Are Important Innovations Rewarded? Evidence from Pharmaceutical Markets

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Abstract

This paper focuses on the relationship between therapeutic value and different measures of market rewards (the number of patents, price, market share, and total revenues) of a new treatment. Using an assessment of therapeutic value provided by the French Haute Authorité de Santé (HAS), I find a weak relationship between most measures of rewards and this assessment of therapeutic value, suggesting that the returns to developing a "me-too" product are not very different from developing treatments with greater therapeutic effects. One interpretation is that the HAS score is a poor assessment of therapeutic value, in which case the use of similar health technology assessments by governments and other payers should be re-examined. Alternatively, if the HAS score is informative, the results suggest countries are spending too much on less innovative products, and that a re-balancing of innovation incentives may be worth considering if therapeutic value is highly related to social welfare.

1 Introduction

Drug prices are among the most controversial issues in health policy. Despite accounting for only 12.3% of total spending on health in the US and a median of 15% in the OECD,[1] pharmaceutical prices have risen faster than inflation. High profile cases in recent years, including Sovaldi and Epipen, have also brought increased scrutiny. Critics note that pharmaceutical firms have enjoyed an average return on equity of 16-17%, twice the average across all sectors.[2] At the same time, pharmaceutical treatments are credited with significant reductions in the burden of cardiovascular diseases, HIV/AIDS, multiple sclerosis, and many others. Innovation policy

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[1] OECD (2016), Pharmaceutical spending (indicator), Accessed on 29 December 2016.

[2] See Aswath Damodaran's data on equity risk premia here.

must balance the incentives for developing such treatments with the ability of patients or payers to pay for them. A critical question, therefore, is the extent to which drug prices and policies that underpin them, such as patent protection and data exclusivity, have provided the correct incentives for innovation. Specifically, if more important innovations provide higher returns to society, then innovation policy should provide them higher rewards.

In most markets, economists measure the value of an innovation using estimates of demand. Markets aggregate information about a product's quality, and we expect price to reflect this. In practice, this approach is difficult to apply in pharmaceutical markets, for reasons outlined in the following section. As a result, the link between price (or profits) and social value – essential for innovation incentives – may be weak.

Alternative measures of innovation are often based on patents. Unfortunately, in the case of pharmaceuticals, patent counts are not ideal as a measure of innovation, as the criteria for a patent have little to do with therapeutic value. In the lengthy process of drug development, patent applications are often filed well before information on therapeutic value exists, and (as in other sectors) most patents filed ultimately have little commercial value as the products with which they are associated fail in development. Since patent terms do not vary with therapeutic value, there is little reason to believe that patent terms favor investment in the most therapeutically important drugs.

Prior work has established that overall, pharmaceutical R&D investment responds to market size, particularly patent-protected market size (Acemoglu & Linn (2004), Kyle & McGahan (2012), de Mouzon et al. (2015)). There are a number of prominent examples where innovation incentives provided by price and/or patents may be insufficient. The so-called neglected diseases attract little R&D investment despite a heavy burden, mainly because the ability to pay in countries most affected is low. More recently, antimicrobial resistance has increased the need for novel antibiotics, but expected profits under current pricing policies have stimulated little interest from pharmaceutical firms: new antibiotics should be used sparingly in order to preserve their efficacy, but low volumes reduce profits. In response to cases like these, some have proposed "delinkage" of price and quantity from pharmaceutical profits in order to change the direction of R&D (Kremer & Glennerster (2004)).

This paper focuses not on the overall level of drug prices, but rather on the relationship between therapeutic value and different measures of market rewards (the number of patents, price, market share, and total revenues) of a new treatment. I use an assessment of therapeutic value provided by the French Haute Authorité de la Santé (HAS), which is independent of price. I find a weak relationship between most measures of rewards and this assessment of therapeutic value, suggesting that the returns to developing a "me-too" product are not very different from developing a breakthrough. Of course, incremental innovation may yield considerable benefits as well (Arcidiacono et al. (2013), Bokhari & Fournier (2013), Hult (2016), Yin (2013)), but the results presented here suggest that a re-balancing of innovation incentives may be worth considering.

2 Determinants of drug prices

Pharmaceutical markets are generally far from the competitive ideal in which many buyers and suppliers trade with full information. On the supply side, barriers to entry limit competition. Some of these barriers are the result of public policy. Pharmaceuticals are usually considered either experience goods or credence goods: their quality is difficult to observe *ex ante*, and sometimes even *ex post*.[3] The Food and Drug Administration (FDA) and its equivalents in other countries provide certification of a minimum level of safety and (perhaps) efficacy, and this certification is costly to obtain. In addition, new drugs are usually protected by patents, and may also benefit from other forms of exclusivity. Other barriers could include reputation, brand name, or relationships with prescribers. We typically expect the resulting market power to result in higher prices than would be the case in a more competitive market. Thus, while older (off-patent) drugs may continue to provide therapeutic benefits, they are likely to have much lower prices than newer (on-patent) drugs that provide a similar level of therapeutic benefits.

A key feature of pharmaceutical supply is that the fixed costs of drug development are generally large relative to the marginal costs of production. While higher marginal costs could plausibly be related to higher quality, through the use of superior ingredients, more expensive packaging, etc., there is little evidence that the level of fixed costs is related to drug quality. Instead, fixed costs are largely determined by the size and duration of clinical trials necessary to demonstrate the safety and efficacy of a drug, and the difficulties in enrolling patients. Consequently, product-specific costs may not be an important determinant of drug prices, at least for on-patent drugs.

Pharmaceutical markets have an atypical demand side as well. Information problems are prevalent. While regulatory approval to market a product reduces the information asymmetry somewhat, significant uncertainty remains about how a new treatment should be used, and who should consume it. Patients may lack the expertise to choose an appropriate treatment, which is why new drugs are usually available only with a doctor's prescription. However, since doctors do not pay for the drugs they prescribe, their choices may not reflect prices even if they have good information on a treatment's quality. In addition, patients with insurance coverage may be insensitive to price.

A response to the resulting problem of moral hazard is the negotiation of prices between drug producers and governments (which are the insurers or payers in many health care systems). If payers act as perfect agents for consumers or patients, and patients care about therapeutic benefits, then we would expect negotiated prices to reflect the therapeutic value a drug can provide. However, other factors affect negotiated prices as well. In particular, suppliers negotiate having already sunk the large costs of drug development, which weakens their bargaining power. Any price that covers the marginal cost of production is theoretically possible. This potential for hold-up reduces the incentive to invest in costly innovation, so forward-looking payers must share some of the surplus with suppliers in the short-run in order to assure continued innovation in the future.

