MARKET HETEROGENEITY AND DRUG INNOVATION

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DEDICATION

To God, our Father.

To my parents, Uhil and Young Sil.

And to my wife, Hyo Eun, and our boys, Jacques and Pascal.

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ABSTRACT

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The Induced Innovation Hypothesis (IIH) describes the causal effect of market size (i.e., product demand) on innovation output – larger value markets offer larger profit potential which leads to higher rates of new product entry. Empirical literature has supported the IIH but the estimated effects of market size on pharmaceutical innovation are curious in two respects: they are much higher than predicted and they vary across innovation measures (e.g., new molecules, new non-generic drugs, new patents). I propose and investigate an extended Induced Innovation Hypothesis (eIIH) which posits how non-size characteristics of markets or "market heterogeneity" (e.g., compositional structure, R&D riskiness) together with aggregate market size can influence the introduction rate of new drugs and associated outputs. My empirical approach exploits a panel dataset constructed from publicly available data from the U.S. Food and Drug Administration, Agency for Healthcare Research and Quality, and World Health Organization that links market size and heterogeneity measures with innovation counts associated with New Drug Application (NDA) approvals. Consistent with previously reported estimates, I find that a 1% increase in market size produces a 2%-6% increase in innovation entry under a traditional IIH setup. However, in closer alignment with theoretical predictions, controlling for market population characteristics such as disease severity, physiology types, and treatment preferences lowers the estimated effect of market size to the 1%-4% range. These results appear reasonably robust across different innovation count measures with significance levels sensitive to specification and variable construction choices. Thus, initial evidence suggests that an extended IIH can provide a more informative model of induced drug innovation than the traditional IIH. It also suggests how policy levers might be more effectively used to direct pharmaceutical innovation toward under-served as well as un-served markets.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1.

INTRODUCTION AND MOTIVATION

1.1 INTRODUCTION

With health care spending reaching almost 18% of U.S. GDP in 2010 and prescription drugs accounting for approximately 10% of this, the demand for and supply of new medicines has been a hot topic for national discussion.[1] But in fact the public's strong interest in drug innovation for several decades now is what has motivated innovation-promoting policy interventions including the Orphan Drug Act of 1983, the Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch) of 1984, the FDA Modernization Act of 1997, and the Medicare Modernization Act of 2003. Yet despite any and all increases in new drug products attributed to these policy-driven incentives, concerns over drug industry output are still being voiced. For instance, the 10% annual decline in the number of new molecular entities receiving FDA approval from 1996-2006 has been reported as cause for alarm;[2] despite the fact that the number of all products receiving FDA approval increased by 4% annually during that same time period (see Figure 1.1). While it turns out the 1996-2006 window is unrepresentative of longer-term industry dynamics, these statistics underscore the technical uncertainties spanning different stages of the drug innovation process as well as different drug product types; since understandably, the success probability of creating a dosing extension for an existing drug should be substantially less than the success probability of creating a new-to-the-world molecule. Nevertheless, if drug firms have some ability to factor these uncertainties into their decision-making then innovation output ought to be influenced by the profit-maximizing behavior of industry. In such a case, what would be key

[1] Center for Medicare and Medicaid Services NHE Fact Sheet (www.cms.gov/Research-Statistics-Data-and-Systems accessed on July 10, 2013).
[2] Pharma Focus Asia, Issue 9, 2008.

explanatory variables involved in a drug firm's profit-maximizing equation? Identifying such variables, particularly those which are observable, could provide firms, policy-makers and other industry stakeholders with a more comprehensive set of tools to improve industry efficiency while also better aligning private incentives with public objectives.

1.2 MOTIVATION

The Induced Innovation Hypothesis (IIH) provides the natural first step for asking and addressing this key explanatory variables question. The IIH describes the causal effect of market size on innovation output.[3] Markets representing larger value (due to higher demand) offer larger profit potential thereby leading to higher rates of new product entry. However, the IIH does not consider the influence of any other market characteristic beyond aggregate market size. And while the empirical literature supports the IIH in the context of drug innovation, the IIH lacks in its ability to explain why the estimated coefficients of market size are of substantially greater magnitude than what IIH theory would predict and also why they vary across innovation measure types (e.g., new molecules versus new non-generics).[4]

Hence, I am motivated to ask: can the Induced Innovation Hypothesis be extended to make finer predictions regarding new drug product entry? Would such an "extended Induced Innovation Hypothesis" (eIIH) be able to better explain the empirical evidence on induced effects across innovation count measures associated with approved New Drug Applications (NDAs)? Traditional IIH setups ignore or, more precisely, implicitly assume markets are homogeneously composed relative to each other. My point of departure is that potential markets are not all homogeneous or, equivalently, not all equally heterogeneous in their market composition. Thus, perhaps such "market heterogeneity," in conjunction with and/or separately from market size, can

[3] See for instance Schmookler (1962); Ahmad (1966); Fellner (1971); Binswanger & Ruttan (1978).
[4] In particular, Acemoglu & Linn (2004) estimate the inducement effects of (potential) market size to be 4-6% for new non-generic drugs and as high as 12% for new generic drugs. Their theoretically predicted inducement effect is 1%.

induce innovation via demand-side (e.g., different disease population needs) and/or supply-side (i.e., different R&D strategies) mechanisms.

Elucidating the potential relationships between market characteristics and the rate of drug innovative output has important public and private sector implications. It can help shed light on whether perceived drug industry productivity issues are the rational result of weakening economic incentives. It can help pave the way for both retrospective and prospective analyses of innovation incentives, e.g., drug reimbursement policies (Medicare, Medicaid.), drug approval regulatory policies (diversity requirements in clinical trials, market and patent exclusivity extensions), post-marketing regulatory policies (medical education allowances, direct-to-consumer marketing rules), etc. And it can improve market efficiency by helping industry stakeholders (firms, investors, brokers, regulators) to potentially conduct more accurate market forecasts and investment analyses.

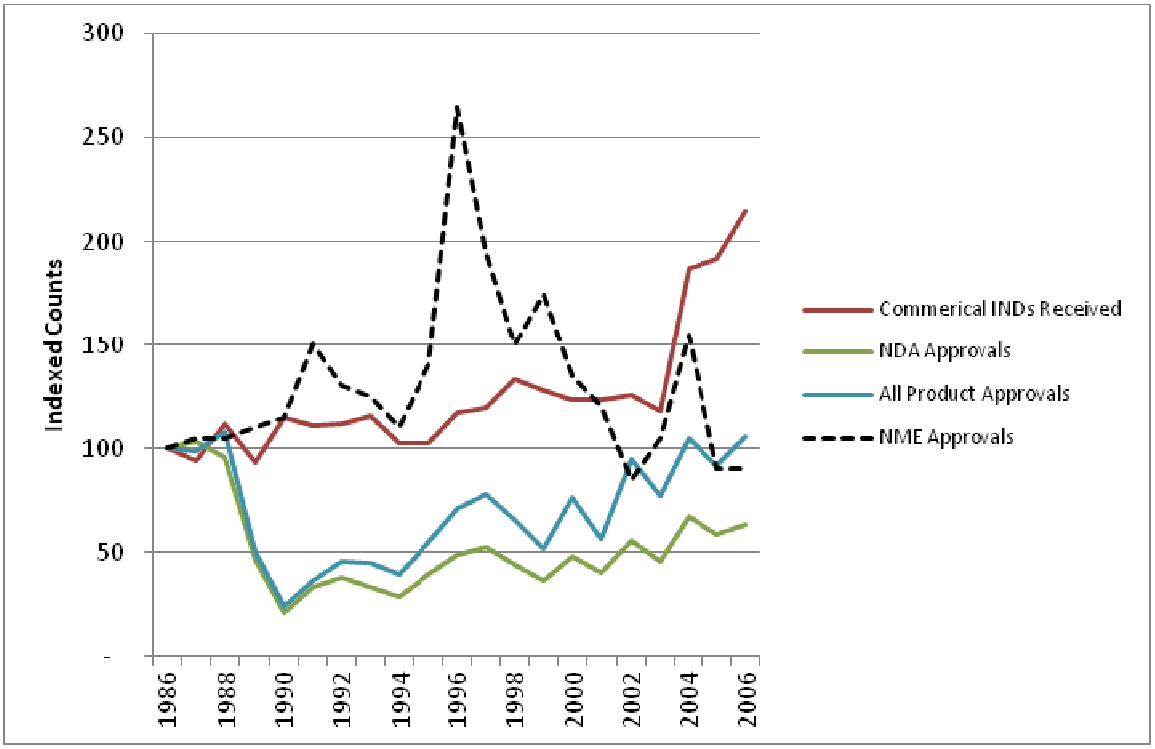

Figure 1.1. FDA Approval Activity for 1986-2006

CHAPTER 2.

OBJECTIVES AND BACKGROUND

2.1 OBJECTIVES

The traditional IIH posits the positive causal effect of market size on innovation rate. This study aims to expand the IIH's scope by examining the potential explanatory role of market characteristics other than aggregate market size. In other words, can market characteristics, separately from and in concert with aggregate market size, have inducement effects on drug innovation entry? I propose to investigate this matter via two specific research questions. First, for a given market size, will the innovation rate – as reflected by outputs associated with drug approvals – be higher the more heterogeneously, or non-homogeneously, composed the population (Research Question #1)? Second, does accounting for market heterogeneity produce market size estimates that are more consistent with theoretical predictions (Research Question #2)?

At a conceptual level, besides being illuminating in cases when markets might have different innovation rates despite having the same aggregate sizes (i.e., dollar values), accounting for non-size market characteristics in an eIIH can contribute to making the IIH more of a complete story. Further, recognizing the non-trivial role of market heterogeneity in influencing innovation rates provides complementary evidence to the IIH literature that drug innovation is not only an economically rational activity undertaken by firms but also a welfare-enhancing response to market-specified demands (e.g., matching product qualities to patient needs/preferences).[5] This suggests that the market entry of "less innovative" drug products such as me-too drugs and drug

[5] See references listed in footnote 3.

reformulations may have no less social value ex ante (on a cost-benefit weighted basis) than the discovery of new first-in-class drugs and new molecular entities.

From an empirical perspective, the full impact of non-size market characteristics may have been mis-estimated in prior research due to market homogeneity assumptions and/or omitted variable bias (via unaddressed confounding and/or interaction term effects). Consequently, traditional IIH methodologies may have estimated the coefficient on market size with error.[6]

2.2 INTUITION

Since my hypothesis has not been previously suggested or described in the literature to my knowledge, I present two illustrations – one simplified, one detailed – of the underlying intuition involved.

The first example, outlined in Appendix 10.1, accounts for market heterogeneity in terms of exogenously given categorical measures and serves to illustrate how non-size market characteristics could affect entry from the supply side. The intuition here is that the expected cost of a successful entry may be lower (or higher) by undertaking a second entry attempt within the current project than by undertaking a new project altogether. So having the ability to make multiple entry attempts in a single project may allow the firm to increase (or decrease) innovation productivity. Thus, the number of attempts per project, *a*, or "R&D riskiness" is a non-size market characteristic which could influence innovation product entry.

The second example, outlined in Appendix 10.2, builds on the first example by accounting for market heterogeneity in terms of a quasi-categorical set of potentially endogenous measures. It also accounts for a potential demand-side influence of market heterogeneity. Specifically, it considers two disease categories G_1 and G_2 with respective sizes M_1 and M_2 (without loss of

[6] For instance, if those markets with the largest value are also the most heterogeneous, not controlling for heterogeneity may bias upward the coefficient on market size, i.e., predicts too high a rate of entry.

generality, say $M_1 \geq M_2$). When drug development projects can exploit G_1 and G_2 as separately homogeneous sub-groups rather than as one presumptively homogeneous group, the expected number of new product entries (e.g., new drug molecules) increases as does the expected number of new indication approvals.

The concept of a product innovation attempt in these two illustrations is quite general. While the ability of firms to make multiple product innovation attempts per project can depend on supply-side (e.g., product R&D technology) and/or demand-side (e.g., sub- or specialized need) characteristics of the market in question, the number of innovation attempts per project is likely a function of the number of product attempt candidates per project and/or the number of "attempt success contexts" available for exploitation.[7] Moreover, this latter metric can be some reflection of the variety of needs and/or preferences composing a given market.[8] Attempt success contexts might be especially important when the number of product attempt candidates per project is structurally limited, as in the case of pharmaceuticals where there is usually only one attempt candidate per project.[9] For example, consider a disease market with no sub-indication variety (say erectile dysfunction) and a disease market with some sub-indication variety (say diabetes which is composed of the Type I and Type II sub-indications). Here, the diabetes market provides each project with two "attempt success contexts" in which to demonstrate clinical benefit (i.e., in Type I patients and Type II patients) whereas the erectile dysfunction market provides only one "attempt success context." Since entry in pharmaceuticals is correlated to the number of attempts possible, the availability of attempt success contexts is a potentially important driver of

[7] My theoretical setup will account more fully for how the number of attempts affects both supply-side costs and demand-side revenues.

[8] The firm's incentive for pursuing FDA approval in more than one sub-indication within the same disease category (i.e.,. expanding the scope of the drug label) is to expand their drug's scope of use (if physicians are assumed to prescribe drugs strictly for their labeled sub-indications) or at least improve their drug's priority use position relative to other drugs in treatment protocols (if physicians are assumed to prescribe drugs "off-label").

[9] Firms invest only in the best-in-project product candidate at any given point in the drug development process (i.e., firms only pursue one molecular candidate per project) because the conventional wisdom is that any problem associated with the best-in-project candidate will likely also be associated other within-project candidates. In other words, the success probabilities of within-project candidates are seen to be very highly correlated (i.e., not i.i.d.).

drug innovation productivity.[10] This illustrates how non-size market characteristics such as those associated with attempt success contexts can have inducement effects which operate distinctly from the traditional IIH mechanism.

2.3 DEFINITIONS

2.3.1 MARKET SIZE

Determining market size depends on defining the market as well as its measurement units. For this study, I am concerned with defining markets according to drug-use categories (e.g., disease population) and measuring them in terms of dollar value (e.g., drug spend) as these approaches are most relevant to the IIH setup. Also important but unaddressed in prior studies is the question of what levels of market boundary granularity are most relevant for analyzing the effects of market size. Figure 2.1 shows the plausible variations for calculating market size according to disease population categories (e.g., "treatment-active" versus "unsatisfied treated"). However, given the scope of my study I only give empirical consideration to this issue and table theoretical considerations for future examination.

2.3.2 MARKET HETEROGENEITY

There are various ways in which to characterize market heterogeneity or a market's non-homogenous composition. To help determine which/how characteristics enter my theoretical and empirical models, I propose an initial classification framework that considers whether an attribute impacts drug labeling and to what level of market granularity the attribute applies.[11] I am thus able to distinguish between four attribute groups as shown in the quadrants of Figure 2.2: those having non-label impacts at the group-level (i.e., those associated with aggregative aspects such

[10] Refer to footnote 72.

[11] This framework is described in specific reference to the drug industry but can easily be generalized to other contexts by changing the drug labeling impact dimension to another type of market barrier (regulatory, competitive, etc.).

as geographical location); those having label impacts at the group-level (i.e., associated with efficacy and safety); those having non-label impacts at the individual-level (i.e., associated with tolerability/compliance; and those having label impacts at the individual-level (i.e., associated with black-box warnings).

In situations where an attribute produces a simple segmentation effect (i.e. the characteristic effectively partitions the market into a mutually-exclusive-collectively-exhaustive set of sub-markets), ceteris paribus the characteristic in question exerts its potential inducement influence by basically changing the granularity of market boundaries. In other words, a segmentation effect in practice reduces to a direct market size effect. Since my research effort proposes to examine non-size market characteristics with innovation entry inducement effects which are not reducible to a direct "market size" effect, I am not interested in characteristics represented by the lower left-hand quadrant in Figure 2.2. Rather, I focus on characteristics classified in the other quadrants which may account for compositional differences across markets that can produce partitioned (additively separable) or non-partitioned (non-additively separable) subsets.[12] As will be specified in later chapters, I derive these attributes of market heterogeneity from disease severity, physiology types, and treatment preference considerations.

2.3.3 INNOVATION ENTRY

I am interested in innovation entry as reflected by outputs associated with New Drug Applications approved by the U.S. Food and Drug Administration. I refer to such innovation outputs as innovation count measures since for my research purposes they can be defined along two dimensions, measure type and count type.

