.205**	-0.130
	(0.0809)	(0.1000)	(0.0995)	(0.0956)
Observations	231	231	231	231
R-squared	0.715	0.457	0.458	0.466
Instruments		B	C	D
Sargan Test		8.923	8.846	31.23
Degree freedom		12	12	24
P-value		0.709	0.716	0.147

Note: All standard errors are clustered at the ATC-1 level.

*** means significance at 1% level, ** at 5 % level and * at 10% level. Year dummies included are not shown.

Table 8: Determinants of the number of NCEs per therapeutic class Linear model, 2-digit ATC categories

Count Models	(7)	(8)	(9)
VARIABLES	N_c^t	N_c^t	N_c^t
W_c^t	4.63e-08*	1.36e-07***	1.13e-07***
	(2.39e-08)	(5.05e-08)	(3.05e-08)
Corresponding Elasticity	0.103	0.303	0.252
ALIMENTARY_TRACT_AND_METABOLISM	1.798***	0.748***	1.727***
	(0.101)	(0.290)	(0.157)
ANTIINFECTIVES_FOR_SYSTEMIC_USE	2.000***	0.548*	1.784***
	(0.128)	(0.298)	(0.232)
ANTINEOPLASTIC_IMMUNOMODULATING	1.725***	0.487	1.284***
	(0.221)	(0.313)	(0.410)
ANTIPARASITICS	-0.353***	-1.101***	-0.905***
	(0.136)	(0.391)	(0.130)
BLOOD_AND_BLOOD_FORMING_ORGANS	1.195***	0.401	1.465***
	(0.153)	(0.313)	(0.211)
CARDIOVASCULAR_SYSTEM	2.051***	1.059***	1.972***
	(0.115)	(0.265)	(0.193)
DERMATOLOGICALS	1.165***	0.230	1.098***
	(0.107)	(0.251)	(0.132)
GENITO_URINARY_SEX_HORMONES	1.086***	0.0937	1.010***
	(0.111)	(0.183)	(0.142)
MUSCULO_SKELETAL_SYSTEM	1.274***	0.234	1.170***
	(0.0871)	(0.268)	(0.161)
NERVOUS_SYSTEM	1.723***	0.704**	1.573***
	(0.114)	(0.294)	(0.162)
RESPIRATORY SYSTEM	1.459***	0.475**	1.465***
	(0.0978)	(0.210)	(0.115)
SYSTEMIC HORMONES	0.282**	-0.501**	0.0607
	(0.121)	(0.207)	(0.122)
Observations	74	74	74
Method	Poisson	IV-Poisson	Trunc-Poisson
Instruments		A	A
Control Function (IVs)			Yes

Note: All standard errors are clustered at the ATC-1 level.

*** means significance at 1% level, ** at 5 % level and * at 10% level. Year dummies included are not shown.

Table 9: Determinants of the number of NCEs per therapeutic class Count model, 1-digit ATC categories

Count Models	(10)	(11)	(12)	(13)
VARIABLES	$N^t_{c'}$	$N^t_{c'}$	$N^t_{c'}$	$N^t_{c'}$
$W^t_{c'}$	8.85e-08***	5.67e-07***	2.86e-07***	1.73e-07***
	(1.87e-08)	(1.42e-07)	(1.06e-07)	(3.13e-08)
Corresponding Elasticity	0.0630	0.404	0.203	0.123
ALIMENTARY_TRACT_AND_METABOLISM	0.382***	-0.515**	-0.0908	-0.00909
	(0.125)	(0.233)	(0.151)	(0.171)
ANTIINFECTIVES_FOR_SYSTEMIC_USE	1.314***	-0.128	0.890***	0.978***
	(0.0998)	(0.285)	(0.223)	(0.141)
ANTINEOPLASTIC_IMMUNOMODULATING	0.861***	-0.313	0.633***	0.616***
	(0.151)	(0.260)	(0.209)	(0.167)
ANTIPARASITICS	-0.0607	-	-0.967***	-0.899***
	(0.184)	-	(0.158)	(0.227)
BLOOD_AND_BLOOD_FORMING_ORGANS	0.774***	-0.165	0.652***	0.579***
	(0.156)	(0.356)	(0.184)	(0.136)
CARDIOVASCULAR_SYSTEM	0.683***	-0.240	0.256	0.357*
	(0.139)	(0.234)	(0.170)	(0.189)
DERMATOLOGICALS	0.191	-0.531**	-0.382***	-0.356**
	(0.121)	(0.260)	(0.125)	(0.180)
GENITO_URINARY_SEX_HORMONES	0.411***	-0.338	-0.00946	0.0476
	(0.138)	(0.259)	(0.167)	(0.201)
MUSCULO_SKELETAL_SYSTEM	0.390***	-0.618**	-0.0599	-0.0713
	(0.109)	(0.268)	(0.140)	(0.152)
NERVOUS_SYSTEM	0.399***	-0.461*	-0.0534	-0.00339
	(0.113)	(0.250)	(0.138)	(0.174)
RESPIRATORY SYSTEM	0.510***	-0.289	0.136	0.180
	(0.140)	(0.251)	(0.157)	(0.194)
SYSTEMIC HORMONES	0.188***	-0.565**	-0.650***	-0.628***
	(0.0730)	(0.266)	(0.0904)	(0.122)
Observations	231	231	231	231
Method	Poisson	IV-Poisson	Trunc-Poisson	Trunc-Poisson
Instruments		D	A	D
Control Function (IVs)			Yes	Yes