[3] For example, patients taking a statin for high cholesterol may not directly observe an improvement in their health status (they may not "feel" better). While their cholesterol levels can be monitored, monitoring can be costly and the levels themselves may depend on factors unrelated to the statin therapy, such as diet.

The market for most pharmaceuticals is not limited to a single country. This introduces another complication, which is the possibility of free-riding on the innovation incentives created by other payers. Some countries, especially those that are too small to have a meaningful impact on innovation incentives through paying higher prices, may place more importance on affordable access than on dynamic investment, and thus insist on a low price; others may face tight budget constraints that require low prices. External reference pricing, a policy of setting a country's price as a function of the price in other countries, can then propagate a low price in one market to many others.

Hold-up and free-riding (particularly with reference pricing) could disproportionately affect important products, depending on how well payers act as agents for patients. Political pressures may lead payers to value the short-run benefits of increased access through lower prices more than the long-run benefits of future innovation, as these benefits can be realized well after the current government leaves office. Drugs that treat prevalent diseases pose more of a budgetary challenge, and may induce payers to hold out for prices much lower than they would tolerate for rare disease treatments.

3 Regulatory environment

3.1 Drug approval

Approval of both new drugs and generic equivalents is the domain of the Food and Drug Administration (FDA) in the US. Sponsors of new chemical entities must provide clinical evidence of safety and efficacy; the FDA reviews this evidence, and sometimes solicits the advice of expert committees. The FDA plays no role in price-setting, and cost-effectiveness is not a criterion for approval.

The European Union has multiple agencies with roles in the approval of pharmaceuticals, and the regulatory environment has undergone a number of important changes in the past 25 years. Each member state has a national authority that must comply with European directives on pharmacovigilance, safety, and efficacy to ensure some degree of uniformity across countries, and a pan-EU European Medicines Agency (EMA) was created in 1995. [4] Like the FDA, the EMA plays no role in pricing. Rather, pricing and reimbursement are considered national competencies and handled country by country.

3.2 Patents and exclusivity

In order to reward products with high therapeutic value, or commit not to hold up developers, governments have a number of policy options. They can commit to higher prices or quantities

[4] The EMA's primary role is the evaluation of innovative products via the centralized procedure, which grants a marketing authorization valid in all member states as well as Iceland, Norway, and Lichtenstein. As of 2004, the centralized procedure is required for some categories of products, including those for HIV, cancer, diabetes, and autoimmune disorders as well as biologics. For others, applicants may seek approval via the decentralized or mutual recognition procedures using national authorities. A key difference is that the former guarantees that an identical product is authorized throughout the EU, while variations in strength, dosing, pack size, and brand names may result from the others.

for more important drugs, refrain from external reference pricing, or award patents and other forms of exclusivity. In practice, patents and exclusivity are most commonly used. In part, this is a result of trade agreements that include intellectual property requirements. For example, membership in the EU is conditional on harmonizing IP to the standards in other EU countries. The TRIPS Agreement established IP requirements for WTO members. One reason for the inclusion of IP in such trade pacts is that it reduces the potential for free-riding on the innovation incentives created in other countries.

Patents are particularly important in pharmaceuticals because of the cost structure. New pharmaceutical products rely heavily on patents in order to recoup the large sunk costs of discovery and clinical development. Although other sectors now also have high rates of patenting, patents are especially critical to pharmaceuticals for several reasons. Imitation of a drug is relatively easy (though this is less true for biologics). As a result, first-mover advantage is likely to be rather limited. While trade secrets are an alternative means of protecting some innovations, regulations limit their use for drugs. In addition, at least some types of patents are extremely effective for pharmaceuticals. A product patent that covers the molecule structure of an active ingredient is difficult for imitators to invent around. Pharmaceuticals are often covered by many other patents, each covering different aspects of the product, with different expiration dates.

Statutory patent protection in the US and Europe is now 20 years from the date of the patent application. Product patent applications must be filed early in the development process, soon after discovery. Delaying an application increases the risk of pre-emption by a competitor or invalidation due to the existence of prior art. Because the rest of the development process, regulatory approval, and pricing and reimbursement negotiations can take years, the remaining term of protection on the initial product patent is usually far less than 20 years.

While patent terms begin at the time of patent application, usually well before a product reaches the market, data exclusivity terms usually begin once a product is launched. This addresses a distortion in research incentives that is associated with fixed patent terms: the longer a drug spends in development, the less the remaining patent term, shifting incentives towards products for which clinical development is shorter (Budish et al. (2015)). Because of concerns that the remaining patent life would provide inadequate incentives to invest in risky research and development, 1984 Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act) included a number of provisions related to patents and market exclusivity. First, originators are guaranteed 5 years of market exclusivity, regardless of patent status, upon approval of a new drug application; orphan drugs receive 7 years, and new formulations that are not new chemical entities receive 3. Second, originators are eligible for up to 5 years of patent extension to compensate for development and regulatory delays. Finally, originators may receive an additional 6 months of exclusivity, added to patent terms and other exclusivities, for conducting pediatric trials. The Biologics Price Competition and Innovation Act of 2009 established a period of 12 years of market exclusivity for new biologics, without exclusivity for follow-ons, and also includes the 6-month pediatric extension.

The counterpart of a patent term extension in the US is a supplementary protection certificate (SPC) in European countries, created in 1993. Because patents in the EU are country-

specific, an SPC is also country-specific and granted only to the holder of the "basic" (usually product) patent in the country. It does not technically extend a patent, but prevents the approval of a medicinal product covered by the patent. However, the term of the SPC is calculated based on the difference between the patent application date and the first marketing authorization in the European Economic Area, rather than the date at which the product is actually marketed in the country granting the SPC. It is capped at 5 years, like the Hatch-Waxman extension, and there also exists a 6-month pediatric extension.

Until 2005, European policies on exclusivity varied across member states. Belgium, France, Germany, the Netherlands, Sweden and the United Kingdom granted 10 years of data exclusivity, while other member states provided 6. During a data exclusivity period, no generic applicant can rely on the clinical trial data of the reference product. Beginning in 2005, policies were harmonized across countries. New drugs approved since then receive 8 years of data exclusivity. Following the expiration of this data exclusivity, generic firms can file applications based on the reference product dossier, but the reference product enjoys 2 years of market exclusivity during which no generic can be launched. If the originator finds a new use or develops an over-the-counter version of its product, it may receive one additional year beyond this. This policy applies to biologics as well as small-molecule drugs.