Measure type refers to the type of innovation output being counted. Examples of measure types associated with drug innovation include new molecules, new formulations, and new labeling

[12] The link between patient heterogeneities and drug responses has long been a recognized tenet of medical thinking. However, such a marker of market heterogeneity is rarely, if ever, explicitly reflected in conventionally defined measures of "market size."

content. A corollary issue to consider in this definitional process is the potentially ordered nature of categorizations based on degrees of "innovativeness." For instance, a new drug class is considered to be a more costly but also a more clinically meaningful entry than a new drug formulation. Given the potential link of output innovativeness with both demand- and supply-side inducement mechanisms involved in innovation inducement, this issue is a core component of my theoretical treatment of the eIIH setup in Chapter 4.

Count type refers to the type of count used to measure innovation output; in other words, the possible measurement units that can be used for counting entry. Examples of count types relevant to drug innovation include number of NDAs filed and number of patents linked with NDAs. I would also include here count types that quantify "new drug labeling content" – such as the number of new document filings associated with NDAs. In other words, I expand the scope of drug innovation to encompass drug information generation in addition to drug compound generation. This makes sense in three ways: (1) if drug development is indeed attrition-based, it would mean that innovation activity and innovation production are highly correlated and can share the same empirical measures; (2) once a lead drug compound is identified and ready for clinical trials, all of the value-added investment from that point forward is for the sake of generating a clinical data package that will support safety and efficacy claims for FDA approval, for provider/payor/patient marketing, and ultimately for its safe and effective use in clinical practice; and (3) even if a drug does not end up entering the market, the value of the new information generated during development has value that is explicitly acknowledged by the FDA's 505(b)(2) approval process.[13]

[13] "Section 505(b)(2) expressly permits FDA to rely, for approval of an NDA, on data not developed by the applicant - such as published literature or the agency's finding of safety and/or effectiveness of a previously approved drug product." (Source: www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069943.htm, accessed July 15, 2013).

2.4 CONTRIBUTION

In proposing and testing an extended Induced Innovation Hypothesis, this study seeks to determine the importance of non-size market characteristics in influencing drug innovation entry and to explain how these inducement effects can vary across innovation count measures, As a result, my dissertation makes a number of contributions to the research literature. First, I produce new empirical results confirming the Induced Innovation Hypothesis and consistent in magnitudes with – albeit distinct from, by definition and by construction – previously reported estimates. Second, these results are reasonably robust to some variations in the definitional scope and count units of drug innovation measures as well as market size measures. In particular, I extend the concept of innovation output to include new drug "information." Third, I identify and test the effects of alternative definitions of market size prompted by my theoretical setup. Empirically noteworthy is that I find a size construct based on the treatment-controlled portion of disease population that tracks well, and perhaps even better than aggregate market size, with IIH/eIIH predictions. Finally, my findings have implications for the creation of new/refined policy levers and private-sector R&D strategies in drug innovation. For instance, this study informs the public debate on the value of "me-too" drugs and various drug extensions by establishing how patient population compositional characteristics, rather than just simple cost-leveraging group-think by firms, can drive innovation output that may be valuable to less obvious patient sub-populations and their needs.

2.5 OUTLINE

The rest of this dissertation is composed of seven additional chapters. In Chapter 3, I review the prior literature to point out what important questions have been addressed or remain to be answered relating to my research question scope. In Chapter 4, I establish a new theoretical framework and its associated comparative statics for an extended Induced Innovation

Hypothesis. In Chapter 5, I review the empirical strategy I exploit to confirm/refute my testable hypotheses. In Chapter 6, I describe my public data sources and the dataset I assemble on disease population characteristics as well as drug innovation activity. In Chapter 7, I review my results as well as their robustness to changes in specification, identification, variable construction, and measurement units. In Chapter 8, I discuss my findings as well as the threats to validity and limitations of my research approach. Finally, in Chapter 9, I identify several promising avenues for follow-up work and summarize with my conclusions.

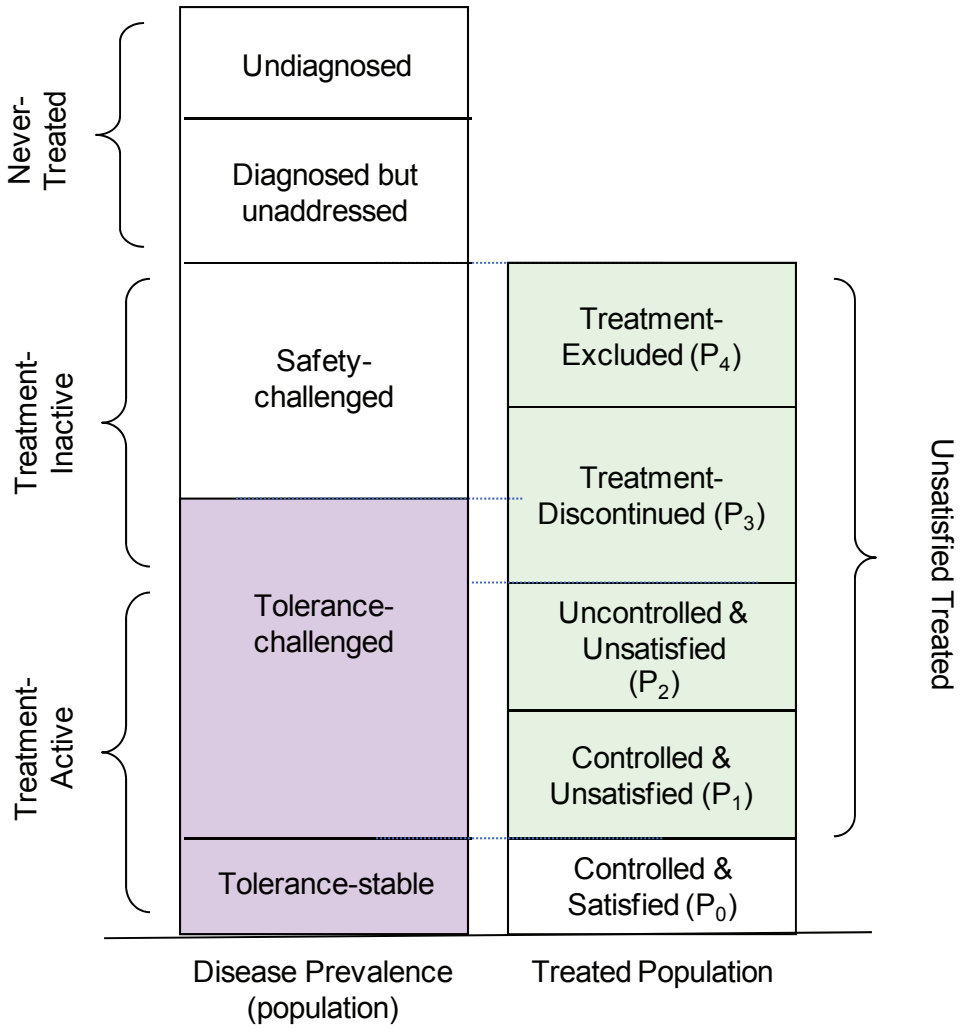

Figure 2.1. Example of Framework for Disease-Based Market Definition

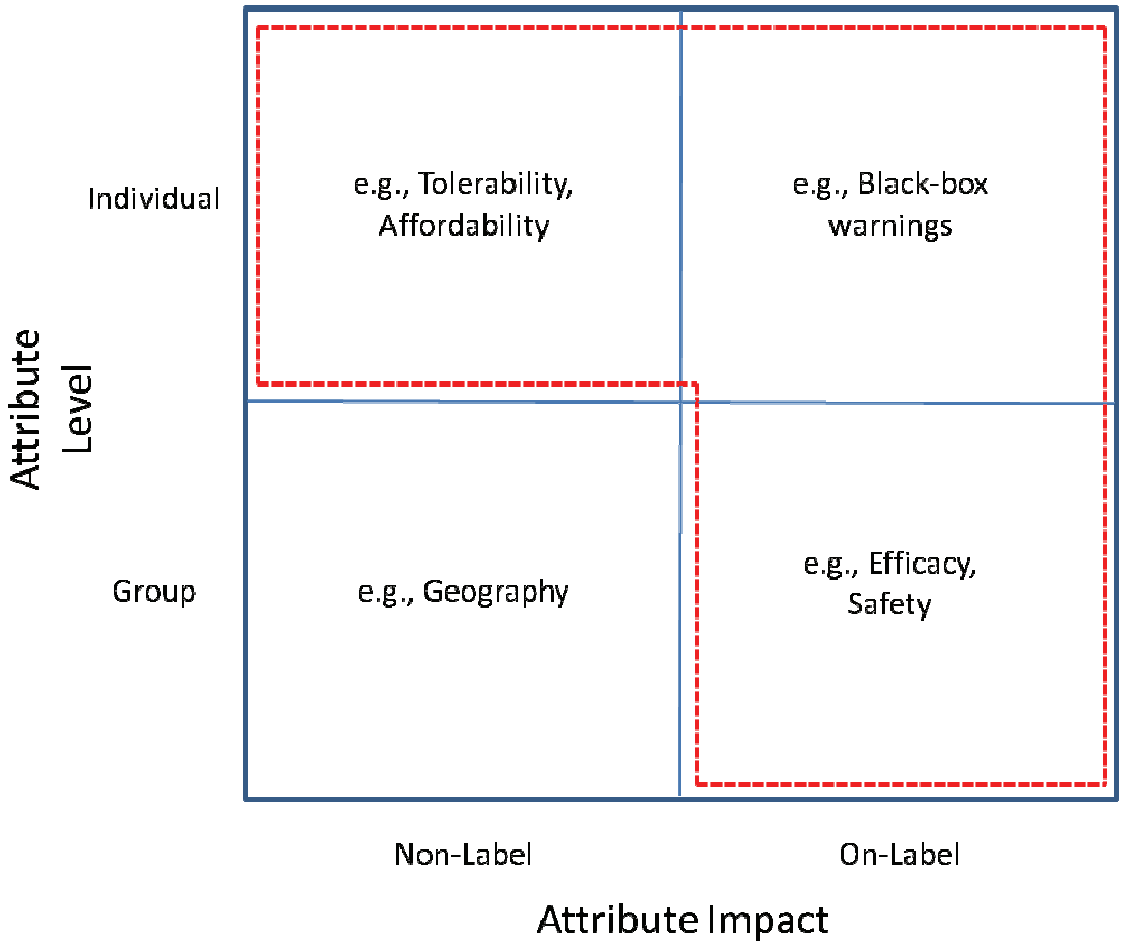

Figure 2.2. Example of Framework for Market Heterogeneity Characteristics

Note: Dotted line denotes characteristic groups with non-trivial attributes of market heterogeneity.

CHAPTER 3.

LITERATURE REVIEW

While the Induced Innovation Hypothesis in its traditional form is intuitively accessible, empirical examinations of the role of market size (i.e., profit incentives) in engendering innovation have been limited. Moreover, to my knowledge there has been no explicit examination – theoretical or empirical – of whether and how additional market characteristics may induce innovation. Nevertheless, there are three bodies of prior research that are related to and could inform my proposed undertaking.

3.1 INDUCED INNOVATION

The springboard reference for my research study is Acemoglu & Linn (2004). Seeking to empirically test the Induced Innovation Hypothesis, the authors use markets defined according to FDA drug classification groupings to show that potential market size – constructed from the number of potential drug category patients and their incomes – influences new drug entry. In order to demonstrate the causality of this relationship, Acemoglu & Linn exploit demographic shifts across income categories as an exogenous source of variation for their identification strategy. With this approach they find potential market size has a significant effect on the entry of new drugs and that this result was consistent across innovation count measures (e.g., for both non-generic and generic molecules). However, an unexplained surprise is that their coefficients on market size were significantly higher than what was predicted by their model as well as conventional theory. Specifically, the authors report that a 1% increase in potential market size produces a 12% increase in the entry rate of generics; a 4% increase in the entry rate of non-generics; and a 4% increase in the entry rate of new chemical entities – all significantly higher

than the 1% increase in innovation rate predicted by their traditional IIH setup.[14] The authors attribute this discrepancy to the pharmaceutical industry's systematic errors in estimating potential market size but only provide weak substantiation for this claim.

Further work in Acemoglu et al. (2006) finds no explicit evidence of demand-induced innovation in pharmaceuticals from the 1965 introduction of Medicare. However, the authors do argue that their results are inconclusive because there appears to be no "first stage" of Medicare increasing the market size of drugs used by the elderly. In addition to Acemoglu & Linn (2004) as well as Acemoglu et al. (2006), the only studies to explicitly measure the effect of changes in demand on pharmaceutical innovation outputs (rather than upstream or downstream surrogates such as R&D spend or health outcomes) are Cerda (2003), Finkelstein (2004), and Yin (2008). Although using different methodologies and datasets, all three authors reach similar conclusions to Acemoglu & Linn (2004). Cerda (2003) uses the same identification strategy (exogeneity of demographic changes) but follows a somewhat different empirical methodology to conclude that a 1% increase in potential market size causes a 1.42% increase in drug entry. Finkelstein (2004) uses the natural experiment of three different policy changes to demonstrate that the policy changes affecting reimbursement of costs of vaccination were associated with a significant increase in the number of clinical trials (250% increase) to develop new vaccines against the relevant diseases. And most recently, Yin (2008)follows the methodology of Finkelstein (2004) by using the natural experiment of the 1983 Orphan Drug Act to show a significant increase in the number of clinical trials (69% increase overall, 232% increase for more prevalent orphan diseases) for new drugs against orphan diseases in response to the ODA's market demand incentives.

Other research to date that empirically examines demand-induced pharmaceutical innovation includes Grabowski & Vernon (2000), Kremer (2002), Lichtenberg & Waldfogel (2003), and DellaVigna & Pollet (2004). Grabowski & Vernon (2000) examine the determinants of

[14] It is interesting to note, however, that neither Acemoglu & Linn (2004) nor Finkelstein (2004) finds empirical evidence of induced innovation when innovation is measured by patent counts.

pharmaceutical R&D using pooled firm data from 1974-1994 to argue that expected returns and cash flows are important explanatory variables of firm research intensities. Kremer (2002) argues that insufficient pharmaceutical industry research in third world diseases such as malaria are due to the lack of market potential incentives. Lichtenberg & Waldfogel (2003) use the natural experiment of the 1983 Orphan Drug Act to argue a demand-induced innovation effect that can be tied to relative declines in mortality of individuals with rare diseases. DellaVigna & Pollet (2004) investigates whether the stock market responds to demographics-driven changes in the size of the market for a number of products. However, in contrast to the empirical studies mentioned previously, these additional research efforts only consider surrogate measures related to drug innovation rates.

Induced innovation by innovation type (product vs. process) has been investigated by Adner & Levinthal (2001), Bandyopadhyay & Acharyya (2004), and by innovation degree (radical vs. incremental) by Fontana (2008). In the pharmaceuticals industry, Scott Morton (1999) finds a positive relationship between generic drug entry and expected revenues in the target market, although she is not able to exploit a potentially exogenous source of variation in market size. DiMasi & Paquette (2004) analyze entry speed of second-in-class drugs to find that the vast majority were in development prior to the approval of the first-in-class drug, suggesting that a "development race" model better characterizes new drug development than does a model of *post hoc* imitation. However, how market size influences product output ("induced innovation") across different innovation measure types remains largely unaddressed by the literature.

3.2 PRODUCT DIFFERENTIATION

There are two basic microeconomic approaches to analyzing product differentiation.[15] First is the Representative Consumer or Symmetric Aggregate Demand model where consumers have

[15] Carlton & Perloff (1994), pp. 200-234.

preferences regarding commodities, e.g., dessert type (see Spence (1976), Dixit & Stiglitz (1977), Mussa & Rosen (1978)). The second approach is the location/spatial model where consumers have preferences regarding attributes/characteristics of commodities (see Sutton (1991), Chen & Riordan (2007), Yin (2008)).[16] The latter's setup is monopolistic competition where each consumer views him/herself and each firm's product as occupying particular locations in some defined product characteristic space; products closer together are better substitutes and consumers receive more (less) pleasure from a product the closer (farther) away they are located from it. Representative consumer models can follow either the product or characteristic approach while location models can only follow the characteristic approach.

Another promising approach that deserves particular attention is the "spokes" spatial model employed by Chen & Riordan (2007) to study non-localised oligopoly competition with product variety and differentiation. This model allows for market expansion effects and does not require incumbents to change locations as new firms enter the market. However, the same variable (N) is used to represent both the extent of the market as well as the extent of consumer heterogeneity (number of preference "segments"). Additionally, the model lacks a separate market volume variable to reflect disease prevalence, such as the θ used by Yin (2008).

Hybrid models have also been proposed such as the informative advertising model for a market of heterogeneous products established by Grossman and Shapiro (1984) which combines the monopolistic competition framework of Chamberlin (1931) to account for the product's "information" dimension with the circular spatial competition model of Salop (1979) to account for a "location" dimension. Similar results are obtained by the more generalized hybrid (or Probabilistic Discrete Choice/Random Utility) models proposed by Sattinger (1984), Perloff & Salop (1985) and Deneckere & Rothschild (1992).