Note: All standard errors are clustered at the ATC-1 level.

*** means significance at 1% level, ** at 5 % level and * at 10% level. Year dummies included are not shown.

Table 10: Determinants of the number of NCEs per therapeutic class Count model, 2-digit ATC categories

Count Models	(14)	(15)	(16)	(17)
VARIABLES	$N^t_{c'}$	$N^t_{c'}$	$N^t_{c'}$	$N^t_{c'}$
$\beta_{c'}$				
ALIMENTARY_TRACT_AND_METABOLISM	0.248*	-0.206	-0.184	-0.180
	(0.146)	(0.282)	(0.197)	(0.195)
ANTIINFECTIVES_FOR_SYSTEMIC_USE	1.191***	0.778**	0.970***	1.055***
	(0.139)	(0.341)	(0.196)	(0.156)
ANTINEOPLASTIC_IMMUNOMODULATING	0.883***	0.342	0.565***	0.537***
	(0.143)	(0.331)	(0.207)	(0.186)
ANTIPARASITICS	-0.737	-	-12.68	-
	(1.010)	-	(485.9)	-
BLOOD_AND_BLOOD_FORMING_ORGANS	1.049***	0.345	0.842***	0.788***
	(0.186)	(0.426)	(0.256)	(0.230)
CARDIOVASCULAR_SYSTEM	0.653***	0.265	0.373**	0.407**
	(0.143)	(0.274)	(0.171)	(0.168)
DERMATOLOGICALS	-0.000612	-0.343	-0.661*	-0.616*
	(0.229)	(0.452)	(0.343)	(0.342)
GENITO_URINARY_SEX_HORMONES	0.218	-0.403	-0.179	-0.158
	(0.233)	(0.322)	(0.297)	(0.296)
MUSCULO_SKELETAL_SYSTEM	0.326*	-0.0223	-0.131	-0.0421
	(0.193)	(0.491)	(0.259)	(0.251)
NERVOUS_SYSTEM	0.0758	-0.255	-0.566**	-0.548**
	(0.187)	(0.401)	(0.277)	(0.277)
RESPIRATORY SYSTEM	0.423**	0.169	0.104	0.144
	(0.185)	(0.291)	(0.224)	(0.224)
SYSTEMIC HORM	0.169	-0.357	-0.579	-
	(0.365)	(0.287)	(0.642)	-

Note: All standard errors are clustered at the ATC-1 level.

*** means significance at 1% level, ** at 5 % level and * at 10% level. Year dummies included are not shown.

Table 11: Determinants of the number of NCEs per therapeutic class Count model, 2-digit ATC categories