Competition authorities in the US and the EU have raised concerns about a number of practices in the pharmaceutical industry, many of which are related to patents. Patents create entry barriers for a fixed term in order to reward innovation. For many products, the cost of applying for additional patents is small compared to the potential benefit of blocking competition, creating incentives for innovators to apply for secondary patents related to methods of manufacturing, new uses, etc. The worry of competition authorities is that these patent "thickets" extend the effective patent term beyond what is socially optimal. Pharmaceutical firms argue that lengthy development times have reduced the remaining term of patent protection below this level, so that secondary patents are essential in order to maintain R&D investment incentives. In addition, they claim that secondary patents can represent meaningful incremental innovation that yields social benefits.

Patents are awarded for inventions that meet several criteria (applicable to all inventions), not on the basis of therapeutic value. In pharmaceuticals, the first patent application is filed well before clinical trials have been completed, so little information on therapeutic value exists at that point. Subsequent patents filed that relate to the same product also provide 20 years of protection if granted, though the importance of these secondary patents may be considerably less than the first. Similarly, data exclusivity policies are not tied to therapeutic value. It is not obvious, therefore, that patent terms, the number of patents, and realized market exclusivity are positively correlated with therapeutic importance. Patent criteria do not include it, and while the incentive to file additional patents may be higher for more commercially valuable products, so is the incentive for generic firms to enter.

3.3 Pricing and reimbursement

As discussed above, the presence of insurance (leading to moral hazard on the part of patients), information asymmetries about quality and therapeutic value, and supplier market

power present challenges for payers. Unchecked, these features are likely to result in both high prices and inappropriate use. In response, insurers and/or government agencies usually negotiate price with pharmaceutical firms, at least for some drugs. While technically a firm needs only a marketing authorization to sell in most countries, in practice, reimbursement by insurers is critical for reaching patients.[5] In developing countries, insurance markets are not as widespread and consumers are more likely to pay out-of-pocket. However, price controls may be imposed, as in India and South Africa, for example.

As part of negotiations over pricing and reimbursement, firms provide additional evidence or arguments as to the therapeutic benefits associated with their products. In some countries, health technology assessments explicitly require such evidence, sometimes including clinical trials comparing the new product to one or more existing treatments, yielding a cost-effectiveness measure that determines whether the product will be reimbursed. In others, both price and volume are bargained over. In the US, price and position on a formulary may both be negotiated with individual insurers.

An important feature of these negotiations, and a limitation of any analysis of drug prices, is that firms often agree to secret rebates. Such rebates may facilitate third-degree price discrimination across payers. This is especially true in the presence of external reference pricing, a policy that links the price in country i to the prices in a basket of other countries. The implications of this approach to pricing have been documented previously (Kyle (2007)). Empirical study of pricing is complicated by the fact that prices are certainly observed with error. For an idea of the order of magnitude, an analysis of 39 products in the US estimated rebates from 12-66% based on a comparison of list prices to reported sales.[6]

4 Data

4.1 Measure of importance

Most economic studies of innovation measure importance using patent data (e.g., number of patents or patent citations) or market data (e.g., sales or estimates of welfare derived from structural demand models).[7] As discussed above, neither of these approaches is well-suited for this setting. In pharmaceutical markets, it is rare to have information on the price faced by patients, or even their choice set, which may be the result of negotiations between producers and payers over a position on a formulary. The potential agency issues arising from the role of physicians and payers also complicate the interpretation, particularly in the presence of marketing efforts to physicians or unobserved rebates to payers, as do the information problems noted above. From a practical standpoint, demand estimation across a large number of therapeutic classes and countries is also a non-trivial undertaking.

I instead rely on the fact that many countries undertake an assessment of therapeutic value,

[5] The market for drugs that are not reimbursed is relatively small in developed countries, although exceptions exist, such as cosmetic treatments and contraceptives.

[6] https://www.bloomberg.com/graphics/2016-drug-prices/

[7] A summary of drug quality measures and their use in economics is provided in Feng & Maini (2016).

often as part of pricing and reimbursement negotiations.[8] In France, under a policy introduced in 2002, each new drug is graded according to its absolute and relative advantage to existing products, or SMR ("Service Médical Rendu") and ASMR ("Amélioration du Service Médical Rendu"), respectively.[9]. The SMR, which is one of "Major or important," "Moderate or weak," or "Insufficient," determines the rate of reimbursement by national insurance. The ASMR is a score from I, for drugs that represent a major improvement over the existing standard of care, to V, for drugs that provide no additional benefit. The agency responsible for these assessments is the Haute Authorité de Santé, which bases them on clinical data, including comparator trials, and relies on a committee of experts for advice. Health technology assessments are generally conducted in a similar fashion in other countries, though the weight put on various criteria vary (World Health Organization (2015)).

ASMR scores are assigned *prior* to negotiating price, which is the responsibility of separate committees.[10] That is, ASMRs are not cost-effectiveness evaluations (which are functions of price), like those produced by the NICE in the UK or IQWIG in Germany. In the US, the FDA classifies drugs as standard or priority, and now has several expedited review programs in place, including Accelerated Approval, Fast Track, and Breakthrough Therapies. However, the ASMR scores are somewhat more informative. Not only is there more variation, but the comparison is to existing products on the market. Thus, I argue they provide a useful measure of therapeutic value.

Of course, this measure has a number of shortcomings as well. As in any bureaucracy, the committee of experts may be biased, or lack the necessary competencies to assess clinical value. Though the assessment occurs prior to price negotiations, committee members probably understand that assigning a favorable score to a new drug may have important budgetary implications, since the score is an argument used by firms for a higher price. Another concern is that a drug's relative value may change over time, as new competitors enter or as new information becomes available, and an ASMR assigned several years earlier may no longer be an accurate assessment. Despite these limitations, the availability of a common grading scheme across many new products simplifies empirical study.