[16] e.g. chocolate flavor.

3.3 AGGREGATION-HETEROGENEITY

Micro and market level models are linked in consumer demand estimations but this linkage has generally depended on relatively strong assumptions of individual behavior being valid at the market level (Deaton & Muellbauer (1980)). Thus, such models are vulnerable to aggregation bias when aggregation factors have substantial heterogeneity and substantial nonlinearity in their effects.

Lewbel (1985) notes the associated problem of changes in demographic characteristics being forced to be virtually equivalent to changes in prices. A common fix is to let some of the demand equation parameters vary demographically (e.g., Stoker (1979)) but while this procedure allows for interactive demographic and price effects, it is specific to the functional form of the starting model.

Browning et al. (1999) document the empirical evidence for population variation or heterogeneities in tastes and preferences.[17] In particular, they discuss the construction of the "mongrel" (aggregate representative) agent for which it can be necessary to apply different weighting schemes across the population. They point out that accounting for entry and exit decisions can also force the introduction of heterogeneity among agents.

Blundell & Stoker (2005) survey theoretical and empirical work in demand analysis and aggregation over individuals.[18] In particular, they review empirical evidence for how demand varies nonlinearly with heterogeneity in incomes (e.g., Engel's Law with regard to food expenditures)[19] and heterogeneity in needs/tastes (e.g., Barten (1964), Pollak & Wales (1981), Ray (1983), Browning (1992)), and suggest incorporating distributional information into aggregate

[17] "Any careful reading of the empirical microeconomics literature… reveals [that]… accounting for heterogeneity is required to calibrate dynamic models to microeconomic evidence." (Browning et al. (1999))

[18] "Aggregation problems are among the most difficult problems faced in either the theoretical or empirical study of economics. Heterogeneity across individuals is extremely extensive…The conditions under which one can ignore a great deal of the evidence of individual heterogeneity are so severe as to make them patently unrealistic…Aggregation problems remain among the most vexing in all of applied economics." (Blundell & Stoker (2005))

[19] Foellmi & Zweimuller (2006) also examine the influence of income distribution on demand-induced innovations.

relationships in order to capture the effects of heterogeneity across individuals. They interestingly note, “One typically considers sums or averages as reported in national income accounts as the relevant aggregates because they are usually the most interpretable and relevant for pricing or policy analysis. But one could consider many other kinds of aggregates or statistics from the population…The choice of aggregate may even be informed by empirical regularities in individual data. For example, if an individual model is best specified with the logarithm of observed income, the geometric mean of income might be a more natural aggregate than total income or average income.”

In summary, innovation-inducing market characteristics may be implicitly addressed by prior IIH empirical research in the form of category fixed effect controls. However, unaddressed by this literature is the possible role of non-aggregate size characteristics of “market heterogeneity” and the associated implications of omitted variable bias. For example, characteristics that describe demand-side compositional heterogeneity could include income-based, needs-based, and/or preferences-based measures. Correcting for the direction and extent of this bias could be further complicated in the event that market heterogeneity is a potential confounder of market size. As noted by Huber (2008): “…[genetic] variations apparently explain significant differences in the efficacy of drugs…What were once inexplicable ‘side effects’ are now predictable interactions between the drug’s chemistry and healthy parts of the patient’s… That leaves drug companies in control of which patients — or make that biochemical profiles — the health-care system will help next, and companies are free to favor profiles that pay their bills.”

CHAPTER 4.

THEORETICAL FRAMEWORK

Since to my knowledge my research questions are novel, my theoretical setup establishes two new and complementary models of induced innovation which explicitly account for how market characteristics and sunk costs influence drug innovation output.[20] The first approach develops a de novo model, Model I, incorporating market heterogeneity in terms of exogenously given categorical measures. The second approach, producing Model II, follows the informative advertising model for heterogeneous products from Grossman and Shapiro (1984) and captures market heterogeneity as quasi-categorical (i.e., categorical, continuous, and mixed) measures some of which are endogenously determined.

4.1 MODEL SETUP I: CATEGORICAL MARKET HETEROGENEITY

Figure 4.1 provides an overview schematic of this theoretical set-up.

I adopt the traditional assumption that physician prescribing closely follows drug labeling.[21] This is what gives firms the commercial incentive to pursue regulatory-driven innovation efforts, regardless of how incremental the innovation might or might not be.

4.1.1 SUPPLY-SIDE SETUP

First, I assign the following ordinal values to drug innovation measure types to reflect the path-dependent notion that an innovation of type θ is derived from a "parent" innovation of type $(\theta - 1)$:

[20] I was compelled to pursue more than one model with the aim of understanding whether/how inducement effects may vary according to the definitional variability of market heterogeneity.
[21] Therefore, I can equate "attempt success contexts" to "disease sub-indications."

$$\theta = \begin{cases} 1,\ most\ innovative\ (e.g., new\ drug\ class) \\ 2,\ more\ innovative\ (e.g., new\ drug\ molecule) \\ 3,\ less\ innovative\ (e.g., new\ drug\ indication) \\ 4,\ least\ innovative\ (e.g., new\ drug\ formulation) \end{cases}.$$

Next, I describe an innovation measure type θ project as a θ-step series of incremental product innovation attempts that cumulatively yields product innovations of types $j = 1, \dots, \theta$. Thus, at least one product innovation attempt must be successful at a given step in order for a product innovation attempt to occur at the next step. The cumulative output of successful attempts at different steps across projects/firms is what defines market entry across different innovation measure types, θ.

Now I specify the associated cost variables as follows:

F_θ is the project's exogenously given fixed cost of pursuing θ-type innovation attempts;
C_θ is the project's exogenously given variable cost of pursuing each θ-type innovation attempt;
a_θ is the expected number of θ-type innovation attempts per project;
s_θ is the expected number of successful θ-type innovation attempts per project;
p_θ is the exogenously given i.i.d. probability that any particular θ-type innovation attempt is successful; and
τ_θ is the project's expected probability of any successful θ-type innovation attempt.

Since the expected cost of conducting the j[th] step of an innovation measure type θ project is

$$F_j \prod_1^{j-1} \tau_i + C_j(a_j \prod_1^{j-1} s_i),$$

then the firm's total expected cost, $E[K_{j\leq\theta}]$, for the innovation measure type θ project is

$$\mathrm{E}\left[\mathrm{K}_{\mathrm{j}\leq\theta}\right] = [\mathrm{F}_0 + \tau_0(\mathrm{F}_1 + \tau_1(\mathrm{F}_2 + \cdots \tau_{\theta-1}(\mathrm{F}_\theta)..)] + [\mathrm{s}_0\mathrm{a}_0(\mathrm{C}_0 + \mathrm{s}_1\mathrm{a}_1(\mathrm{C}_1 + \cdots \mathrm{s}_{\theta-1}\mathrm{a}_{\theta-1}(\mathrm{C}_\theta)..)]$$

$$= (F_0 + C_0 a_0 s_0) + \sum_1^\theta \left(F_j \prod_1^{j-1} \tau_i + C_j\left(a_j \prod_1^{j-1} s_i\right)\right).$$

Using industry-based assumptions for pharmaceuticals, we can simplify this expression to give for the two innovation measure types of particular interest,

$$E[K_{\theta\leq 2}] = F_0 + \left[F_1 + \frac{C_1}{p_1}\right] + [\tau_1 F_2 + a_2 C_2],$$

and

$$E[K_{\theta\leq 3}] = F_0 + \left[F_1 + \frac{C_1}{p_1}\right] + [\tau_1 F_2 + a_2 C_2] + [\tau_1 \tau_2 F_3 + a_2 a_3 p_2 C_3],$$

which shows that a_2 and a_3 drive any cross-market variations in expected project costs.[22] Note that since there is generally only one product innovation attempt candidate per pharmaceutical project, in effect a_2 represents the number of attempt success contexts.[23]

For ease of notation, I rewrite the expected cost function for $E[K_{\theta\leq 2}]$ as

$$E[K] = F + a \cdot C \qquad (**1)$$

where $a = a_2$ (i.e. number of attempt success contexts), $F = F_0 + \left[F_1 + \frac{C_1}{p_1}\right] + \tau_1 F_2$, and $C = C_2$.

4.1.2 DEMAND-SIDE SETUP

To model the demand-side of firm entry decisions in the drug industry, consider a disease category $\mathbb{C}$ with total market size M. If $\mathbb{C}$ is composed of I distinct "sub-markets" (for example, disease sub-indications) exogenously defined and represented by the ordered partition $\{\mathrm{G}_1|\ldots|\mathrm{G}_\mathbf{I}\}$ where G_j has size M_j, then without loss of generality say that $M_1 \geq \cdots \geq M_j \geq \cdots \geq M_I$.[24] Firm entry into disease category $\mathbb{C}$ will be the determined by an I-stage game as follows. Stage 1 involves the set of firms ($\boldsymbol{f}_1$ in count) who attempt to enter into (i.e. receive FDA product approval for) all I sub-markets, $\mathrm{G}_1,\ldots,\mathrm{G}_\mathbf{I}$, and are successful in entering at least one sub-market.[25] Stage 1

[22] i.e., $C_0 = 0\ and\ \tau_\theta = s_0 = s_0 = 1, a_1 = \frac{1}{p_1}, s_2 = p_2 a_2$.

[23] See footnote 9.

[24] i.e., mutually exclusive and collectively exhaustive.

[25] or projects, but in the drug industry the norm is one drug development project per firm per drug category.

concludes when G_I can no longer support any new entrants. Stage 2 then involves the set of firms ($\boldsymbol{f}_2$ in count) who attempt to enter into the I-1 remaining sub-markets $G_1,\ldots, G_{I-1}$, and are successful in entering at least one sub-market. Stage 2 continues until G_{I-1} can no longer support new entrants. By extension, stage j involves the set of firms ($\boldsymbol{f}_j$ in count) who attempt to enter into the remaining I+1-j sub-markets $G_1,\ldots, G_{I+1-j}$, and are successful entering at least one sub-market. Stage j continues until G_{I+1-j} can no longer support new entrants. The final stage, stage I, involves the set of firms ($\boldsymbol{f}_I$ in count) who attempt to enter the last remaining sub-market, G_1.

Now define a partition of $\mathbb{C}$ that is based on the I stages of the firm entry game rather than the originally identified I sub-markets. Let V_j denote the market opportunity associated with attempt/entry stage j, where V_j spans $G_1,\ldots, G_{I+1-j}$. Then $\{V_I|\ldots|V_I\}$ represents this alternative partition of $\mathbb{C}$ to $\{G_I|\ldots|G_I\}$. If the size of V_j is denoted by M_{V_j} then $M = \sum_{j=1}^{I} M_j = \sum_{j=1}^{I} M_{V_j}$. Figure 4.2 shows an illustrative example of this alternative "V" partitioning.

4.1.3 Innovation Entry

Now the firm's (project-specific) profit maximization function for conducting an innovation measure type $\theta = 3$ project in disease category $\mathbb{C}$ is

$$E\left[\Pi^{C}_{\theta\leq 2}\right] = p \cdot (m_1^C + m_2^C + \cdots + m_I^C) - E\left[K^C_{\theta\leq 2}\right] = \left(p \sum_{j=1}^{I} m_j^C\right) - (F + I \cdot C),$$

where m_j^C is the equilibrium sales for a successful product entry in G_j, $p = p_1 \cdot p_2$, and the cost expression comes from (**1). In equilibrium, we will have $E\left[\Pi^C_{\theta\leq 2}\right] = 0$, which implies $\sum_{j=1}^{I} m_j^C =$

$\frac{F+I\cdot C}{p}$. If costs do not vary across sub-markets, then entry will only be attempted at stage j if $m_j \geq \frac{\frac{F}{j}+C}{p}$ and $M_{V_j} \geq \frac{F+j\cdot C}{p}$.[26] So there are scale benefits to attempting entry when *j*>1.

Please note, however, that to facilitate my comparative static analysis I will adjust the $\{m_j \geq \frac{\frac{F}{j}+C}{p}$ for *j*>0} constraint to,

$$\{m_1 \geq \frac{F+C}{p} \text{ and } m_j \geq \frac{C}{p} \text{ for } j>1\}. \qquad (**2)$$

This reflects the stylistic fact that firms often initiate drug innovation projects by targeting a core disease sub-indication and, usually only if this is feasible, then also conducting clinical trials in other sub-indications.[27, 28]

So in terms of market entry with respect to disease category $\mathbb{C}$, I am interested in calculating two particular output metrics: the number of successful firms/projects ($\boldsymbol{f}$) and successful product entries ($\boldsymbol{e}$). Note that $\boldsymbol{f}$ and $\boldsymbol{e}$ are equivalent to the number of new molecular entity approvals ($N^{\mathrm{C}}_{\theta=2}$) and number of new drug indication approvals ($N^{\mathrm{C}}_{\theta=3}$), respectively, in disease category $\mathbb{C}$.

If $\mathrm{e_j}$ is the expected number of successful product entries into sub-market $\mathrm{G_j}$ then $\boldsymbol{e}_j = \frac{M_j}{m_j}$ and we can calculate $\boldsymbol{e}$ as

$$\boldsymbol{e} = \sum_{\mathrm{j}=1}^{\mathrm{I}} \boldsymbol{e}_j = \sum_{\mathrm{j}=1}^{\mathrm{I}} \frac{M_j}{m_j} = \frac{p\cdot M_1}{F+C} + \sum_{\mathrm{j}=2}^{\mathrm{I}} \frac{p\cdot M_j}{C} = \left(\frac{p\cdot M_1}{F+C} - \frac{p\cdot M_1}{C}\right) + \sum_{\mathrm{j}=1}^{\mathrm{I}} \frac{p\cdot M_j}{C},$$

or

$$N^{\mathrm{C}}_{\theta=3} = \frac{p}{C}\left(M - \frac{1}{\frac{C}{F}+1}\cdot M_1\right) \qquad (**3)$$

[26] I have dropped the $\mathbb{C}$ to simplify the notation.

[27] This has been traditionally presumed to be the largest or most lucrative sub-indication; designated here as M_1.

[28] Drug research has conventionally held a "one-out" policy in compound testing, although the definition of "out" can vary.

I can then deduce the following non-trivial comparative statics for $\boldsymbol{e}$, or equivalently, $N^{\mathrm{C}}_{\theta=3}$:

$$N^{\mathrm{C}}_{\theta=3} \uparrow M,$$
$$N^{\mathrm{C}}_{\theta=3} \downarrow M_1; \text{ and} \qquad (**4)\ ^{29,\ 30}$$
$$N^{\mathrm{C}}_{\theta=3} \perp I.$$

From (**4) I can make three interesting observations. First, since an increase in M_1 (for a given size, M) means that the market is becoming more concentrated (less heterogeneous), my model shows that the number of new drug indication approvals increases as the market becomes more heterogeneously composed. Second, only two factors with cross-market and cross-time variation have influence on the number of new drug indication approvals: total market size (M) and the size of the largest sub-market (M_1). A final observation is that another raw measure of market heterogeneity, the number of sub-groups (*I*), has no apparent influence on the number of new drug indication approvals. The latter two observations, however, seem to be just straightforward consequences of my stylistic setup in (**2).[31]

Next, determining the number of new molecular entity approvals, $N^{\mathrm{C}}_{\theta=2}$, or $\boldsymbol{f} = \sum_{\mathrm{j}=1}^{\mathrm{I}} \boldsymbol{f}_j$, can be a trickier exercise because calculating $\boldsymbol{f}_j$, the expected number of firms successfully entering sub-market $\mathrm{M_j}$, requires the calculation of $\mathrm{M}_{\mathrm{V_j}}$ which is sensitive to the particular sub-market structure of $\mathbb{C}$.[32] So for completeness this would suggest I consider several sub-market structure scenarios (see Figure 4.3) in determining $\boldsymbol{f}$.[33] However, to facilitate my analysis I take as standard the case where the sub-markets of a disease category are relatively heterogeneous in size (see Figure

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[29] $\frac{\partial \boldsymbol{e}}{\partial C} = p\left(-\frac{1}{C^2}\cdot M + \left(\frac{1}{\left(\frac{C}{F}+1\right)^2}\right)\left(\frac{1}{F}\right)\cdot M_1\right) = \frac{p}{C^2}\left(-M + \frac{\frac{1}{F}}{\left(\frac{1}{F}+\frac{1}{C}\right)^2}\cdot M_1\right)$ which implies $\frac{\partial \boldsymbol{e}}{\partial C} \gtrless 0$ iff $\frac{M_1}{M} \lessgtr \frac{\left(\frac{1}{F}+\frac{1}{C}\right)^2}{\frac{1}{F}}$. For empirically relevant values of *F* and *C*, this means $\frac{\partial \boldsymbol{e}}{\partial C} < 0$.