Count Models	(14)	(15)	(16)	(17)
VARIABLES	$N_{c'}^t$	$N_{c'}^t$	$N_{c'}^t$	$N_{c'}^t$
$\alpha_{c'} W_{c'}^t$				
ALIMENTARY_TRACT_AND_METABOLISM	2.78e-07***	1.02e-06***	4.12e-07***	4.36e-07***
	(7.42e-08)	(2.86e-07)	(1.08e-07)	(9.18e-08)
ANTIINFECTIVES_FOR_SYSTEMIC_USE	1.28e-07***	1.45e-07***	2.66e-07***	1.64e-07***
	(2.53e-08)	(4.53e-08)	(6.88e-08)	(3.03e-08)
ANTINEOPLASTIC_IMMUNOMODULATING	7.86e-08***	2.57e-07	3.04e-07***	2.14e-07***
	(1.87e-08)	(1.80e-07)	(7.45e-08)	(4.00e-08)
ANTIPARASITICS	6.10e-05	-	0.000689	-
	(6.79e-05)	-	(0.0267)	-
BLOOD_AND_BLOOD_FORMING_ORGANS	-1.58e-08	4.75e-07	1.96e-07**	1.04e-07*
	(4.13e-08)	(2.93e-07)	(9.31e-08)	(6.20e-08)
CARDIOVASCULAR_SYSTEM	1.02e-07	2.70e-07**	2.09e-07**	1.81e-07**
	(7.06e-08)	(1.27e-07)	(9.94e-08)	(7.99e-08)
DERMATOLOGICALS	3.22e-06**	4.75e-06	4.83e-06***	4.84e-06***
	(1.43e-06)	(9.35e-06)	(1.62e-06)	(1.62e-06)
GENITO_URINARY_SEX_HORMONES	5.96e-07**	2.09e-06***	7.88e-07**	8.68e-07***
	(2.71e-07)	(6.17e-07)	(3.11e-07)	(3.08e-07)
MUSCULO_SKELETAL_SYSTEM	1.28e-07**	2.93e-07	3.46e-07***	1.87e-07***
	(5.65e-08)	(6.42e-07)	(9.57e-08)	(6.10e-08)
NERVOUS_SYSTEM	1.22e-06***	1.50e-06	1.86e-06***	1.95e-06***
	(3.60e-07)	(1.26e-06)	(4.54e-07)	(4.51e-07)
RESPIRATORY SYSTEM	3.58e-07**	3.21e-07***	4.85e-07**	4.56e-07**
	(1.81e-07)	(1.16e-07)	(1.98e-07)	(1.93e-07)
SENSORY ORGANS	3.79e-06***	3.16e-06***	3.57e-06***	3.77e-06***
	(8.58e-07)	(8.60e-07)	(9.05e-07)	(9.08e-07)
SYSTEMIC HORM	5.37e-07	3.63e-05	-7.41e-06	-
	(2.66e-05)	(4.43e-05)	(5.65e-05)	-
Corresponding Elasticity	0.150	0.350	0.342	0.252
Observations	231	231	231	221
Method	Poisson	IV-Poisson	Trunc-Poisson	Trunc-Poisson
Instruments	-	D	A	D
Control Function (IVs)	No		Yes	Yes

Note: All standard errors are clustered at the ATC-1 level.

*** means significance at 1% level, ** at 5 % level and * at 10% level. Year dummies included are not shown.

Table 11 - continued

ATC class ($\mathcal{C}$)	Mean $\alpha W_{c'}^t$	Mean $\frac{1}{\alpha E\left(N_{c'}^t\right)}$
	(Elasticity)	
A: ALIMENTARY TRACT AND METABOLISM	0.169	1,581,130
B: BLOOD AND BLOOD FORMING ORGANS	0.211	5,105,871
C: CARDIOVASCULAR SYSTEM	0.111	2,770,592
D: DERMATOLOGICALS	0.249	157,823
G: GENITO URINARY SYSTEM AND SEX HORMONES	0.285	685,940
J: ANTIINFECTIVES FOR SYSTEMIC USE	0.311	2,739,536
L: ANTINEOPLASTIC&IMMUNOMODULATING AGENTS	0.421	2,068,826
M: MUSCULO-SKELETAL SYSTEM	0.158	3,768,493
N: NERVOUS SYSTEM	0.407	377,481
R: RESPIRATORY SYSTEM	0.110	1,254,843
S: SENSORY ORGANS	0.413	145,829
All	0.252	1,809,658