4.2 Sample definition

My primary source of information is the Base de Données Publique des Médicaments, which includes marketing authorizations from the Agence National de Sécurité du Medicament (ANSM) and ASMRs from the HAS. I focus on products first launched globally from 2000 through early 2016, for which an ASMR rating in France was assigned within two years of launch. This definition excludes over-the-counter products and new presentations (i.e., different strengths or package sizes) of previously approved substances, but does include new combinations of ingredients and new uses of existing chemicals if launched under a new brand name. I distinguish

[8] Prior to 1992, the FDA classified new drug applications based on an internal assessment of therapeutic potential and novelty. Lu & Comanor (1998) use this classification in a study of strategic pricing of new drugs.

[9] This measure is relatively new to the economics literature, but has been exploited in Régnier & Ridley (2015) and Kyle & Williams (2017)

[10] The Union nationale des caisses d'assurance maladie (Uncam) fixes the reimbursement rate, and the Comité économique des produits de santé (CEPS) fixes the price.

between products designated as new chemical entities (NCEs) by the US FDA or EMA and all others. The resulting sample has 258 drugs.

ASMRs can be specific to patient subgroups (those with a particular gene expression, for example) and indications or uses. They are also updated over time; pricing agreements between the French government and firms are typically renegotiated every 3-5 years, and an assessment of clinical benefits often precedes these negotiations. For simplicity, I take the best ASMR ever assigned to a drug (across all patient groups and indications) and the modal ASMR for comparison.

A summary of this sample of drugs is provided in Table 1. More than half of the drugs in this sample were considered by HAS to offer no meaningful therapeutic advantage relative to treatments already available. Among those receiving the best score were imatinib (Glivec/Gleevec), which treats several types of cancer, and two vaccines (Prevnar, for pneumoccocus, and Mencevax, for meningitis). Sofosbuvir (Sovaldi, for hepatitis C), ivacaftor (Kalydeco, for cystic fibrosis), and abatacept (Orencia, for rheumatoid arthritis) were classified as ASMR II, or having an important advantage over existing treatments. Total uses refers to the number of evaluations for which the drug was considered "important" by the HAS (and therefore reimbursed). Total countries refers to the number of countries in which the product was launched as of 2016, out of the set of countries for which I have data.

Table 1: Summary of ASMR scores for sample of drugs

Best ASMR score	Sum			Mean		
	Non-NCE	NCE	Orphan	Total uses	Total countries	N
Major	0	7	2	2.00	44.43	7
Important	1	29	7	1.91	35.07	30
Moderate	0	38	8	2.42	36.68	38
Minor	2	54	8	1.28	31.95	56
Non-existent	34	92	7	0.96	34.75	127
Total	37	220	32	1.44	34.72	258

4.3 Revenues and patents

I link this sample to two datasets produced by IMS Health. The first is the MIDAS database, which provides quarterly revenues and units in many countries at the pack level. The MIDAS dataset to which I have access covers 2000Q2-2016Q2, and includes 51 countries with data during this entire time period. Most of Europe is included, with the exception of Denmark and the Netherlands, as are the major emerging markets of Brazil, Russia, India and China in addition to Thailand, South Africa, Indonesia, and Malaysia.

I match based on local brand name listed in MIDAS and the trade name listed in the French data. I then consider all other products with the same brand name as the matched brand to be the same drug, and all other products with the same molecule as these matched brands to be alternative versions (generics or other licensed brands) of this drug. I define competitors using Anatomical Therapeutic Chemical (ATC) codes, which group drugs based on their therapeutic

and chemical properties. As is standard, I assume that drugs with the same ATC3 are imperfect substitutes. For example, A10B includes non-insulin based treatments for diabetes, while N03A includes antiepileptics.[11]

I use the MIDAS data to determine the quarter in which the originator product and subsequent generics were launched in each country. I supplemented these launch dates with information from other sources in cases where the dates were missing or suspect.[12] I convert MIDAS sales figures, which are in nominal local currency units, into 2009 US dollars based on the average monthly exchange rate in each quarter and the implicit GDP deflator for the US. Using trade and chemical names, I also match to IMS Lifecycle Patent Focus, which provides information on patent applications and grants around the world that are associated with each drug. This yields information on the primary product patent, as well as secondary patents issued for new uses, manufacturing processes, etc.

The resulting dataset used for the analysis below has one observation per drug-country, conditional on launch. The relative price is missing when the product is the first in the ATC3, so no comparator products exist, or when quantities are too low to impute the price.[13] Because the calculation of revenues within 3, 5 or 10 years requires at least that many years of observation, the number of products declines as the window widens.

Table 2: Summary statistics

Variable	Mean	Std. Dev.	Min.	Max.	N
Patents granted in country	3.97	4.8	0	56	9031
Unit price relative to average in ATC3	1.94	2.4	0	38.66	4814
Market share	0.06	0.16	0	1	8997
Share of generics in ATC3	0.25	0.32	0	1	8997
Number of drugs in ATC3	10.99	10.44	0	124.4	9031
Number of drugs with generic entry in ATC3	0.66	3.2	0	98.95	9031
Log of country revenues, 3 years post-launch	5.34	3.8	0	15.36	7205
Log of country revenues, 5 years post-launch	7.02	3.5	0	16.23	6633
Log of country revenues, 10 years post-launch	8.9	2.97	0	17.47	3261

5 Empirical analysis

Are important innovations rewarded? To answer this question, I test for differences across drugs with different assessments of therapeutic value. Specifically, I focus on the number of patents, realized market exclusivity, relative prices, market shares, and ultimately revenues. I also compare these relationships across countries with different pricing environments.

Throughout, I focus on the version of a product with the same international product name,

[11] For simplicity, I restrict my sample here to products assigned to a single ATC3.

[12] Specifically, I used IMS Lifecycle New Product Focus and regulatory websites in the US and Europe. Regulatory data is less easily accessed in the developing countries in my sample.

[13] Quantities are recorded in 1000s, and rounded to 0 in many cases. It is therefore not possible to calculate a per-unit price.

as provided in the MIDAS data. For example, for imatinib, this is Glivec; its local brand name in some countries, including the US, is Gleevec, but I treat this as the same product. Generic versions of imatinib are not included when I look at prices, shares, or revenues because I am interested in the rewards to the innovator firm. Parallel imports of Glivec are included, because the innovator profited from the first sale,[14] as are licensed versions sold by other firms.

5.1 ASMRs and patents

For lack of a better alternative in many cases, economic studies rely on patent-based measures to value innovation. Patents are also one of the main policy instruments used by governments to reward innovation. Thus, the question of whether drugs with greater therapeutic benefits have more patents is important both for assessing the appropriate use of patent measures in economic studies as well as the efficacy of this policy tool.