[30] As would be basically expected, $N \uparrow p$ while $N \uparrow F, C$.

[31] However, in section 5.d.iii, I show that when the sub-market structure is unconcentrated then $\boldsymbol{e} \downarrow I$.

[32] This is also true for the size of $\boldsymbol{e}_1$. Recall our earlier assertion that $\boldsymbol{e}_1 = \frac{p\cdot M_1}{F+C}$ and $\boldsymbol{e}_j = \frac{p\cdot M_j}{C}$ for j>1. From this it is straightforward to deduce from our ordering in $\{\mathrm{G_I}| \ldots |\mathrm{G_I}\}$ that $\boldsymbol{e}_2 \geq \cdots \geq \boldsymbol{e}_I$. However, we still cannot deduce anything about the relative size of $\boldsymbol{e}_1$!

[33] For now I set aside the "orphan disease" case where the total market size of a disease category is insufficient to support any product entry, i.e., $\mathrm{M} < \frac{\mathrm{F+C}}{\mathrm{p}}$.

4.3(a)).[34] Quantitatively, I model this as occurring when there is a "large enough" size difference between the two largest sub-markets, M_1 and M_2, i.e., $\frac{M_1}{M_2} \geq 1 + \frac{F}{C}$. This right-hand absolute constraint can be seen to follow naturally from my stylistic setup in (**2).

I then can calculate the size of $\mathrm{V_j}$ for 1<j<I to be,

$$M_{\mathrm{V_j}} = \left(1 + \frac{F}{C}\right) \cdot \left(M_j - M_{j+1}\right) + (j-1) \cdot \left(M_j - M_{j+1}\right) = \left(\frac{F}{C} + j\right) \cdot \left(M_j - M_{j+1}\right),$$

where the first term is the opportunity in $\mathrm{V_j}$ offered by G_1 and the second term is the total opportunity in $\mathrm{V_j}$ offered by $G_2, \ldots, G_j$. For *j*=1, the size of $\mathrm{V_1}$ is given by,

$$M_{\mathrm{V_1}} = M_1 - \left(1 + \frac{F}{C}\right) \cdot M_2,$$

while for *j*=I, the size of $\mathrm{V_I}$ is given by,

$$M_{\mathrm{V_I}} = \left(1 + \frac{F}{C}\right) \cdot M_I + (I-1) \cdot M_I = \left(\frac{F}{C} + I\right) \cdot M_I.$$

Now I can also calculate the portion of $\boldsymbol{e_i}$ (the number of successful product entries in sub-market G_i) associated with $\mathrm{V_j}$ (i.e., occurring at stage *j* of the I-stage entry game) to be,

$$\boldsymbol{e_i^j} = \begin{cases} \frac{M_j - M_{j+1}}{m_i} = \frac{p}{C} \cdot \left(M_j - M_{j+1}\right), & \text{for } 1 < j < I, \\ \frac{M_{\mathrm{V_1}}}{m_1} = \frac{p}{C} \cdot \left(\frac{1}{\frac{F}{C}+1} \cdot M_1 - M_2\right), & \text{for } j = 1, \\ \frac{M_{\mathrm{V_I}}}{m_I} = \frac{p}{C} \cdot \left(\left(\frac{F}{C} + I\right) \cdot M_I\right), & \text{for } j = \mathrm{I}. \end{cases}$$

We can also write $\boldsymbol{e_i^j} = p \cdot a_j$, so we can determine that,

[34] Other potential scenarios include an "under-sized" sub-market structure case (when one or more sub-markets are not attractive, initially or marginally, to potential entrants), i.e., when $\frac{C}{p} > M_k$ for some $\mathrm{k\ where\ I} \geq \mathrm{k} \geq 1$; an "un-concentrated" sub-market structure case where sub-markets are relatively evenly balanced in size (see Figure 7.2.b), i.e. when there is "not enough" size difference between the largest and smallest sub-markets such that $\frac{M_1}{M_I} < 1 + \frac{F}{C}$. Both of these scenarios severely limit the incentive to conduct innovation project attempts.

$$\boldsymbol{f_j} = \tau_j \cdot a_j = \frac{\tau_j \cdot \boldsymbol{e_i^j}}{p} = \begin{cases} \frac{\tau_j}{C} \cdot \left(M_j - M_{j+1}\right), & \text{for } 1 < j < I, \\ \frac{\tau_1}{C} \cdot \left(\frac{1}{\frac{F}{C}+1} \cdot M_1 - M_2\right), & \text{for } j = 1, \\ \frac{\tau_I}{C} \cdot \left(\left(\frac{F}{C} + I\right) \cdot M_I\right), & \text{for } j = \text{I}. \end{cases}$$

Therefore,

$$\boldsymbol{f} = \sum_{j=1}^{I} \boldsymbol{f_j}$$

$$= \frac{\tau_1}{C} \cdot \left(\frac{1}{\frac{F}{C}+1} \cdot M_1 - M_2\right) + \sum_{j=2}^{I-1} \frac{\tau_j}{C} \cdot \left(M_j - M_{j+1}\right) + \frac{\tau_I}{C} \cdot \left(\left(\frac{F}{C} + I\right) \cdot M_I\right)$$

$$= -\frac{\tau_1}{C} \cdot \left(\frac{1}{1+\frac{C}{F}} \cdot M_1\right) + \frac{\tau_I}{C} \cdot \left(\left(\frac{F}{C} + I\right) \cdot M_I\right) + \sum_{j=1}^{I-1} \frac{\tau_j}{C} \cdot \left(M_j - M_{j+1}\right)$$

$$= -\frac{p}{C} \cdot \left(\frac{1}{1+\frac{C}{F}} \cdot M_1\right) + \frac{\tau_I}{C} \cdot \left(\left(\frac{F}{C} + I\right) \cdot M_I\right) + \frac{1}{C} \sum_{j=1}^{I} \left(\tau_j - \tau_{j-1}\right) M_j$$

$$= \frac{p}{C(1-p)} \left[M - \sum_{j=1}^{I} \tau_j \, M_j\right] - \frac{p}{C} \left[\frac{M_1}{1+\frac{C}{F}}\right] + \frac{\tau_I}{C} \cdot \left(\left(\frac{F}{C} + I\right) \cdot M_I\right)$$

$$= \frac{p}{C(1-p)} \left[\sum_{j=1}^{I} (1-p)^j \, M_j\right] - \frac{p}{C} \left[\frac{M_1}{1+\frac{C}{F}}\right] + \frac{\tau_I}{C} \cdot \left(\left(\frac{F}{C} + I\right) \cdot M_I\right).$$

And since $\mathrm{M_j} \geq \mathrm{M_{j+1}}$ and $(1-\mathrm{p})^{\mathrm{j}} \geq (1-\mathrm{p})^{\mathrm{j+1}}$, I use Chebyshev's Inequality[35] to provide the tractable approximation,

$$\boldsymbol{f} \gtrsim \frac{p}{C(1-p)} \left[\frac{M(1-p)}{p} \cdot \frac{\tau_I}{I}\right] - \frac{p}{C} \left[\frac{M_1}{1+\frac{C}{F}}\right] + \frac{\tau_I}{C} \cdot \left(\left(\frac{F}{C} + I\right) \cdot M_I\right),$$

or

$$N_{\theta=2}^{\mathrm{C}} \gtrsim = \frac{1}{C} \left[\frac{\tau_I}{I} \cdot M - \frac{p}{1+\frac{C}{F}} \cdot M_1 + \left(\frac{F}{C} + I\right) \cdot \tau_I \cdot M_I\right].$$

[35] Chebyshev's Inequality states that if $\mathrm{a_i} \geq \mathrm{a_{i+1}}$ and $\mathrm{b_i} \geq \mathrm{b_{i+1}}$ then $(\sum_{\mathrm{i=1}}^{\mathrm{n}} \mathrm{a_i b_i}) \geq \frac{1}{\mathrm{n}} (\sum_{\mathrm{i=1}}^{\mathrm{n}} \mathrm{a_i})(\sum_{\mathrm{i=1}}^{\mathrm{n}} \mathrm{b_i})$ for all positive real numbers $\mathrm{a_i}$ and $\mathrm{b_i}$.

This yields the following non-trivial[36] comparative statics for $\boldsymbol{f}$, or equivalently, $N_{\theta=1}^{C}$:

$$N_{\theta=2}^{C} \uparrow M,\ M_I,\ I^{>}; \text{ and}$$

$$N_{\theta=2}^{C} \downarrow M_1,\ I^{<}, \qquad (**5)$$

where $I^{>}$ and $I^{<}$ satisfy the conditions $I > \sqrt{\frac{M}{M_I}}$ and $I < \sqrt{\frac{M}{M_I}}$ respectively.[37]

Equivalently, I can restate these comparative statics as:

$$N_{\theta=2}^{C} \uparrow M,\ HET, \qquad (**6)$$

where HET is a composite measure of market heterogeneity. For example, this could be calculated in the form of a Herfindahl- Hirschman Index of sub-market shares, i.e., $HET = \sum_{i=1}^{I}(\frac{M_I}{M})^2$.

Until now we have examined attempt and entry dynamics for two drug innovation measure types, new molecular entities ($\theta = 2$) and new indications ($\theta = 3$). To say something about new formulations ($\theta = 4$) only requires further specifying the expected cost expressions in the previous section; in particular, to make explicit the presence of a_3, the $\theta = 4$ associated component of C_3. For ease of notation, following the simplification used in Sections 4.1.1 and 4.1.2 above I will rewrite the expected cost function for $E[K_{\theta \leq 4}]$ as $E[K] = F + j \cdot (C + h \cdot D)$, where $h = a_3$, $F = F_0 + \left[F_1 + \frac{C_1}{p_1}\right] + \tau_1 F_2 + \tau_1 \tau_2 F_3$, $C = C_2$, and $D = p_2 C_3$. In essence, this will produce comparative statics for the $\theta = 4$ relevant market characteristic *H*[38] similar to what we have already derived for the market characteristic I under the $\theta = 3$ analysis. Note the presence

[36] As would be basically expected (again as in footnote 29), $N \uparrow p$ while $N \uparrow F, C$.

[37] $\frac{\partial f}{\partial I} = sgn\left|\frac{M}{I} + I \cdot M_I\right.$, which is globally minimized at $I = \sqrt{\frac{M}{M_I}}$ since the second derivative is $\frac{2M}{I^3} > 0$.

[38] For example, this can be some count or metric reflecting the compositional heterogeneity of a disease market's physiological sub-types.

now of an $(j \cdot h)$ interaction term which we will want to keep in mind for our empirical specification.

In summary, innovation product entry is increasing in market size and also in market heterogeneity as reflected by the number of sub-markets (I), the size of the largest sub-market (M_1), and the size of the smallest sub-market (M_{I}). Specifically, $N^{\mathrm{C}}_{\theta=2}$ (the number of new drug molecules) and $N^{\mathrm{C}}_{\theta=3}$ (the number of new drug indications) are both increasing in M and M_1. Further, $N^{\mathrm{C}}_{\theta=2}$ (the number of new drug molecules) is influenced by M_{I} and also -- if M_{I} is large enough relative to M – by I.

4.2 Model Setup II: Quasi-Categorical Market Heterogeneity

I next consider a theoretical set-up in which I establish more detailed demand and supply equations that can capture the potential additional effects of non-categorical market characteristics. This ultimately allows me to make more specific predictions about a broader range of innovation measure types. Also advantageous to this model is that firm choices such as the number of clinical trials are treated as endogenous variables, whereas they were considered exogenously determined in the Model I setup.

This alternative product innovation model presumes the flow of product innovation attempts (and as a result, innovation entry) is generated by an industry-specific sequence of R&D steps, each defined by one of four attrition step regimes. I then solve for the non-cooperative Nash equilibrium in prices (P), phase II trials (r_2), and product safety quality (φ), where firms select the profit-maximizing values of these endogenous variables taking as given the prices ($\bar{P}$), phase II trials ($\bar{\mathrm{r}}_2$), and product safety quality ($\bar{\varphi}$) chosen by all other firms. Specifically, my plan is to first calculate symmetric market equilibria under the oligopolistic competition condition which takes as given the number of innovation entries. I next make innovation entry endogenous under the free-entry condition of symmetric monopolistic competition. Once I have expressed innovation entry in

terms of the exogenous variables defined by pharmaceutical industry-specific market characteristics and sunk costs, I can then deduce testable hypotheses concerning the causal relationship between market characteristics and new drug entry.

In particular, I am concerned in this exercise with how market composition – defined by characteristics such as disease sub-types (e.g., determining drug need), physiological sub-types (e.g., determining drug response), and preference sub-types (e.g., determining drug formulation taste) – in addition to market size influences drug innovation entry. Since I am interested in evaluating innovation inducement in terms of "output" rather than "location," I choose to use the informative advertising model for a market of heterogeneous products established by Grossman and Shapiro (1984) as my starting point. Their approach combines the monopolistic competition framework of Chamberlin (1931) to account for the product's "information" dimension with the circular spatial competition model of Salop (1979) to account for a "location" dimension. The corresponding model I derive cannot capture the market expansion effects of new product introductions (see Shaked & Sutton (1990)) and it limits patients to receiving at most one drug per disease. Importantly, however, I am able to appropriately capture the "drug safety" (exclusionary information) dimension and the "drug efficacy/tolerability" (preference location) dimension. Thus, I can investigate the potential innovation inducement effects of drug response/taste heterogeneity as well as cross-product competition.

Figure 4.4 provides a visual overview of my theoretical Model II set-up.

4.2.1 SUPPLY-SIDE SETUP

I define product innovation as the firm's effort to identify products for market launch (i.e. innovation entry) by undertaking R&D projects which are winnowed down through a sequence of attrition steps. Each project consists of one or more product prototypes (denoted by the count variable, a). Each attrition step consists of one or more tests (denoted by the count variable, r)

for each product prototype. My setup completely describes any innovation step with two measures, the attrition step cost structure variable (κ) and the attrition step flow variable (λ).

I calculate these two variables as follows:

$$\kappa = \frac{C_f}{C_f + C_m},$$

where

C_f = fixed cost incurred during the innovation step;
C_m = marginal cost per test per innovation step;
C_f and C_m cannot both be zero (so that κ always remains well-defined); and
$\lambda = 1 - (1 - p)^{ar}$,

where

p = exogenous probability of technical success of any product prototype in any test;
a = number of product prototypes per innovation step; and
r = number of tests per product prototype per innovation step, with $0 < p < 1$ and $n, r \geq 1$.

My main assumption in employing this expression for λ is that all prototypes and tests have orthogonal relationships to one another.

Note that κ holds two values of interest in my analysis[39]:

$$\kappa = \begin{cases} 0, & \text{when } C_f = 0, \text{i. e. constant returns to scale; or} \\ \neq 0, & \text{when } C_f \neq 0, \text{i. e. nonconstant returns to scale.} \end{cases}$$

Further note that the flow variable, λ, also holds two values of interest in my analysis:

$$\lambda = \begin{cases} p, & \text{when } a = r = 1, \text{i. e. hurdle attrition is in effect; or} \\ 1 - (1 - p)^{ar}, & \text{when } a > 1 \text{ or } r > 1, \text{i. e. quota attrition is in effect.} \end{cases}$$

[39] This makes **K** essentially a "returns-to-scale" variable.

The hurdle attrition criteria describes those R&D contexts when any prototype during a given attrition step can qualify ("qualified-in-class") to pass-through to the next R&D stage. The quota attrition criteria describes those R&D contexts when only a pre-specified number of product prototypes ("best-in-class" quota) can qualify to pass-through.

In summary, I can categorize any product innovation attrition step as belonging to one of four possible regimes as shown in Figure 4.5.

Now for the case of pharmaceutical innovation production, we assume and/or determine the following values and constraints for our particular variables of interest:

p_s is the exogenous probability of a compound (product prototype) succeeding in any Phase s trial for any mix of disease sub-conditions/-types;
r_s is the number of Phase s trials conducted per compound per firm;
τ_s is the probability of a compound project reaching stage s and corresponds to attrition step flow variable, λ, described earlier;
φ is the probability of the test compound causing a safety issue in any tested group of patients[40];
F_s is the cost of testing a specific prototype in a specific context at stage s;
c is the marginal cost of a marketed product;
a_s is the number of compounds (attempts) at stage s per firm;
a is the number of marketed products (entries) per firm;
n_s is the number of compounds (attempts) at stage s for all firms; and
n is the number of marketed products (entries) for all firms.