Table 12: Elasticties and Market Size Generating One Innovation per class

7.3 Additional Tables

ATC Class	ICD10 Chapter	ICD10 Blocks	Disease Title
A14, A16	IV	E00-E90	Endocrine, nutritional and metabolic diseases
Other A	XI	K00-K93	Diseases of the digestive system
B	III	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
C	IX	I00-I99	Diseases of the circulatory system
D	XII	L00-L99	Diseases of the skin and subcutaneous tissue
G	XIV	N00-N99	Diseases of the genitourinary system
H	IV	E00-E90	Endocrine, nutritional and metabolic diseases
J	I	A00-B99	Certain infectious and parasitic diseases
L	II	C00-D48	Neoplasms
M	XIII	M00-M99	Diseases of musculoskeletal system and connective tissue
N1,N2,N3	VI	G00-G99	Diseases of the nervous system
N4,N5,N6,N7	V	F00-F99	Mental and behavioral disorders
P	I	A00-B99	Certain infectious and parasitic diseases
R	X	J00-J99	Diseases of the respiratory system
S1	VII	H00-H59	Diseases of the eye and adnexa
S2	VIII	H60-H95	Diseases of the ear and mastoid process
V	XIX	S00-T98	Injury, poisoning and certain other consequences of external causes

Table 13: International Classification of Diseases and ATC drug categories

Part I	First Stage OLS				
	(1) N_c^t	(2) N_c^t	(3) $N_{c'}^t$	(4) $N_{c'}^t$	(5) $N_{c'}^t$
Exogenous Variables					
ATC 1 Dummies					
ATC=1	-520,902	1.674e+06***	-71,384	-73,370	126,559
	(412,709)	(313,368)	(64,261)	(64,382)	(75,776)
ATC=2	1.382e+06	-1.285e+06***	-1.042e+06***	-1.042e+06***	-958,351***
	(796,758)	(218,251)	(113,633)	(113,868)	(57,769)
ATC=3	-74,779	389,321	-88,429	-80,242	54,147
	(791,142)	(526,964)	(103,646)	(104,823)	(51,337)
ATC=4	1.844e+06**	-1.175e+06***	270,314***	263,554***	-289,982**
	(785,959)	(53,656)	(72,067)	(72,024)	(114,341)
ATC=5	4.969e+06***	59,068	-509,201***	-513,894***	-569,995***
	(959,893)	(347,890)	(114,421)	(113,525)	(56,469)
ATC=7	-1.180e+06*	-3,339	113,142*	109,560*	-142,390*
	(659,621)	(170,307)	(58,539)	(58,111)	(68,503)
ATC=9	116,226	209,676	608,828***	600,530***	360,580
	(520,704)	(367,647)	(87,030)	(86,475)	(212,734)
ATC=10	507,542	-264,436	208,649*	181,564	-224,673***
	(802,016)	(284,108)	(115,297)	(114,767)	(57,375)
ATC=11	-471,161	941,988	191,954**	187,484**	-131,826
	(712,665)	(1.221e+06)	(81,466)	(82,168)	(104,594)
ATC=13	-2.489e+06***	-440,332	-234,258**	-250,259**	-188,754*
	(503,609)	(451,827)	(94,549)	(93,712)	(88,608)
ATC=14	-396,866	20,557	-214,776	-215,580	-209,891
	(474,993)	(498,769)	(216,301)	(217,314)	(150,582)
Time Dummies					
Time_1	-274,687	-127,264	-360,962**	-349,357**	16,678
	(745,978)	(614,196)	(147,105)	(145,820)	(184,656)
Time_2	-1.478e+06*	-768,552	-392,985	-383,928	159,166
	(678,640)	(2.434e+06)	(224,137)	(220,573)	(275,349)
Time_3	-1.246e+06	125,328	-259,201	-251,423	317,205
	(1.708e+06)	(692,843)	(252,345)	(249,592)	(260,051)
Time_4	2.283e+06	932,277	525,628	532,433	968,701*
	(1.956e+06)	(1.308e+06)	(572,411)	(571,705)	(539,184)
Time_5	-1.131e+06	760,836	-236,149	-231,774	-73,396
	(1.191e+06)	(804,415)	(291,953)	(292,213)	(266,379)