If therapeutic benefits are closely tied to market rewards, then firms have incentive to file for more patents on more important (both therapeutically and financially) products, and we might observe a positive correlation for this reason. However, the criteria for granting a patent may not differentiate much between a breakthrough treatment and a marginal one, in which case the relationship might not be very strong.

Figure 1 presents a summary of this relationship. This chart is based on one observation per drug-country, taking the total number of patents related to a drug in a country as of mid-2016. On average, major innovations do not have significantly more patents than those classified as having a non-existent improvement over existing therapies. If anything, it is the less important innovations that are more likely to have a large number of secondary patents. While the enforcement of patents or the incentive to patent vary across countries, the pattern holds in both relatively rich countries as well as others.

5.2 ASMRs and relative prices

In a typical market, prices may reflect quality. For the reasons outlined earlier, the market for pharmaceuticals is not typical. Information asymmetries may imply that patients, prescribers and payers are unable to distinguish between effective drugs and those that offer less value, so that effective drugs command no price premium. Alternatively, payers may negotiate more aggressively for important drugs that could consume more of a limited budget.

A comparison of prices across competing drugs is not straightforward due to dosing differences. In addition, prices change over time as competition and demand change. Nevertheless, as a cursory attempt, I calculate the average price per unit (usually a pill or capsule) for each new drug relative to the average unit price of competing products in the same country and quarter. I then take the average of this relative price during the first two years following launch. This gives some sense of the price premium a new product commands.

The second subplot in Figure 1 shows that there is no strong relationship between the price premium and the level of therapeutic benefits. If anything, the most innovative products have smaller price premia. The less innovative categories have a number of outlier observations in

[14] Unfortunately, I don't know where the initial sale occurred, so measurement error enters here as well.

which the price of a new product is more than 20 times the average of competing products. These outliers are more frequent in the sample of rich countries than in the poorer ones.

In a study of drugs introduced in the US prior to 1987, Lu & Comanor (1998) find that drugs classified by the FDA as having higher therapeutic potential launched at higher relative prices. The weaker relationship I find could reflect many factors: the ASMR may be different from the FDA's measure, and the US market may be very different from other rich countries. I return to cross-country differences in section 5.5 below.

5.3 ASMRs and market shares

If information asymmetries are limited, we would expect the best drugs to attract the most users, all else equal. Prescribers may be unaware of, or insensitive to, prices; patients with insurance coverage may also ignore them. In practice, the product that offers the highest clinical benefit may not be the most cost-effective, and efforts to steer prescribers and patients towards less expensive alternatives may mean that therapeutically superior drugs do not have the highest market share. In addition, information asymmetries may delay the adoption of new products, and be particularly severe for the most novel products (i.e. those with a new mechanism of action).

The third subplot of Figure 1 compares the average market share (measured in revenues) within a country and ATC3 class within two years of launch across products with different ASMR ratings. For this measure of market rewards, major innovations do appear to have some advantage over the less important categories. Considerable heterogeneity remains, and the differences are not statistically significant. However, the ordering is consistent with greater rewards to greater therapeutic benefits, and this is true in both the rich and poorer subsamples.

5.4 ASMRs and revenues

Ultimately, what matters for R&D investment from the perspective of a firm is the difference between revenues and costs. While I do not observe costs, I can compare revenues across products. Although revenues are measured with error (because secret rebates are not observed), this is in some sense the best comparison: it is the net effect of price, market share, and exclusivity. In addition, the previous analysis considered the distribution of revenues *within* countries. If major innovations reach more countries, then their total revenues could exceed those of less important therapies.

The last three subplots of Figure 1 show how the log of global revenues varies by ASMR score. Because the adoption of new technologies is generally not instantaneous, I compare global revenues 3, 5 and 10 years after the first introduction (restricting the sample of drugs to those with at least 3, 5 or 10 years of data, so the sample size declines with each subplot). By 10 years, it seems that most of the major innovations are clearly established as successes relative to the other categories, although only five drugs received the best ASMR score prior to 2006. There is little difference between the other categories.

The figures presented above do not control for many other factors that determine a product's success. In particular, the intensity of competition may vary across countries and disease

markets; this is itself a function of the price and quality of competing products. Accounting for this in a complete econometric model is beyond the scope of this paper. However, Table 3 presents a summary of regressions that include fixed effects for country and broad therapeutic class (ATC1), as well as an indicator variable for whether a drug received orphan status from the EMA, where I take the best ASMR score ever assigned to a drug. Table 4 restricts the sample to NCEs only.

If therapeutic value is linked to market rewards, we should expect all coefficients on ASMR categories to be positive and ordered from highest for "major" to lowest for "minor" (the omitted category is ASMR V, or non-existent benefit relative to existing treatments). No specification, across both tables, yields this pattern. The number of patents bears little relationship to the level of therapeutic value: in both tables, the category with the highest number of patents is "moderate." Though important drugs have high prices relative to the omitted category, the coefficient on this category is the smallest of the remaining four. The results are somewhat more encouraging for market share. The most innovative category has the largest coefficient, followed by the important category, and the difference between the two is also significant. These results suggest that prescribers have sufficient information about therapeutic value to direct patients towards the best products. Overall, the evidence that revenues are increasing in therapeutic value is weak, with the same pattern as relative prices. The middle categories (important and moderate) have significantly higher revenues in both the full sample as well as the NCE subset.

Other variables have coefficients in line with expectations. Orphan drugs, which by definition cater to small markets, have lower revenues on average. Competition variables should be interpreted with caution, as these are endogenous. With that caveat, it appears that competition from other drugs lowers market share, but not relative prices or revenues, perhaps reflecting greater advertising or high demand. Markets with a high share of generics see smaller market shares and revenues; because generics are likely to reduce the average price in the category, relative price is higher.

5.5 Differences across rich countries

The trade-off between access to innovation and providing long-run incentives for investment is likely to differ across countries. In particular, richer countries and those large enough to influence investment may have a higher willingness to pay for future innovation, through longer market exclusivity or higher prices, relative to poorer countries or those with a small effect on global revenues. Countries also differ in the extent of insurance coverage or cost-sharing, price sensitivity on the part of patient or prescriber, information, etc.