Note the variables I consider to be endogenous are n, n_s, a, a_s, r_2 and φ. In particular, r_2 is endogenous because there are two counter-acting incentives for firms in making their choice of r_2. The first incentive is for firms to justify an increase r_2 in order to increase τ_2, i.e. the

[40] New drug compounds are more often successfully developed by achieving differentiated safety profiles because researchers know what they want the molecule not to do and are in better position to make proactive design adjustments.

probability of getting the test compound into phase III and beyond.[41] The second incentive is for firms to choose to decrease r_2 in order to limit R&D costs.

Therefore, assuming that $F_1 = F_2 = F_3 = 0$ and $\varphi \perp r_2$, the representative firm's expected cost function is expressed by

$$E[Costs] = [F_0 + \tau_1 F_1 + \tau_1\tau_2 F_2 + \tau_1\tau_2\tau_3 F_3] + [a_1 r_1 C_1 + a_2 r_2 C_2 + a_3 r_3 C_3]$$

$$= F_0 + \left(\frac{1}{p_1}\right)(1)C_1 + (1)r_2 C_2 + \tau_3(1)C_3$$

$$= F_0 + \frac{C_1}{p_1} + r_2 C_2 + \tau_3 C_3.$$

So if f_s denotes the number of firms engaging in pharmaceutical R&D at stage s (where $f = f_4$) then I can further deduce the following:

$$f = \frac{n}{a} = \frac{n}{p_3\tau_3},$$

$$n_3 = f_3 a_3 = \left(\frac{n}{p_3\tau_3}\right)(\tau_3) = \frac{n}{p_3},$$

$$n_2 = f_2 a_2 = \left(\frac{n}{p_3\tau_3}\right)(1) = \frac{n}{p_3\tau_3}, \text{ and}$$

$$n_1 = f_1 a_1 = \left(\frac{n}{p_3\tau_3}\right)\left(\frac{1}{p_3}\right) = \frac{n}{p_3\tau_3 p_1}.$$

4.2.2 DEMAND-SIDE SETUP

My aim is to accurately capture the product space and preference structure of the pharmaceutical market. The pharmaceutical space is primarily defined by differentiated products known as new molecular entities (NMEs). Preference structure is primarily defined by a mix of discrete (drug safety) and continuous (drug efficacy/tolerability) influences. Since location models are useful in

[41] This phenomenon can be readily observable in the real-world with drug licensing agreements where the "salami slicing" of development rights by sub-indication is standard practice.

capturing non-discrete effects while advertising models are useful in capturing non-discrete effects, I will follow the blended model proposed by Grossman & Shapiro (1984).

I begin with a horizontal address model where the market for a given drug is a unit circle. Potential market size, or disease prevalence, is characterized by the density of consumers, d, who are uniformly distributed on the circle. Patients sharing a disease sit on the same circle and consume one unit of the nearest drug if

utility to consumption = $u - tx - P > 0$,

where

u = patient's utility from consumption of a drug for disease treatment,
P = the unit price of the drug,
n = the total number of drugs or firms (which we initially assume as given),
x = consumer's distance to the nearest drug (maximum value of $\frac{1}{2n}$ where n is the total number of drugs in that market), reflecting heterogeneous drug response,
t = linear transport cost, reflecting a reduction in therapeutic benefit due to heterogeneous drug response or consumers' drug choice preferences, and
δ = the market size (volume of consumers).

Now if I define N_k to be the set of consumers for whom the representative firm's drug is their kth preferred choice, I can calculate the following expressions for each N_k:

$$N_1 = \frac{\delta}{n} + \frac{\delta\,(\bar{P}-P)}{t},$$

$$N_k = \frac{(\bar{P}-P)}{2t} + \frac{k}{2n} \qquad \text{for k = 2,…,n-1, and}$$

$$N_n = \frac{\delta}{n} - \frac{\delta\,(\bar{P}-P)}{t}.$$

Aggregating these expressions gives the representative firm's overall demand function as

$$x(P,\varphi) = N_1\varphi_1 + \cdots + N_k\varphi_k + \cdots N_n\varphi_n,$$

where φ_k is the probability of not being ruled out due to a safety issue with the representative firm's drug.

If φ is the probability choice of the representative firm's drug causing a safety issue in a patient while holding constant $\bar{\varphi}$, the fixed probability choice of any other drug causing a safety issue, then I can calculate φ_k as

$$\varphi_k = (1-\varphi)\bar{\varphi}^{k-1} \qquad \text{for k = 1,…,n.}$$

Thus, my fully specified expression for the representative firm's demand is

$$x(P,\varphi)$$

$$= \left(\frac{\delta}{n} + \frac{\delta(\bar{P}-P)}{t}\right)(1-\varphi) + \sum_{k=2}^{n-1}\left(\frac{\bar{P}-P}{2t} + \frac{k}{2n}\right)(1-\varphi)\bar{\varphi}^{k-1} + \left(\frac{\delta}{n} - \frac{\delta(\bar{P}-P)}{t}\right)(1-\varphi)\bar{\varphi}^{n-1}$$

$$= (1-\varphi)\left[\left(\frac{\delta}{n} + \frac{\delta(\bar{P}-P)}{t}\right) + \frac{\bar{P}-P}{2t}\sum_{k=2}^{n-1}\bar{\varphi}^{k-1} + \frac{1}{2n}\sum_{k=2}^{n-1}k\bar{\varphi}^{k-1} + \left(\frac{\delta}{n} - \frac{\delta(\bar{P}-P)}{t}\right)\bar{\varphi}^{n-1}\right]$$

$$= (1-\varphi)\left[\begin{array}{c}\left(\frac{\delta}{n} + \frac{\delta(\bar{P}-P)}{t}\right) + \frac{\bar{P}-P}{2t}\left(\frac{1-\bar{\varphi}^{n-2}}{1-\bar{\varphi}}\right)\bar{\varphi} + \frac{1}{2n}\left(\frac{\bar{\varphi}}{1-\bar{\varphi}}\right)\left(1 - n\bar{\varphi}^{n-2} + \frac{1-\bar{\varphi}^{n-1}}{1-\bar{\varphi}}\right) \\ + \left(\frac{\delta}{n} - \frac{\delta(\bar{P}-P)}{t}\right)\bar{\varphi}^{n-1}\end{array}\right].$$

Assuming $\bar{\varphi}^{\,n}$ is very small, I will use the following approximation for demand to facilitate calculations:

$$x(P,\varphi;n,\bar{P},\bar{\varphi}) = (1-\varphi)\left[\left(\frac{\delta}{n} + \frac{\delta(\bar{P}-P)}{t}\right) + \frac{\bar{P}-P}{2t}\left(\frac{1}{1-\bar{\varphi}}\right)\bar{\varphi} + \frac{1}{2n}\left(\frac{\bar{\varphi}}{1-\bar{\varphi}}\right)\left(1 + \frac{1}{1-\bar{\varphi}}\right)\right]$$

$$= \frac{\delta(1-\varphi)}{n}\left[1 + n\left(\frac{\bar{P}-P}{t}\right)\left(1 + \frac{\frac{\bar{\varphi}}{2}}{\delta(1-\bar{\varphi})}\right) + \frac{\bar{\varphi}\left(1-\frac{\bar{\varphi}}{2}\right)}{\delta(1-\bar{\varphi})^2}\right].$$

Therefore, the representative firm's expected revenue function is expressed by

$$E[Revenue] = \mathrm{p}_3\tau_3(P-c)x(P,\varphi;n,\bar{P},\bar{\varphi})$$

$$= \mathrm{p}_3\tau_3(P-c)\frac{\delta(1-\varphi)}{n}\left[1+n\left(\frac{\bar{P}-P}{t}\right)\left(1+\frac{\frac{\bar{\varphi}}{2}}{\delta(1-\bar{\varphi})}\right)+\frac{\bar{\varphi}\left(1-\frac{\bar{\varphi}}{2}\right)}{\delta(1-\bar{\varphi})^2}\right].$$

Some of the assumptions I make so that I can more accurately capture the idiosyncrasies of the pharmaceutical industry while simplifying my calculations include:

- physicians are fully informed and can immediately prescribe the optimal drug for every patient (who is not excluded from receiving any available drug because of safety reasons);
- disease patient sub-populations for clinical trial testing are mutually-exclusive-and-collectively-exhaustive;
- drug safety/efficacy response is determined at the disease sub-population level;
- drug safety/efficacy responses are determined at the disease patient level in an independently distributed manner (i.e. $\varphi \perp r_2$); and
- off-label usage is negligible.

4.2.3 SYMMETRIC OLIGOPOLY EQUILIBRIUM[42]

For a given disease market of size *d*, the representative firm chooses x, P, τ_3 and φ, to solve

$$\max \pi(P, \tau_3, \varphi;\ n, \delta, t, c, F_i, C_i, p_i) = E[Revenue] - E[Costs]$$

$$= \mathrm{p}_3\tau_3(P-c)x(P, \varphi; n, \bar{P}, \bar{\varphi}) - \left[F_0 + \frac{C_1}{p_1} + r_2C_2 + \tau_3C_3\right].$$

One first-order condition (FOC#1) that can now be solved is

$$\frac{\partial\pi(P,\tau_3,\varphi)}{\partial P} = 0 = \mathrm{p}_3\tau_3[x + (P-c)x']$$

which implies

$$P = \frac{\bar{P}+c}{2} + \frac{t}{2n}\frac{\left[1+\frac{\bar{\varphi}\left(1-\frac{\bar{\varphi}}{2}\right)}{\delta(1-\bar{\varphi})^2}\right]}{\left[1+\frac{\frac{\bar{\varphi}}{2}}{\delta(1-\bar{\varphi})}\right]}.$$

[42] Please refer to Appendix 10.4 for backup calculations.

Setting $\bar{P} = P$ and $\bar{\varphi} = \varphi$ for the symmetric oligopoly equilibrium case thus gives the profit-maximizing solution for P,

$$\boxed{P = c + \frac{t}{n}\left[1 + \frac{1}{(1-\varphi)[\frac{2\delta(1-\varphi)}{\varphi}+1]}\right]}. \qquad (*1)$$

Another first-order condition (FOC#2) that can be solved is

$$\frac{\partial\pi(P,\tau_3,\varphi)}{\partial r_2} = 0 = p_3(P-c)x\tau_3' - C_2 - C_3\tau_3'.$$

Now since $\tau_3' = -(1-p_2)^{r_2}\ln(1-p_2) = -(1-\tau_3)\ln(1-p_2)$ and by setting $\bar{P} = P$ and $\bar{\varphi} = \varphi$ for the symmetric oligopoly equilibrium case as well as substituting for $(P-c)$ from (*1), I can deduce the profit-maximizing solution for τ_3 (and therefore r_2) as being

$$\boxed{\tau_3 = 1 + \frac{C_2}{\ln(1-p_2)\left[\frac{tp_3\left[(2\delta-1)(1-\varphi)^2+1\right]^2}{2n^2(1-\varphi)^2[(2\delta-1)(1-\varphi)+1]} - C_3\right]}}. \qquad (*2)$$

Note that $\tau_3 < 1$ which implies that $\left[\frac{tp_3\left[(2\delta-1)(1-\varphi)^2+1\right]^2}{2n^2(1-\varphi)^2[(2\delta-1)(1-\varphi)+1]} - C_3\right] > 0$. Thus, I can derive the following hypotheses regarding τ_3:

$$sgn\left|\frac{\partial\tau_3}{\partial t} > 0;\right.$$

$$sgn\left|\frac{\partial\tau_3}{\partial\delta} = sgn\frac{\partial}{\partial\delta}\right|\frac{\left[(2\delta-1)(1-\varphi)^2+1\right]^2}{[(2\delta-1)(1-\varphi)+1]} = (2\delta-1)(1-\varphi)^2 + (1-2\varphi) \gtrless 0.$$

Since τ_3 is a function of r_2 and $\frac{\partial r_2}{\partial\tau_3} = \frac{-1}{(1-\tau_3)\ln(1-p_2)} > 0$, these comparative static for τ_3 hold correspondingly for r_2.

4.2.4 MONOPOLISTICALLY COMPETITIVE EQUILIBRIUM[43]

Building further on the equations derived under symmetric oligopolistic competition, we exploit the fact that firm profits goes to zero with the free entry-exit condition of monopolistic competition. This free-entry condition (FEC) is given by

$$\begin{aligned}&\pi(P,\tau_3,\varphi,n)=0\\&=\mathrm{p}_3\tau_3(P-c)x(P,\tau_3,\varphi)-\left[F_0+\frac{C_1}{p_1}+r_2C_2+\tau_3C_3\right]\\&=\tau_3[\mathrm{p}_3(P-c)x-C_3]-r_2C_2-\left[F_0+\frac{C_1}{p_1}\right].\end{aligned}\qquad (*3)$$

From FOC#2,

$$[\mathrm{p}_3(P-c)x-\mathrm{C}_3]=\frac{\mathrm{C}_2}{(\frac{\partial\tau_3}{\partial \mathrm{r}_2})}=\frac{\mathrm{C}_2}{-(1-\tau_3)\ln(1-p_2)}.\qquad (*4)$$

Substituting $\mathrm{r}_2=\frac{\ln(1-\tau_3)}{\ln(1-p_2)}$ and (*4) into (*3) gives

$$0=\tau_3\left[\frac{\mathrm{C}_2}{-(1-\tau_3)\ln(1-p_2)}\right]-\left[\frac{\ln(1-\tau_3)}{\ln(1-p_2)}\right]C_2-\left[F_0+\frac{C_1}{p_1}\right],$$

which implies

$$\frac{-\ln(1-p_2)}{\mathrm{C}_2}\left[F_0+\frac{C_1}{p_1}\right]=\ln(1-\tau_3)+\frac{\tau_3}{1-\tau_3}=\ln(1-\tau_3)+\frac{1}{1-\tau_3}-1.$$

Setting $K=1-\frac{\ln(1-p_2)}{\mathrm{C}_2}\left[F_0+\frac{C_1}{p_1}\right]$ and rearranging gives

$$e^{-\ln(1-\tau_3)}=-\ln(1-\tau_3)+K,$$

which can then be solved[44] to give

[43] Please refer to Appendix 10.5 for backup calculations.

$$\tau_3 = 1 - e^{W(-e^{-K})+K}. \qquad (*5)$$

Therefore, rearranging (*2) and substituting from (*5) enables me to express innovation entry in terms of only exogenous variables:

$$n^2 = \left[\frac{t\mathrm{p}_3\left[(2\delta-1)(1-\varphi)^2+1\right]^2}{2(1-\varphi)^2[(2\delta-1)(1-\varphi)+1]\left[\mathrm{C}_3-\frac{\mathrm{C}_2}{e^{W(-e^{-K})+K}\ln(1-\mathrm{p}_2)}\right]}\right],$$

or equivalently,

$$\boxed{n = \left[\left(\delta-\frac{1}{2}\right)(1-\varphi)+\frac{1}{2(1-\varphi)}\right]\cdot\sqrt{\frac{t\mathrm{p}_3}{\left[\left(\delta-\frac{1}{2}\right)(1-\varphi)+\frac{1}{2}\right]\left[\mathrm{C}_3-\frac{\mathrm{C}_2}{(1-\tau_3)\ln(1-\mathrm{p}_2)}\right]}}}, \qquad (*6)$$

where τ_3 is a function of F_0, C_1, C_2, p_1, and p_2.