Table 14: First stage Regressions

Part II	First Stage OLS				
	(1) N_c^t	(2) N_c^t	(3) $N_{c'}^t$	(4) $N_{c'}^t$	(5) $N_{c'}^t$
Excluded IVs					
Male population	0.0554*				
Female population	-0.0526*				
Nb of Deaths	-4.256***				
Nb of Male Deaths	8.579***				
Male Pop Above 50 in countries					
served by drugs of own ATC-2 level times ATC-1 dummy					
Male Pop Above 50*ATC=1		-0.488***			0.0388***
Male Pop Above 50*ATC=2		0.179***			0.113***
Male Pop Above 50*ATC=3		-0.894***			0.120***
Male Pop Above 50*ATC=4		-0.241			-0.155
Male Pop Above 50*ATC=5		0.701***			-0.0239
Male Pop Above 50*ATC=6		1.452***			0.0832***
Male Pop Above 50*ATC=7		0.102			0.0235
Male Pop Above 50*ATC=8		0.111			0.0805***
Male Pop Above 50*ATC=9		0.173***			0.214***
Male Pop Above 50*ATC=10		0.0300			0.0211**
Male Pop Above 50*ATC=11		0.0155			0.0722***
Male Pop Above 50*ATC=12		-0.00512			0.0283
Male Pop Above 50*ATC=13		-0.00588			0.0777*
Female Pop Above 50 in countries					
served by drugs of own ATC-2 level times ATC-1 dummy					
Female Pop Above 50*ATC=1		0.425***			-0.0336***
Female Pop Above 50*ATC=2		-0.150***			-0.0942***
Female Pop Above 50*ATC=3		0.786***			-0.102***
Female Pop Above 50*ATC=4		0.206			0.132
Female Pop Above 50*ATC=5		-0.604***			0.0237
Female Pop Above 50*ATC=6		-1.254***			-0.0707***
Female Pop Above 50*ATC=7		-0.0886			-0.0203
Female Pop Above 50*ATC=8		-0.0945			-0.0700***
Female Pop Above 50*ATC=9		-0.147***			-0.185***
Female Pop Above 50*ATC=10		-0.0260			-0.0180**
Female Pop Above 50*ATC=11		-0.0116			-0.0625***
Female Pop Above 50*ATC=12		0.00429			-0.0246
Female Pop Above 50*ATC=13		0.00457			-0.0671*
Observations	74	74	231	231	231
R-squared	0.791	0.937	0.309	0.310	0.509
IVs	A	D	B	C	D
Test Excluded. IVs					
F test	53.64	201.4	640.6	655.5	53.06
P value	1.48e-07	0	0	0	9.10e-08

Note: All standard errors (not shown) are clustered at the ATC-1 level.

***, **, * means significance at 1%, 5 % and 10% levels

Table 14 - Continued 1

Part III	First Stage OLS				
	(1)	(2)	(3)	(4)	(5)
	N_c^t	N_c^t	$N_{c'}^t$	$N_{c'}^t$	$N_{c'}^t$
Excluded IVs					
Pop Above 50 in countries					
served by drugs of own ATC-1 level times ATC-1 dummy					
Pop Above 50*ATC=1			0.000330***		
Pop Above 50*ATC=2			0.00135***		
Pop Above 50*ATC=3			0.00127***		
Pop Above 50*ATC=4			-0.000763		
Pop Above 50*ATC=5			0.00110***		
Pop Above 50*ATC=6			0.000648***		
Pop Above 50*ATC=7			2.00e-05		
Pop Above 50*ATC=8			-0.000182**		
Pop Above 50*ATC=9			0.000455***		
Pop Above 50*ATC=10			6.24e-05		
Pop Above 50*ATC=11			0.000454***		
Pop Above 50*ATC=12			0.000220*		
Pop Above 50*ATC=13			0.000354		
Male pop Above 50 in countries					
served by drugs of own ATC-1 level times ATC-1 dummy					
Male Pop Above 50*ATC=1				0.000705***	
Male Pop Above 50*ATC=2				0.00288***	
Male Pop Above 50*ATC=3				0.00270***	
Male Pop Above 50*ATC=4				-0.00164	
Male Pop Above 50*ATC=5				0.00237***	
Male Pop Above 50*ATC=6				0.00139***	
Male Pop Above 50*ATC=7				4.06e-05	
Male Pop Above 50*ATC=8				-0.000384**	
Male Pop Above 50*ATC=9				0.00101***	
Male Pop Above 50*ATC=10				0.000133	
Male Pop Above 50*ATC=11				0.000993***	
Male Pop Above 50*ATC=12				0.000463*	
Male Pop Above 50*ATC=13				0.000756	
Observations	74	74	231	231	231
R-squared	0.791	0.937	0.309	0.310	0.509
IVs	A	D	B	C	D
Test Excluded. IVs					
F test	53.64	201.4	640.6	655.5	53.06
P value	1.48e-07	0	0	0	9.10e-08

Note: All standard errors (not shown) are clustered at the ATC-1 level.

***, **, * means significance at 1%, 5 % and 10% levels

Table 14 - Continued 2