My final analysis considers whether innovation is rewarded differently across rich countries. I focus on four major developed countries, each with a significant domestic pharmaceutical industry, but different approaches to health care: France, Germany, the UK and the US. Regressions similar to those in the previous section, but now restricted to each country, are in Tables 5-8. The number of observations differs across countries, because not all products were launched in all markets, or indeed even in France: some products were not commercialized after HAS evaluations.

Overall, there are three main points. First, with the exception of France, there is again only

Table 3: Regressions of rewards on best ASMR scores

	Patents	Relative price	Market share	Revenues
	b/se	b/se	b/se	b/se
Major	0.007	0.448**	0.044***	0.284
	(0.245)	(0.205)	(0.009)	(0.186)
Important	1.073***	0.531***	0.027***	−0.011
	(0.149)	(0.130)	(0.005)	(0.118)
Moderate	1.157***	0.624***	−0.009*	0.012
	(0.137)	(0.112)	(0.005)	(0.110)
Minor	1.112***	1.029***	0.018***	−0.411***
	(0.118)	(0.090)	(0.004)	(0.100)
Orphan drug	−0.458***	0.126	−0.001	−0.739***
	(0.175)	(0.150)	(0.006)	(0.164)
Number of		0.026***	−0.003***	0.094***
drugs in ATC3		(0.004)	(0.000)	(0.004)
Share of		1.419***	−0.066***	−1.242***
generics in ATC3		(0.122)	(0.005)	(0.120)
N	9031	4814	8997	7179
Fixed effects		Country ATC1		

* p<0.10, ** p<0.05, *** p< .01.

Table 4: Regressions of rewards on best ASMR scores, NCEs only

	Patents	Relative price	Market share	Revenues
	b/se	b/se	b/se	b/se
Major	−0.288	0.482**	0.038***	0.453**
	(0.246)	(0.229)	(0.009)	(0.188)
Important	0.206	0.490***	0.017***	0.090
	(0.154)	(0.150)	(0.006)	(0.123)
Moderate	0.879***	0.618***	−0.014***	0.183
	(0.141)	(0.130)	(0.005)	(0.114)
Minor	0.776***	0.967***	0.014***	−0.191*
	(0.124)	(0.105)	(0.005)	(0.107)
Orphan drug	−0.442**	−0.056	0.000	−0.705***
	(0.174)	(0.166)	(0.006)	(0.164)
Number of		0.027***	−0.003***	0.087***
drugs in ATC3		(0.004)	(0.000)	(0.005)
Share of		1.568***	−0.067***	−1.046***
generics in ATC3		(0.148)	(0.006)	(0.130)
N	7498	3785	7469	5875
Fixed effects		Country ATC1		

* p<0.10, ** p<0.05, *** p< .01.

Table 5: Regressions of rewards on best ASMR scores for France

	Patents b/se	Relative price b/se	Market share b/se	Revenues b/se
Major	−1.174	0.076	0.120**	3.151**
	(2.344)	(1.363)	(0.051)	(1.235)
Important	2.421*	1.113	0.083***	2.046***
	(1.304)	(0.891)	(0.029)	(0.757)
Moderate	2.008	1.038	0.020	2.279***
	(1.236)	(0.809)	(0.027)	(0.718)
Minor	1.658	1.578**	0.015	−0.645
	(1.056)	(0.706)	(0.023)	(0.659)
Orphan drug	−2.020	−0.391	−0.007	0.561
	(1.343)	(0.863)	(0.030)	(0.834)
Number of		0.009	−0.003***	0.077***
drugs in ATC3		(0.028)	(0.001)	(0.028)
Share of		3.538***	−0.050	−2.806***
generics in ATC3		(1.036)	(0.036)	(1.075)
N	224	170	223	178
Fixed effects		ATC1		

* p<0.10, ** p<0.05, *** p< .01.

a weak relationship between therapeutic value and market rewards as measured by revenues. As in the previous regressions, market share is increasing in the therapeutic value score, but relative price is not. Of course, the two may be simultaneously determined: products with lower relative prices may more successfully steal share from competitors, or expand the market to new users. However, the greater share is not always sufficient to yield higher revenues, which ultimately matter more for R&D investment. Second, despite having different approaches to healthcare, there is striking similarity in some respects across these countries. Products classified as major innovations are not rewarded with higher prices: the coefficient is imprecisely estimated for each country, and only in Germany is the point estimate higher than the other categories. Finally, the results for the US show the least distinction between the different categories. This is the market with the least government intervention, but with the exception of market share, there is little evidence that it rewards innovation to a greater extent than the European countries. Although the mean price is higher, there is less discrimination between the levels of therapeutic value. These results are consistent with other recent work suggesting that the US may be "uniquely inefficient" in its adoption of pharmaceutical innovations (Kyle & Williams (2017)).

5.6 Limitations

An important concern in using the ASMR scores is a scenario like the following. Firms simultaneously develop a new class of drugs that represents a significant improvement over existing

Table 6: Regressions of rewards on best ASMR scores for Germany

	Patents	Relative price	Market share	Revenues
	b/se	b/se	b/se	b/se
Major	−0.839	0.334	0.076	0.175
	(2.336)	(1.307)	(0.063)	(0.838)
Important	2.825**	0.607	0.082**	1.102**
	(1.275)	(0.701)	(0.035)	(0.503)
Moderate	2.083*	0.687	0.015	1.153**
	(1.185)	(0.633)	(0.032)	(0.468)
Minor	1.812*	1.078**	0.097***	−0.313
	(0.980)	(0.539)	(0.027)	(0.412)
Orphan drug	−2.421**	0.159	−0.006	−0.777
	(1.173)	(0.661)	(0.032)	(0.568)
Number of		0.033	−0.005***	0.014
drugs in ATC3		(0.022)	(0.001)	(0.017)
Share of		2.238***	−0.067*	−1.760***
generics in ATC3		(0.707)	(0.035)	(0.566)
N	253	232	253	195
Fixed effects		ATC1		

* p<0.10, ** p<0.05, *** p< .01.