4.2.5 INNOVATION ENTRY

This setup yields the following set of comparative statics. Of particular note are those statics for explanatory variables reflecting market heterogeneity, i.e., t, φ, and r_2.

$$sgn\left|\frac{\partial n}{\partial \delta}\right. = sgn\left|\frac{\partial}{\partial \delta}\frac{\left(\delta-\frac{1}{2}\right)}{\sqrt{\left[\left(\delta-\frac{1}{2}\right)(1-\varphi)+\frac{1}{2}\right]}}\right. = sgn\left|\sqrt{\left[\left(\delta-\frac{1}{2}\right)(1-\varphi)+\frac{1}{2}\right]}-\frac{\frac{1}{2}\left(\delta-\frac{1}{2}\right)(1-\varphi)}{\sqrt{\left[\left(\delta-\frac{1}{2}\right)(1-\varphi)+\frac{1}{2}\right]}}\right.$$

$$= sgn\left|\left(\delta-\frac{1}{2}\right)(1-\varphi)+1 > 0,\right.$$

i.e., innovation entry increases with population volume in a market;

$$sgn\left|\frac{\partial n}{\partial r_2}\right. = sgn\left|\frac{\partial n}{\partial \tau_3}\right. > 0,$$

---

[44] This is done using the Lambert function. Specifically, for $p^{\mathrm{ay+b}} = \mathrm{cy} + \mathrm{d}$, where $\mathrm{p} > 0\ and\ a, c \neq 0$, y can be solved as $\mathrm{y} = -\frac{\mathrm{W}\left(-\frac{\mathrm{a}\ln(\mathrm{p})}{\mathrm{c}}p^{b-\frac{\mathrm{ad}}{\mathrm{c}}}\right)}{\mathrm{a}\ln(\mathrm{p})}-\frac{\mathrm{d}}{c}$, where W is the Lambert function. See http://mathworld.wolfram.com/LambertW-Function.html for more details.

i.e., innovation entry increases with number of segments in a market;

$$sgn\left|\frac{\partial n}{\partial t}\right. > 0,$$

i.e., innovation entry increases with degree of a market's need;

and

$$sgn\left|\frac{\partial n}{\partial \varphi}\right. = sgn\left|-\left[\left(\delta-\frac{1}{2}\right)(1-\varphi)+\frac{1}{2}\right]^{-\frac{1}{2}}+\frac{1}{2}\left(\delta-\frac{1}{2}\right)(1-\varphi)\left[\left(\delta-\frac{1}{2}\right)(1-\varphi)+\frac{1}{2}\right]^{-\frac{3}{2}}\right.$$

$$= sgn\left|-1+\frac{\left(\delta-\frac{1}{2}\right)(1-\varphi)}{2\left[\left(\delta-\frac{1}{2}\right)(1-\varphi)+\frac{1}{2}\right]}\right. < 0\,,$$

i.e., innovation entry decreases in degree of a market's negative drug response.

Thus, I hypothesize a positive inducement effect with three of my measures of market heterogeneity and a negative inducement effect with one of my measures of market heterogeneity.

All comparative dynamics with n_s follow the corresponding predictions for n except with respect to τ_3 (i.e. r_2). However, it is straightforward to deduce the following:

$$sgn\left|\frac{\partial n_3}{\partial \tau_3}\right. = sgn\left|\frac{\partial n}{\partial \tau_3}\right. > 0,$$

$$\frac{\partial n_2}{\partial \tau_3} = \frac{\partial}{\partial \tau_3}\frac{n}{p_3\tau_3} = \left(\frac{\frac{\partial n}{\partial \tau_3}\tau_3 - n}{p_3{\tau_3}^2}\right) = \left(\frac{n}{p_3{\tau_3}^2}\right)\left(-\frac{\tau_3 C_2}{2\,(1-\tau_3)^2\ln(1-p_2)\left[C_3-\frac{C_2}{(1-\tau_3)\ln(1-p_2)}\right]}-1\right) > 0,$$

$$sgn\left|\frac{\partial n_1}{\partial \tau_3}\right. = sgn\left|\frac{\partial n_2}{\partial \tau_3}\right. > 0.$$

These results are promising because they give me the empirical flexibility to exploit a larger dataset (e.g., drugs in clinical development) that can enable a more statistically robust investigation of my testable hypotheses.

My reward for investing in complementary theoretical setups is that: (1) I can make predictions about the potential effects of non-size market characteristics whether they are exogenously given and/or endogenously determined; (2) I can make predictions by innovation measure type; and (3) I have a non-arbitrary framework for establishing model specification and constructing my empirical variables to achieve identification.

4.3 Comparative Statics and Testable Hypotheses

4.3.1 Comparative Statics

The comparative statics from the previous section are illustratively summarized in Figure 4.6.

4.3.2 Testable Hypotheses

Given the specific scope of my research questions as well as the limitations I expect from using publicly available data for this study, I will be unable to test the full prediction set directly taken from my comparative statics. Rather I use these comparative statics to derive (as indicated in Figure 4.7) these two more modest testable hypotheses:

> Hypothesis #1: For a given market size, the number of new drug product entries increases in market heterogeneity; and
>
> Hypothesis #2: Adding one or more measures of market heterogeneity reduces the coefficient on market size.

Although I do not test the predictions in Section 4.3.1 as they specifically relate to the degree of "innovativeness" of innovation output, I use these predictions from theory to inform my empirical strategy and my interpretation of why effects may vary with innovation measure type.

Confirming these testable hypotheses of an extended Induced Innovation Hypothesis may allow for informative and novel predictions, for instance that the inducement effect of market size has been over-estimated in previous empirical studies; innovation output may be increasing in the

number of disease sub-indications; and innovation output may be also influenced by the sizes of the largest and smallest disease sub-indications.

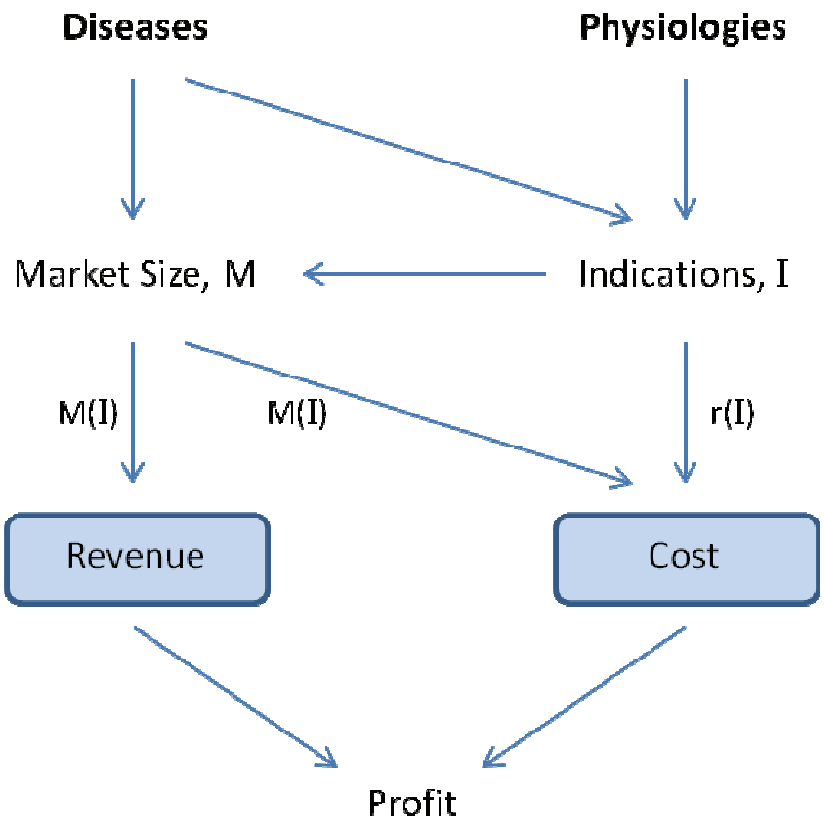


Figure 4.1. Model I - Putative Inducement Mechanisms of Market Characteristics

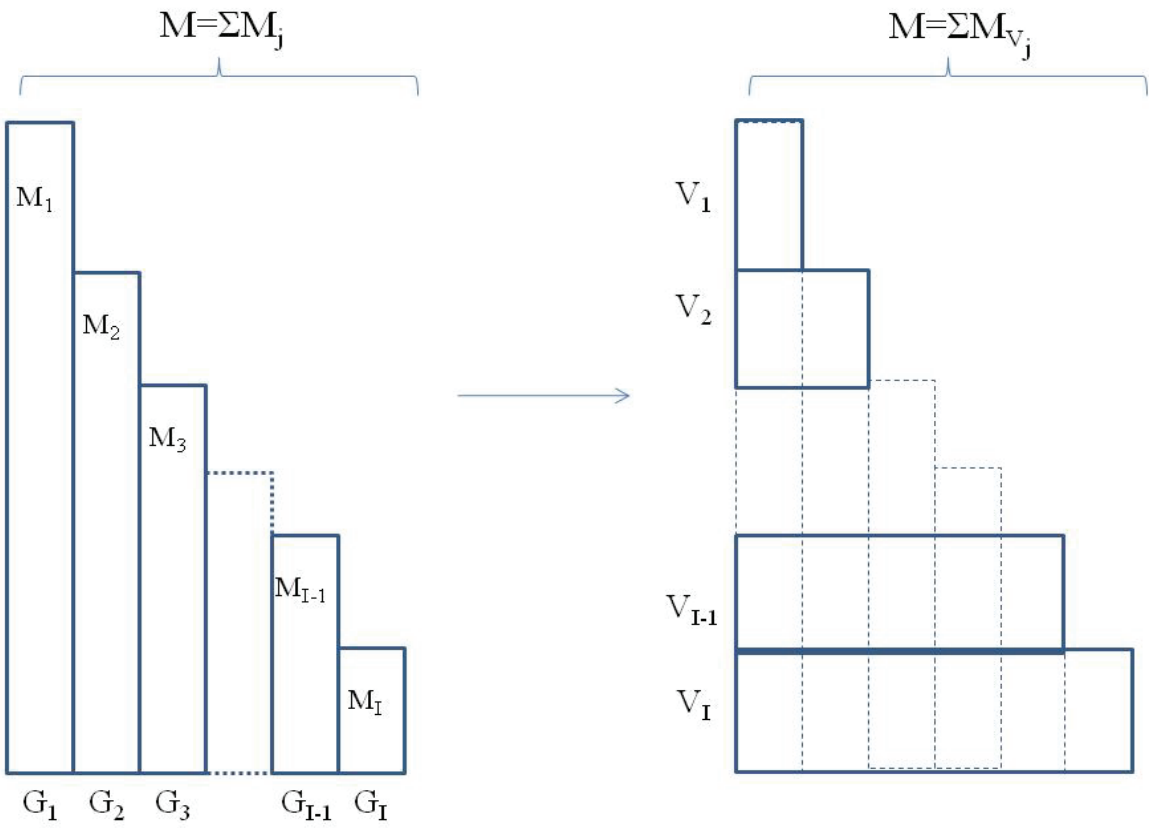


Figure 4.2. Model I - Alternative Sub-Market Partitioning (Illustrative)

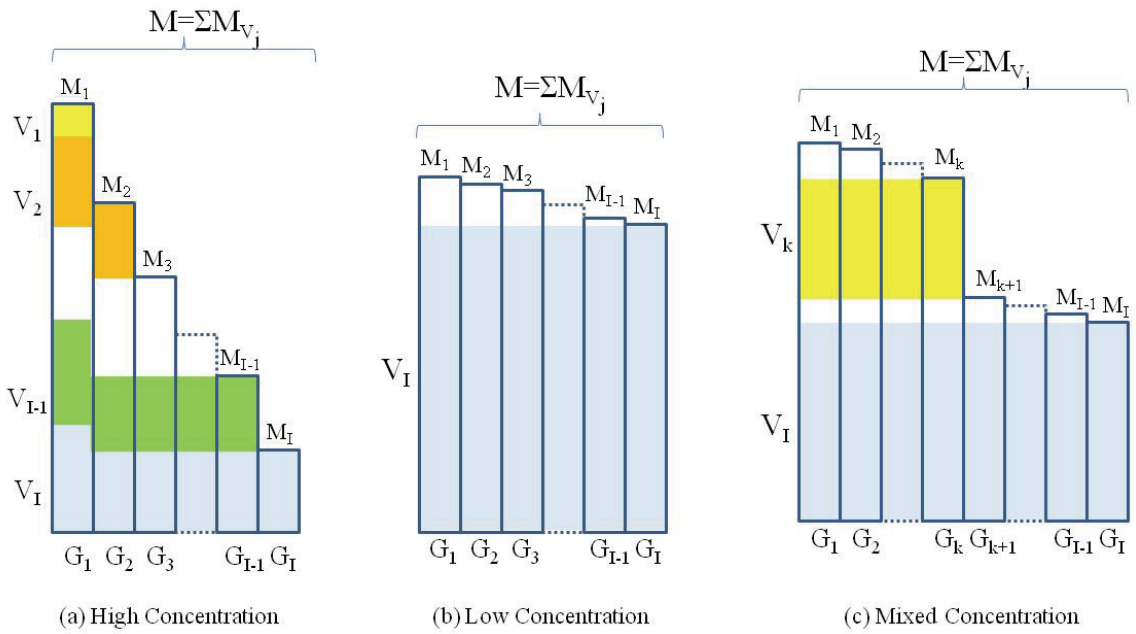


Figure 4.3. Sub-market partitioning scenarios

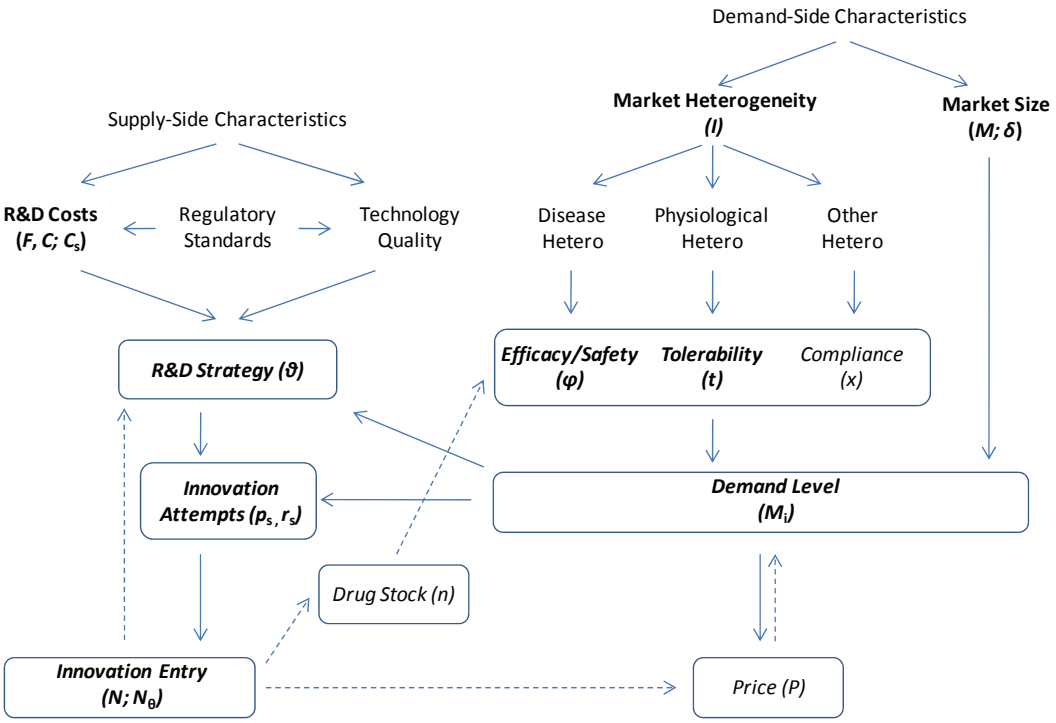
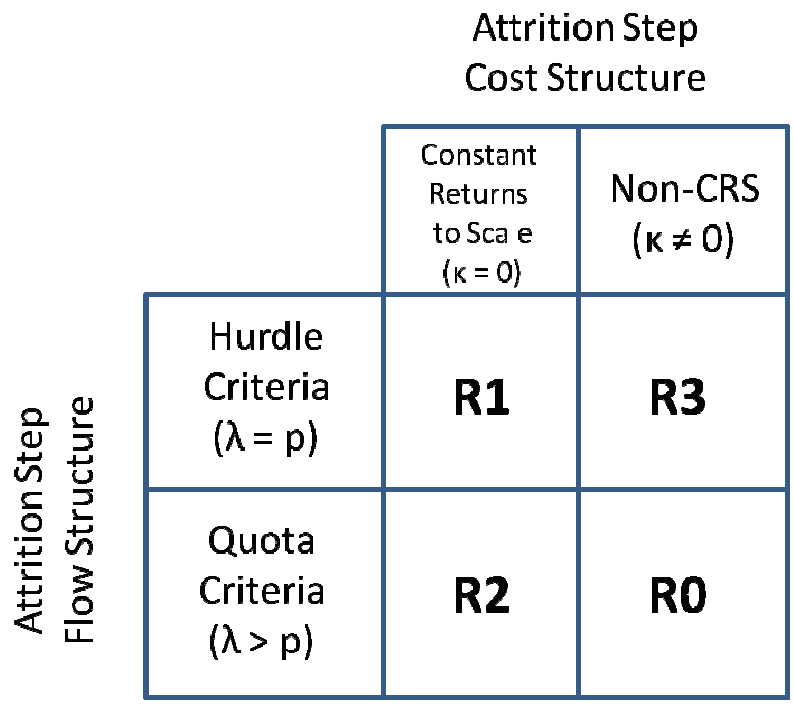


Figure 4.4. Model II - Putative Inducement Mechanisms of Market Characteristics



Note: We define $\kappa = C_f / (C_f + C_m)$ and $\lambda = 1 - (1 - p)^{ar}$ where F denotes the fixed cost incurred during the innovation step, c denotes the marginal cost per product prototype, p denotes the exogenously-determined probability of technical success of any product prototype, and a denotes the number of product prototypes per innovation step. The hurdle attrition criterion identifies qualified-in-class prototypes during an innovation step while the quota attrition criterion identifies the best-in-class prototype(s).