Table 7: Regressions of rewards on best ASMR scores for UK

	Patents	Relative price	Market share	Revenues
	b/se	b/se	b/se	b/se
Major	−0.873	0.588	0.067	1.352
	(2.312)	(1.495)	(0.060)	(1.028)
Important	2.692**	0.865	0.069**	1.564**
	(1.266)	(0.862)	(0.033)	(0.622)
Moderate	2.056*	1.022	−0.003	1.620***
	(1.174)	(0.790)	(0.031)	(0.577)
Minor	1.682*	1.416**	0.023	0.599
	(1.009)	(0.680)	(0.027)	(0.518)
Orphan drug	−1.894	0.534	0.017	−0.145
	(1.221)	(0.857)	(0.032)	(0.722)
Number of		0.088***	−0.003***	0.058***
drugs in ATC3		(0.025)	(0.001)	(0.020)
Share of		3.070***	−0.074**	−2.530***
generics in ATC3		(0.836)	(0.031)	(0.624)
N	238	187	237	187
Fixed effects		ATC1		

* p<0.10, ** p<0.05, *** p< .01.

Table 8: Regressions of rewards on best ASMR scores for US

	Patents b/se	Relative price b/se	Market share b/se	Revenues b/se
Major	−3.410	0.433	0.147*	1.056
	(4.420)	(0.994)	(0.082)	(0.973)
Important	0.552	0.419	0.117***	0.145
	(2.323)	(0.560)	(0.043)	(0.576)
Moderate	3.256	0.626	0.010	0.686
	(2.145)	(0.484)	(0.040)	(0.537)
Minor	0.188	0.396	0.057*	−0.019
	(1.862)	(0.437)	(0.035)	(0.500)
Orphan drug	−2.764	0.082	0.000	−0.612
	(2.285)	(0.554)	(0.042)	(0.688)
Number of		0.045**	−0.007***	0.006
drugs in ATC3		(0.018)	(0.001)	(0.021)
Share of		1.835***	−0.017	−1.665***
generics in ATC3		(0.477)	(0.038)	(0.535)
N	222	207	222	167
Fixed effects		ATC1		

* p<0.10, ** p<0.05, *** p< .01.

treatments. The first from this class to arrive receives a very good ASMR, but the followers are compared to the first-mover and thus receive a low ASMR, because they offer similar benefits. In this case, we might expect each entrant to have roughly similar revenues or market shares, despite having different ASMRs. While I cannot exclude this possibility completely, I checked the comparator drugs used in evaluating new products in several therapeutic classes that had multiple launches during this period. In some cases, the HAS in fact assigned the same ASMR to two similar products arriving around the same time: both Gardasil and Cervarix (HPV vaccines) received an ASMR of III. In another case, Giotrif (afatinib) received an ASMR V, a poorer score than that assigned to earlier tyrosine kinase inhibitors (Iressa (gefitinib) and Tarceva (erlotinib)), but arrived many years after. The class of drugs most "punished" by comparisons to other recent entrants was antiretroviral treatments for HIV. The HAS generally assigned favorable ASMR scores to single molecule innovations, but ASMR Vs to the fixed-dose combination products using these new molecules that were subsequently launched. While combination products are arguably less innovative in a scientific sense, they can provide substantial consumer benefits and the inventors of the component molecules also profit, if the components are still patent-protected. I therefore re-estimated the regressions excluding this class of drugs and confirmed that this does not substantively change the results above.

This study has many other shortcomings. Like most other studies, prices (and revenues) do not reflect rebates that manufacturers negotiate with payers. If these rebates are larger for less important drugs, then the results above will understate the difference between the outcomes for

the "best" drugs and those considered to have minimal benefits relative to existing therapies. More generally, the ASMR measure reflects the opinion of experts in a single country. I assume here that this would not vary considerably across countries, but this should be verified using comparable assessments from others. In addition, while the ASMR precedes price negotiations, it is entirely possible that HAS experts account for the effect of the ASMR score on price, and respond accordingly. For example, worries about the budgetary impact of a product like Sovaldi could induce more skeptical assessments from HAS. Note, however, that this distorts innovation incentives too.

Another key limitation is that while I assume breakthrough innovations are more socially valuable than marginal ones within a disease area, it is entirely possible that a marginal improvement in treating a widespread disease, or one with a very large burden, provides greater welfare than a breakthrough treatment for a disease that affects few people or whose burden is minimal. That is, a new treatment that reduces the duration of the flu by one day may not score very well on the ASMR criteria, but would provide a bit of benefit to more than 3 million people per year affected by the flu in the US each year. In comparison, the FDA recently approved a new drug, considered a breakthrough, to treat spinal muscular atrophy, which affects only about 400 babies per year in the US. The regressions above include course controls for disease area, but clearly an area for improvement is a better measure of disease burden. Unfortunately, consistent measures at a sufficient level of detail are difficult to obtain across countries.[15]

6 Conclusion

Aging populations in many developed countries combined with budgetary pressures associated with the financial crisis of 2008 have increasingly strained health care systems. Drug prices, perhaps more visible than other prices in health care, are frequently criticized in this context. In emerging markets, where populations are younger and growth rates are higher, the introduction of patent protection for pharmaceuticals has also focused attention on drug prices. While there is general agreement that innovation incentives are important, there is considerable debate over whether current policies have appropriately balanced access to treatments with long-run investment incentives.

This paper focuses on a narrower but related question: do innovation policies reward important innovations more than marginal ones? In other words, instead of considering the overall level, I ask whether the expected return from a breakthrough innovation is greater than that from a minor one. I cannot observe returns directly, and innovation is itself very difficult to measure. Given these limitations, I nevertheless provide some evidence on the rewards associated with different assessments of therapeutic value.

In general, I do not find very large differences across the categories of therapeutic benefits. Tools used by governments to reward innovation, namely patents and price, do not distinguish very well between major innovations and minor ones. For patents and related exclusivity policies,

[15] I explored using the data on global disease burden from the Institute for Health Metrics and Evaluation, for example, which provides annual estimates for more than 200 causes. However, these vary in specificity, with more detailed information available for some disease areas than others.

this should be expected, as these are one-size-fits-all. This finding is also consistent with recent work showing that patent citations have little connection to additional quality-adjusted life years, an alternative measure of therapeutic or social value (Abrams & Sampat (2017)). The results here suggest that payers have difficulty committing to rewarding innovation through price, and this is true in both rich countries as well as poorer ones. The most encouraging evidence is that after 10 years, global revenues are higher for more important innovations (though this subsample includes only a handful of drugs). With sufficient time for information about drug importance to diffuse, the market eventually rewards importance, but exclusivity for the innovator during this time is critical if this is to influence R&D investment decisions.

Within several important pharmaceutical markets, however, the revenues derived from minor innovations are close to those from major ones, at least in the first few years post-launch. It is possible that major innovations benefit from other policies that lengthen market exclusivity, and therefore revenues. While patents and data exclusivity rules generally do not distinguish between breakthroughs and me-toos, the former may reach the market sooner. For example, Dranove & Meltzer (1994) found that more important drugs had both faster development times as well as faster approval times at the FDA. More recently, Chambers et al. (2015) analyzed expedited review programs at the FDA, and found a positive correlation between inclusion in these programs and clinical gains. Due to censoring in my data, I am unable to assess whether favorable review times ultimately result in longer effective exclusivity and higher revenues over a drug's entire lifecycle.

These results imply that incentives for investment in breakthrough products are not particularly strong. If such investment is riskier, involving more novel science or more uncertainty, pharmaceutical firms see greater returns from "me-too" products or marginal innovations. Further study of the difference in social benefits derived from these innovation classifications is necessary in order to inform changes to existing innovation and pricing policies.

7 Appendix: Variable definitions

- Patents granted in country: The total number of granted patents associated with drug i in country c as of 2015. This is subject to truncation for more recent drug launches, as patent applications may either still be under review or yet to be filed. Results are similar using patent applications rather than grants.
- Unit price relative to average in ATC3: Price per "standard unit" (typically a pill, capsule, or vial) of drug i in country c divided by the average price per standard unit for all other drugs in the same ATC3 in country c, averaged over the 2 years following drug i's introduction in country c. The glaring shortcoming of this measure is that dosing can vary across products within an ATC3, and ideally this calculation would use price per dose rather than price per unit. Unfortunately, defined daily dose is not available for many of the products in my sample.
- Market share: The share of drug i's revenues in its ATC3 class in country c, averaged over the 2 years following drug i's introduction in country c.

- Share of generics in ATC3: The share of generic units sold in drug i's ATC3 class in country c, averaged over the 2 years following drug i's introduction in country c.
- Number of drugs in ATC3: The number of distinct molecules sold in drug i's ATC3 class in country c at the time of drug i's launch in country c.
- Number of drugs with generic entry in ATC3: The number of distinct molecules with generic equivalents sold in drug i's ATC3 class in country c at the time of drug i's launch in country c.
- Log of country revenues, 3/5/10 years post-launch: The log of the sum of revenues for drug i in country c over the 3/5/10 years following its launch in country c. Revenues are in nominal local currency, converted to US dollars using the average exchange rate in the relevant quarter, and then put in constant US dollars using the GDP deflator.

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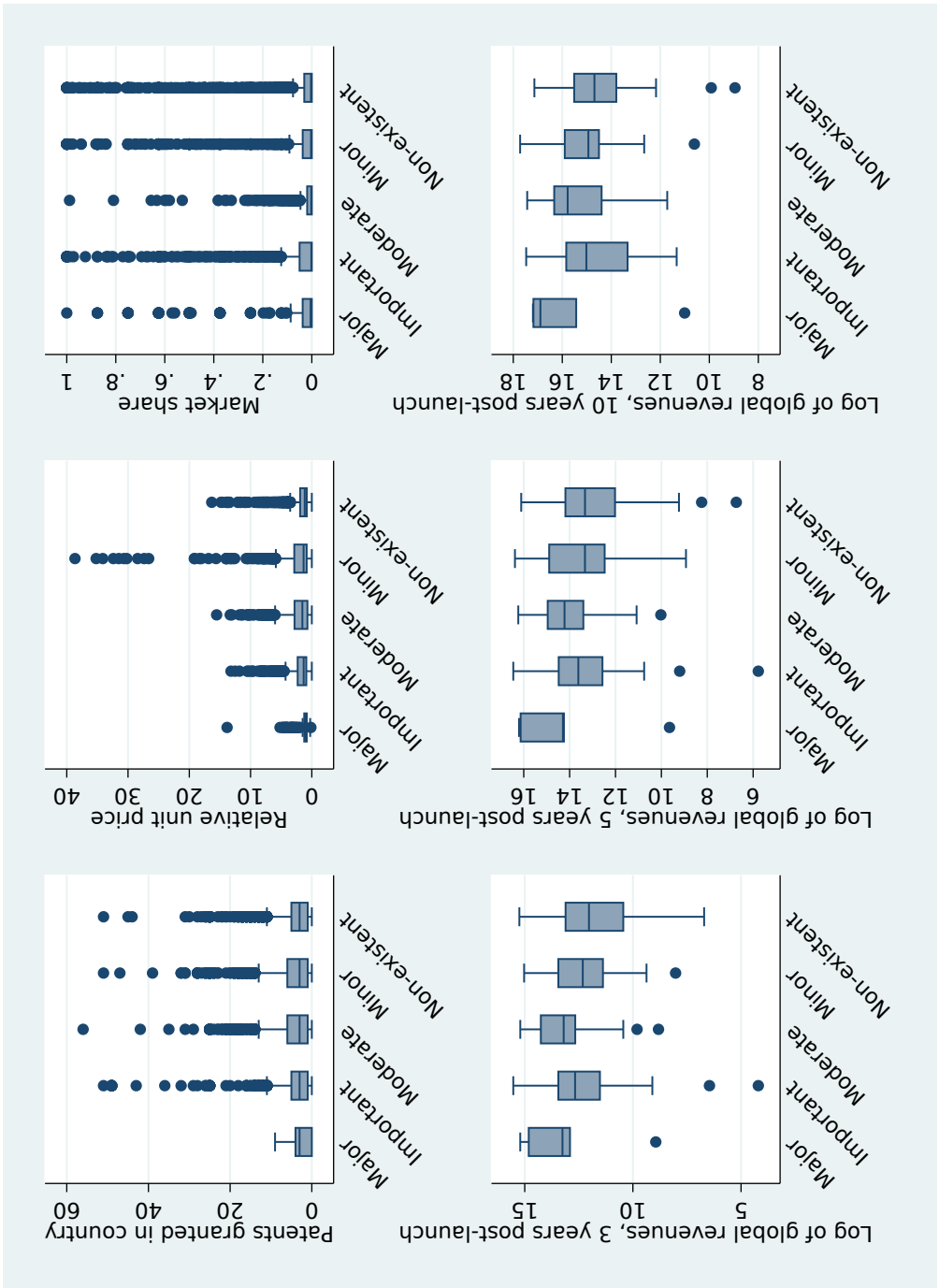

Figure 1: ASMRs and market rewards