Figure 4.5. Product innovation step regimes

	Conditional Inducement Effects on Innovation Entry			
		Market Heterogeneity Characteristics		
Innovation Type (θ)	Total Market (M)	Largest Sub-Group (M_1)	Safety Fit (φ)	Tolerability Fit (t)
Molecule (θ=2)	↑	↓	↑	
Indication (θ=3)	↑	↓	↑	
Formulation (θ=4)	↑			↑

Figure 4.6. Comparative Statics from eIIH Theoretical Setup

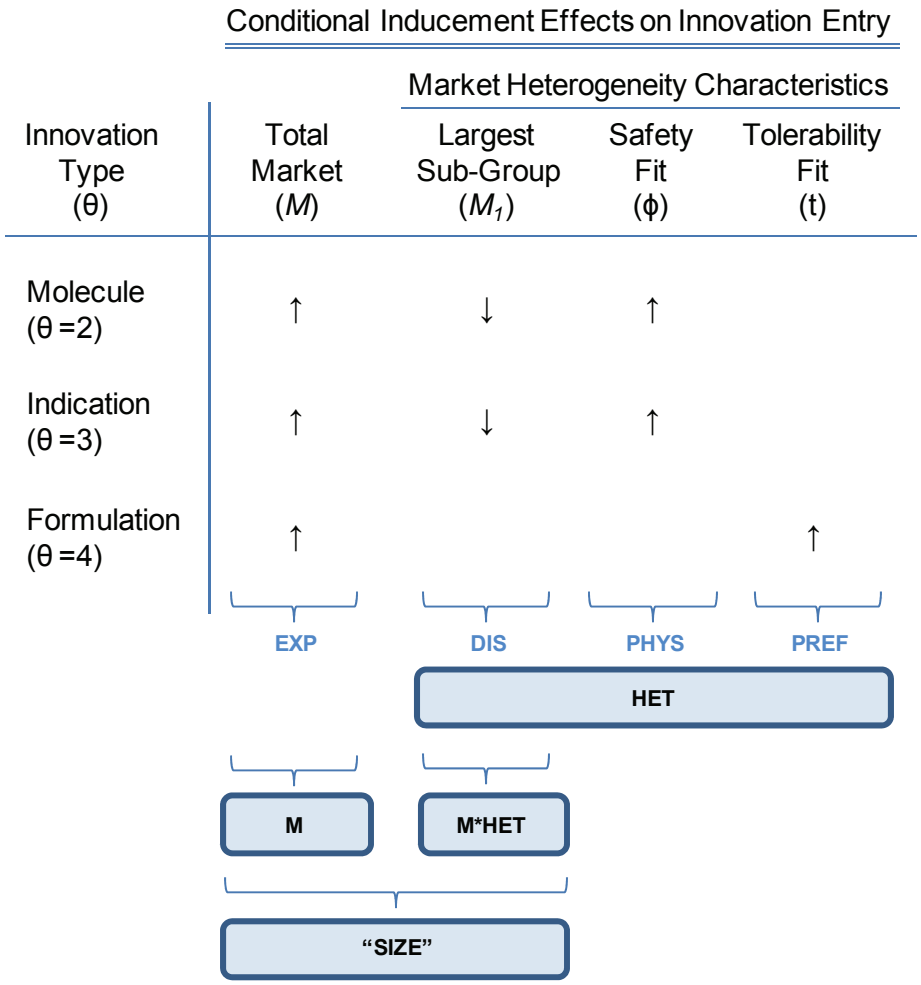


Figure 4.7. Testable Setup for Empirical Testing

CHAPTER 5.

EMPIRICAL STRATEGY

5.1 SPECIFICATION

To guide my model specification efforts, I can draw on the non-arbitrary framework established from my theoretical setup in (*6). Namely, my starting point is a model following the general functional form,

$$N = f(M, m(M, HETi), HETd) \quad ,$$

where

N is an innovation count measure;
M is a size value of the aggregate market in question;
$HETi$ is a measure (or set of measures) of one or more non-size market characteristics that influence N indirectly by interacting with M;
$HETd$ is a measure (or set of measures) of one or more non-size market characteristics that influence N directly;
m is a size function capturing the interaction between M and $HETi$; and
f is a count function that calculates N from M, $HETd$, and $HETi$.

Thus, the base model I wish to estimate is composed as follows, presented in linear-form for expositional purposes:

$$\log N_{ct} = d_{ct} + \alpha \cdot \log M_{ct} + \gamma \cdot \log(M * HET_{ct}) + \omega \cdot \log DIS_{ct} + \varphi \cdot \log PHYS_{ct} + \pi \cdot \log PREF_{ct} + X'_{ct} \cdot \beta + \sigma_c + \mu_t + \varepsilon_{ct} \quad ,$$

such that

N_{ct} equals 1 when N_{ct} = 0 or equals N_{ct} otherwise (i.e. when N_{ct} ≥ 1), where N_{ct} measures the number of drug innovations in disease category c in time period t;

d_{ct} is a dummy variable that equals 1 when N_{ct} = 0;[45]

M_{ct} is the base market size for category c in time period t;

$(M * DIS_{ct})$ is some measure (income-based) of M interacting with one or more variables from the set of non-size characteristics $\{DIS, PHYS, PREF\}$ for category c in time period t;

DIS_{ct} is some measure (income-based) of the disease category's compositional heterogeneity of sub-indications;

$PHYS_{ct}$ is some measure (income-based) of the disease category's compositional heterogeneity of physiological sub-types;

$PREF_{ct}$ is some measure (income-based) of the disease category's compositional heterogeneity of adverse-event tolerability/sensitivity preferences;

X_{ct} is a vector of controls for insurance coverage and special drug status (e.g. orphan or pediatric designations);

ζ_c are a full set of category fixed effects;

μ_t are a full set of time fixed effects; and

ε_{ct} is the residual term.

Thus, with respect to my testable hypotheses, I am looking for whether any of my coefficients of interest – α, γ, ω, φ, and π – hold non-zero values with statistical significance (Research Question #1) and whether α decreases with one or more of these other coefficients being different than zero with statistical significance (Research Question #2).

While I do obtain results with OLS estimation using the linear specification presented here, the empirical findings for my base specification are based on the standard Poisson approach for count regression.

One final observation is that I have not included any explicit controls for drug stock or drug stock growth potential in market c at time t. My rationale for this is that I want to avoid over-

[45] Follows the approach of Acemoglu & Linn (2004) as taken from Pakes and Griliches (1980) despite possible biases from d_{ct} and $\tilde{N}_{ct}$ link.

specification given that my belief that the M*HET variable (discussed in greater detail in Section 5.6) can sufficiently control for potential biases associated with drug stock.

5.2 IDENTIFICATION

My observation unit is market-year so I achieve identification by exploiting variations in the size (drug spend-based measures) and the non-size characteristics (income- based measures) of markets over time. This strategy is facilitated by my use of the International Classification of Diseases ninth revision with Clinical Modification (ICD-9-CM).[46] In contrast to the therapeutic-based market categorizations (e.g., drug class) employed in prior empirical studies, using this disease-based categorization system is noteworthy for several reasons. First, this categorization is demand-based which more closely aligns with the theoretical setup of IIH and eIIH. Second, a disease-based definition can better capture the true demand potential for competing and/or complementary drug innovations because (e.g., it can capture the effects of off-label drug usage). And third, my market categorizations are defined and structured to aggregate/disaggregate in an a priori non-arbitrary manner.

My additional strategies for facilitating identification include taking advantage of fixed effects estimation to exploit the count panel nature of my dataset; reporting Huber-White robust (and cluster-robust, when available) standard errors; using time periods based on three year intervals to improve result robustness; and. using lagged dependent variables to mitigate endogeneity concerns.[47,48]

[46] The National Center for Health Statistics (NCHS) and the Centers for Medicare and Medicaid Services (CMS) have created and officially used this system since 1979 for assigning codes to diagnoses and procedures associated with hospital utilization in the United States.

[47] Huber (1967); White (1980); (Wooldridge (1999).

[48] These time periods will be 3-years in length in my base scheme but in my sensitivity analyses I also consider 1-year and 5-year intervals.

5.3 DEPENDENT VARIABLE: INNOVATION ENTRY

I measure innovation entry across disease market categories by counting outputs associated with New Drug Applications (NDAs) as well Biologic Licensing Applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER). As outlined earlier in Section 2.3.3, my measurement units for innovation entry vary according to count type (e.g., the number of new product codes) and measure type (e.g., for new molecular entities). My concept of drug innovation covers a broad range of outputs from new drugs, new drug products, new drug product attributes, and new drug product information. While public attention is understandably focused on the introduction of new medicines, the issue of whether a drug innovation is breakthrough (reflecting major productivity, say), incremental (reflecting minor productivity, say) or trivial (more reflective of activity rather than productivity) is not central to this study.[49] Nonetheless, I use measure type to examine the variation in size effects according to output "innovativeness." In particular, I exploit the non-arbitrary chemical type codes that the FDA assigns to new drug applications (see

[49] "[Charging FDA user fees]…increased patient access to new drugs and biologics (from FY 1993 to 2010, nearly 1500 NDAs and BLAs [approved])..." (Source: CDER Small Business Webinar on PDUFA, December 19, 2011)

Table 5.1).

Chemical type coding (a numerical code primarily from 1-8) indicates the newness of the compound forming the drug's active ingredient (new molecular entity, or incrementally modified existing molecular entities).[50] I use these codes to identify the three measure types I focus on in this study. The first is "All Application Types" which simply includes all chemical type codes. This is serves as my baseline measure for innovation entry. Second is "New Drugs" which consists of new molecular entities (designated by chemical type code 1) and incrementally modified drugs (reflected by chemical type codes 2-4). And last is "New Molecular Entities" (chemical type code 1). So although it is a secondary concern, the role of output innovativeness is still of interpretive interest.

5.4 Explanatory Variable: Market Size

5.4.1 Construction

I define the aggregate market size as $M_{ct}(v)$ for market c with value basis v at time t.[51]

5.4.2 Value Basis

My base specification uses market size as valued by the total prescription drug expenses for a disease market and I am able to reference this measure directly from MEPS.

I also consider the alternative value measure of total health care expenses for a disease market to observe whether market "potential" (e.g., substituting drugs for other interventional spend) is a relevant consideration in an eIIH context.

[50] "Changing Patterns of Pharmaceutical Innovation," The National Institute for Health Care Management Research and Education Foundation (May 2002).

[51] Whether this construct is better served as a lag or lead measurement is essentially an empirical question which has been previously examined by Acemoglu & Linn (2004) as well as others.

5.5 EXPLANATORY VARIABLES: MARKET HETEROGENEITY

5.5.1 CONSTRUCTION

Per Figure 2.2, my proposed framework for examining market characteristics breaks them down into four types: trivially additive (e.g. disease income/geographic profile); non-trivially additive (e.g. disease sub-indication profile); categorically non-additive (e.g. disease age/race/gender profiles); and non-categorically non-additive (e.g. patient tolerability profiles). Unfortunately, data considerations will limit my ability to test these categorizations separately. Moreover, while I am conceptualizing heterogeneity as it applies to broadest possible set of market characteristics, empirically validating the utility of an eIIH does not require saying anything about specific market characteristics (and their resulting subgroups). Rather I can be satisfied with finding evidence of the influence of market composition regardless of the specific subgroups involved. For instance, say the total drug spend of seniors to non-seniors is 2-to-1 in disease market A and 1-to-2 in disease market B. I describe markets A and B as having equivalent compositional structure (or alternatively, equivalent non-homogeneity) in terms of their age profiles. My concern in this study then is how, if at all, this 2-to-1 compositional ratio (independent of the specific subgroup proportions) influences innovation. I set aside any observation and interpretation of specific subgroup effects to be addressed in future follow-on research.

To further clarify my empirical scope with market heterogeneity by way of example, imagine three disease markets having the same aggregate dollar value size with respect to total drug spend: Market A consists completely of senior men; Market B consists completely of senior women; and Market C consists of non-senior men and non-senior women equally. If market heterogeneity is characterized by age – or more precisely, age grouping – then I would describe all three markets as being equally heterogeneous (or in this case, equally homogeneous) in age since all are composed 100% by a single age group. Now if market heterogeneity is characterized by gender

instead of age, then Markets A and B would have equal heterogeneity (or equivalently, equal non-homogeneity) because they are both composed 100% by a single gender while Market C would be unequally heterogeneous from Markets A and B. Finally, if market heterogeneity is characterized by both age and gender, all three markets would be unequally heterogeneous to each other (i.e., pair-wise).

So although the characterization of market heterogeneity is sensitive to the defining characteristic(s) of a market's composition, what will suffice for this study's objectives is a measure of composition that can capture the degree of a market's heterogeneity regardless of the defining characteristic. Fortunately, the usefulness of such subgroup-independent measures has already been established by well-known constructs of concentration and inequality including the Herfindahl-Hirschman Index[52] and the Gini coefficient.[53]

On this conceptual basis I employ two constructs for market heterogeneity. The first is simply a direct HHI calculation,

$$HHI^h(v) = \sum_{c=1}^{n} [s_c^h(v)]^2$$

where s_c^v is market c's share of total market value based on some market characteristic, h, that categorizes the market into n additively separable sub-markets according to some value basis, v.

I also employ a second derivative construct,

$$H^h(v) = [s_1^h(v) - s_2^h(v)]^2$$

that is specifically applicable to the case of $n = 2$. It has the same interpretation (i.e., a "directionless" measure of concentration) as HHI^h but is effectively a scaled version that allows the difference in measure between full homogeneity and full heterogeneity to range from 0 to 1 (whereas $H2_h$ ranges from 0.5 to 1). I use this second construct to calculate my base measures

[52] Stigler (1964)
[53] Gini (1912)

of heterogeneity both to minimize the arbitrariness with which n, the number of sub-markets, may be determined for market characteristic, h, and to improve my ability to achieve statistical significance,

To capture the degree of a market's non-homogeneity based on market characteristics potentially relevant to profiling disease populations and their demand for drug innovation, I consider three categories of characteristics: "physiology" profiling; "preferences" profiling; and "disease" profiling.

5.5.1.1 PHYSIOLOGY PROFILING CHARACTERISTICS

For $h = age$, $s_1^{age}(v)$is the share of v for the disease subpopulation of patients aged <50 and $s_2^{age}(v)$is the share of v for the disease subpopulation aged >=50.

For $h = race$, $s_1^{race}(v)$is the share of v for the disease subpopulation of patients who are white and $s_2^{race}(v)$is the share of v for the disease subpopulation who are non-white..

For $h = gender$, $s_1^{gender}(v)$is the share of v for the disease subpopulation of patients who are male and $s_2^{gender}(v)$is the share of v for the disease subpopulation who are female.

5.5.1.2 PREFERENCE PROFILING CHARACTERISTICS

For $h = checkup$, $s_1^{checkup}(v)$is the share of v for the disease subpopulation of patients who are male and $s_2^{checkup}(v)$is the share of v for the rest of the disease subpopulation.

For $h = flushot$, $s_1^{flushot}(v)$is the share of v for the disease subpopulation of patients who have had a flu vaccination within the past year and $s_2^{flushot}(v)$is the share of v for the rest of the disease subpopulation.

5.5.1.3 DISEASE PROFILING CHARACTERISTICS

As suggested by the two theoretical approaches and resulting predictions I establish in Chapter 4, it appears empirically sensible to consider disease-associated characteristics of market heterogeneity as being either categorical or non-categorical.

The most obvious categorical aspect of disease heterogeneity lies in a market's categorization system of sub-diseases. Thus, the disease heterogeneity measure I construct from this is $M_1^c(v)$ which measures v associated with the largest sub-disease market within disease market c.

A non-categorical characteristic important for disease-based profiling of market heterogeneity would appear to be disease severity. However, given that the market characteristic of disease severity is likely to directly influence market size, I consider this type of heterogeneity construct to be of the form represented by the M*HET term in my empirical specification. I elaborate on this case further in Section 5.4.2.

5.5.2 VALUE BASIS

Given the eIIH context of my study, I use $v = income$ as the underlying value basis for calculating my heterogeneity measures. For sensitivity purposes, my empirical effort also considers the alternative bases of prescription drug spend and total health care spend.

5.6 EXPLANATORY VARIABLES: SIZE*HETEROGENEITY

5.6.1 CONSTRUCTION

In considering the construction of my market size variable in an eIIH context, it is interesting to note that a second concept of market size besides simple aggregate market size emerges from my setup in (**3), (**5), and (**6). Figure 5.1 provides a stylistic illustration of how such an alternative measure of market size can arise due to market heterogeneity associated with the

disease severity. The practical interpretation of these M*HET constructs (which I anticipated and included in my base specification model earlier) is that they may offer some insight into how inducement effect can vary with the definition and measurement of market size, e.g., whether inducement is driven more by market need or market potential.

Mechanically, my first step is to create two surrogate measures of disease severity based on data that is likely to be publicly available:

$$DSVN_{gct} = PRDVIS_{gct} / DDNWRK_{gct}$$

and

$$DSVX_{gct} = PRDVIS_{gct} / RXTOT_{gct},$$

where PRDVIS is the number of visits to all providers, DDNWRK is the number of working days missed due to illness, and RXTOT is the number of prescription medicines. This ratio of provider visits versus some illness measure aligns stylistically with disease severity. A high ratio reflects a high intensity of physician consultation which seems reasonably reflective of "more severe" disease contexts whereas a lower rate of physician consultation would be reflective of "less severe" disease state conditions.

Next, I define my disease-based M*HET constructs, $C(v)$ and $U(v)$, as follows:

$$C_x(v) = \{component\ of\ M(v)\ for\ subpopulation\ associated\ with\ (DSVXr < 1.3)\};$$
$$C_N(v) = \{component\ of\ M(v)\ for\ subpopulation\ associated\ with\ (DSVNr < 3.7)\};$$
$$U_x(v) = \{component\ of\ M(v)\ for\ subpopulation\ associated\ with\ (DSVXr > 0.6)\};$$
$$U_x(v) = \{component\ of\ M(v)\ for\ subpopulation\ associated\ with\ (DSVNr > 1.3)\};$$ and

where

$$DSVXr = PRDVIS\ /\ (RXTOT + 1);$$
$$DSVNr = PRDVIS\ /\ DDNWRK + 1);$$
$M(v)$ represent aggregate market size as measured by value basis v;
DSV cutoff ranges were approximately set by 30th and 70th percentile DSV levels; and

v is some value basis that will match the value basis for M.

In summary, the role of market size in induced innovation can be effectuated either through M alone, through M*HET alone, or through M and M*HET together. For my base empirical specification, I calculate market size (for the "treated market") as M or more precisely $M(v)$ while I calculate M*HET using $C_N(v)$.

5.6.2 VALUE BASIS

I use $v = prescription\ drug\ spend$ as the value basis for $C(v)$ and $and\ U(v)$ since my specification model employs M*HET as the only market size explanatory variable when HET is a non-categorical disease-based characteristic like disease severity.

5.7 TEST STATISTICS

For fitting and specification comparisons I rely most on two goodness-of-fit statistics current in research , Akaike's information criterion (AIC)[54] and the Bayesian information criterion (BIC).

AIC is most commonly defined as AIC = -2 lnL + 2k, where lnL is the maximized log-likelihood of the model and k is the number of parameters estimated (number of predictors including the intercept). Table 5.2 presents some guidelines on determining AIC significance levels.

BIC is a second measure of fit defined as BIC = -2 lnL + k lnN, where N is the sample size (number of observations). In both cases a smaller statistic indicates the better fitting model.

Addressing my Research Question #2 requires the comparison of size coefficients across specifications. However, the challenge here is that different specifications will give rise to different interpretations for the same coefficient. Nevertheless, I consider the indicative evidence that can be gleaned from two STATA commands, -suest- and –khb-. The former is a post-

[54] Akaike [1974]

estimation command that compares the estimated coefficients between two nested non-linear probability models in the context of GLM regression.[55] The latter also tests coefficients across models of the GLM family but is only experimental for Poisson estimation.[56]

[55] Weesie (1999).
[56] Kohler et al (2011).

Table 5.1. Chemical Type Codes Associated with NDAs/BLAs

Source: FDA Orange Book.

chemical_type

id	code	chemicaltypedescription
1	1	New molecular entity (NME)
2	2	New ester, new salt, or other noncovalent derivative
3	3	New formulation
4	4	New combination
5	5	New manufacturer
6	6	New indication
7	7	Drug already marketed, but without an approved NDA
15	8	OTC (over-the-counter) switch

Table 5.2. AIC Statistic Significance Levels

Source: Hilbe & Greene (2007)

Difference between models A and B	Result if A < B
<0.0 & <=2.5	No difference in models
<2.5 & <= 6.0	Prefer A if $n > 256$
<6.0 & <= 9.0	Prefer A if $n > 64$
10+	Prefer A

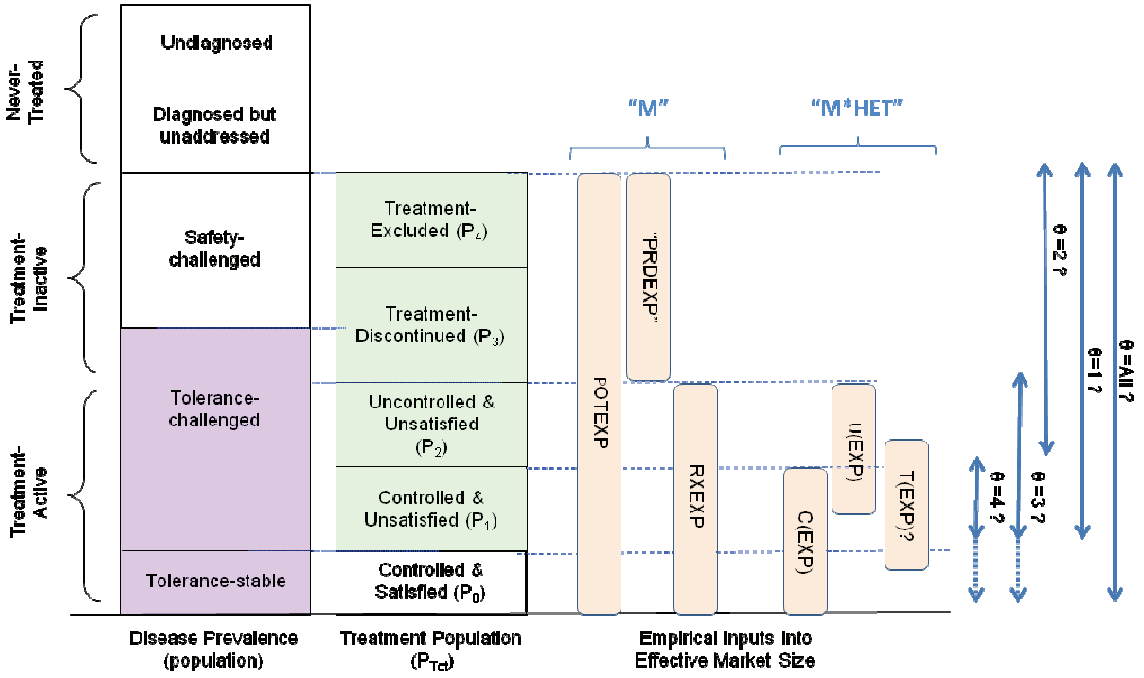


Figure 5.1. Alternative Market Size Constructs

Notes: The pink-shaded boxes labeled under "M" and "M*HET" are possible constructs that are either directly sourced or indirectly derived from MEPS variables. Also shown are the potential links between constructs and the concept of innovativeness (denoted by θ) considered in my Theoretical Model II.

CHAPTER 6.

DATA AND DESCRIPTIVE STATISTICS

6.1 MARKET CATEGORIES

Departing from the traditional IIH empirical approach of using drug-based market categories, I instead rely on the ninth revision of the World Health Organization's International Classification of Diseases (ICD-9). From the 913 disease codes represented at the 3-digit level, I create 128 disease categories by aggregating subsets that derive naturally from the ICD9's coding structure (see Tables 6.1-6.3).

6.2 DEPENDENT VARIABLE: INNOVATION COUNTS

My data on new drug approvals and associated entries (products, formulations, document filings, etc), come from three authoritative primary data sources all maintained by the U.S. FDA. First, my approval-related information comes from the Orange Book which contains comprehensive information (company/brand and molecule names, ingredients, dosages, delivery forms, new drug application filing dates, FDA approval dates, patent expiration dates, market exclusivity dates, marketing discontinuation dates, etc.) on all approved drug products and product changes since 1938. Although annual detail is available starting with 1982, I confine my attention to the 1996-2011 time period to match with the time series data available for my explanatory variables. Second, my drug characteristics information – chemical type, specifically – comes from the

Drugs@FDA datafiles. And third, my NDA-number-to-NDC-code link comes from the National Drug Code Directory (July 2012 update version).[57]

Establishing my dependent variable dataset from these three sources requires two linkage steps as illustrated in Figure 6.1 with NDA number (uniquely assigned to each NDA by the FDA) serving as the variable key.

The final step is assembling my innovation count dataset is to create a disease category variable which associates each NDA with all of its relevant disease markets. The seemingly most direct way of doing this would be to compile the approved indications from each drug's product labels. However, there are several limitations with this approach. For instance, it excludes any consideration of accounting for the common real-world practice of off-label drug use. But the more pressing issue in using product labels in this manner is that there is no systematic way to match these disease categories (FDA drug structured product labels) with the disease categorization system used in my explanatory dataset (ICD9 codes). Thus, I instead create a disease category variable in my dependent variable dataset by using NDC numbers as a variable key to match ICD9 codes sourced from MEPS to innovation data sourced from FDA. In particular, I use the 9-digit version of NDC codes which identifies the drug maker and its drug (but drops any reference to the different drug products available for each drug).

Now since I execute this matching without regard for time, each count item in my innovation data ends up being associated with all relevant ICD9 codes regardless of when the association is identified (through self-reported drug usage associated with illnesses) in MEPS. As I will discuss in CHAPTER 7, this means that the same NDA can count as an innovation entry more than once (i.e., once for each associated disease market). In order to distinguish my innovation entry count

[57] While a "new" version was introduced this summer of 2012, I am using the final July 2012 update of the "old" NDC version because this is the version according to which MEPS data has been recorded.

from a straight count of approved NDAs, I refer to the measure unit of my dependent variable as approved "NDA-indication" counts.

An associated issue that arises with my "NDA-indication" counting approach is determining the entry date of a drug innovation into a given market since my data generating process imputes NDA-indication relationships from MEPS self-reporting without any reference to time. I make the simplifying assumption that firms are acting in full anticipation of all possible disease market opportunities for their drug candidate at the time of their drug's initial market entry. This then means the entry date for all NDA-indication counts associated with a drug would be the approval date for the firm's first original NDA for that particular drug.

The final version of my dependent variable dataset contains 2,731 (80.3%) of the 3,401 NDA numbers listed in EOB for my target time period. However, my dataset coverage is somewhat weak for NMEs -- my LHS dataset only contains 491 (64.0%) of the 767 chemical type=1 drugs approved. Also, due to the limited time window of my dataset, I lack sufficient data to examine efficacy supplements as an innovation measure type category.[58]

6.3 Explanatory Variables: Market Size & Market Heterogeneity

To establish estimates for demand volume or market size over time, I draw upon the well-known Medical Expenditure Panel Survey, a representative sample of U.S. households covering age, income, and drug spend data for ~28,000 individuals. In particular, I draw data from the 13 periods during 1996-2008. The key measures from MEPS I use for my variable constructs include:

[58] Efficacy supplements are drug approvals for additional uses or indications which are added to the approved labeling and can be promoted by the drug's manufacturer.

RXEXP = total prescription drug expenditures for market population;
DDNWRK = # of days missed from work due to illness/injury for market population;
HELD = share of market population holding health insurance;
TTLP = total income for market population;
TOTEXP = total health care expenditures for market population;
PRDVIS = total # of provider visits for market population;
PRDEXP = total provider expenditures for market population;
RXTOT = # of drug prescriptions filled (including refills) for market population;
CHECK = share of market population having had last routine check-up within past year;
FLUSHT = share of market population having had flu vaccination within past 5 years.

As described in CHAPTER 5, my explanatory variables are expressed as income dollars of the market population delineated by each variable. These dollar figures are adjusted to real 1996 dollars using MEPS recommended price indices according to expense type.[59] Further, all population-based values have been scaled down by a factor of 10^6 to facilitate data dispersion and estimation management.

My MEPS dataset includes 804 (88.1%) of the 913 possible WHO ICD9 3-digit numeric codes.

6.4 Dataset Construction

As illustrated in Figure 6.1 which summarizes my dataset setup, I combine my new drug product entry sub-dataset from the electronic Orange Book – via the National Drug Code linking variable and supplemented by application attributes from Drugs@FDA – with my disease market characteristics sub-dataset from MEPS to create one integrated panel dataset where observations for each variable are across 126 disease markets and 3-year time periods between 1996 and 2011. The variable key I use to link these datasets is disease market code as determined by my categorization of ICD9 3-digit codes. Of the 804 ICD9 3-digit numeric codes in

[59] For time-pooling/-averaging expenditures, I follow the MEPS recommendation to use PCHE indices (www.cms.gov/NationalHealthExpendData) which differentiates conversion factors by expense category (e.g., provider versus drugs).

my explanatory variables dataset sourced from MEPS, I am able to match 800 (99.5%) of these disease codes during the linkage process to my dependent variables dataset.

I take several steps to clean and further prepare my dataset for analysis. First, to account for missing/unknown ICD9 codes associated with NDA numbers, I decide to drop observations that are only associated with such non-informative codes.[60] And for remaining NDA numbers still associated with non-informative codes, I reallocate the associated market size values from the NDA number's non-informative ICD9 codes to the NDA number's valid codes. Thus, I eliminate unviable codes while retaining as much "market size" credit to those codes associated with the same NDA.

I make two additional modifications to finalize my baseline dataset. I exclude innovation entry associated with orphan drugs because of (1) the likely left-hand censoring issues (under-reporting) associated with sample sizes in the MEPS surveys, and (2) the biases created by the unobserved drug development incentives created by the Orphan Drug Act. Secondly, I drop 41 disease groupings that are associated mainly with non-drug treatments (surgical or physiological) which leaves my final dataset consisting of 85 disease markets,

Again, it is important to note that I associate ICD9 codes in a time-invariant manner (i.e., regardless of when the association first started) with each NDA number. However, this challenges my ability to preserve the panel nature of my dataset by being able to track which drugs are associated with which disease markets at which points in time. My fix is to give credit in the year that an NDA approval is recorded (regardless of the approval year of the original NDA) to each ICD9 code associated -- at any time during the study period -- with that therapeutic in MEPS. So for example, if Drug X is associated with both hypertension and erectile dysfunction at some point in time my MEPS dataset, then my approach gives inducement credit to both diseases markets for any FDA activity related to Drug X. Further, the "entry" date associated with

[60] Coded in MEPS as -8 and -9, respectively, and which represent <1% of observations.

such credit is defined for both disease markets based on Drug X's original New Drug Application approval date. So if Drug X gets approved in 1999 for erectile dysfunction and in 2003 for hypertension, and also is associated with erectile dysfunction, hypertension and kidney protection as reported in the 2005 MEPS Survey, then I count Drug X as an innovation entry in 1999 for all three disease markets (erectile dysfunction, hypertension, kidney protection). Furthermore, each market gets credited with innovation entry associated with Drug X for 1995 and again for 2005. Therefore, my innovation entry measures are built from approved "NDA-indication" counts and necessarily reflects some double-counting. This construction relies on the implicit assumption that firms have pre-approval foresight of their drug's potential market size. In other words, firms approach the development of a particular drug as one big project commitment, regardless of registration (filing, labeling) histories and strategies, rather than undertaking it as a series of independently opportunistic projects.

As a final check on the real-world validity of my empirical constructions, I have consulted and pressure-tested my various assumptions with a panel of industry experts.[61]

[61] Experts were consulted from each step of the drug innovation value chain: drug discovery; preclinical development; clinical development; manufacturing; commercialization; pricing and reimbursement. The full list of experts I consulted is available upon request.

Table 6.1. Market Categorization Based on ICD9 3-Digit Code Groups (Part 1 of 2)

roup code	Disease category description	3-Digit Code Range	
3.001	Intestinal infectious diseases	1	9
3.002	Tuberculosis	10	18
3.003	Zoonotic bacterial diseases	20	27
3.004	Other bacterial diseases	30	41
3.005	Human immunodeficiency virus	42	42
3.006	Poliomyelitis and other non-arthropod-borne viral diseases of central nervous system	45	49
3.007	Viral diseases accompanied by exanthem	50	59
3.008	Arthropod-borne viral diseases	60	66
3.009	Other diseases due to viruses and chlamydiae	70	79
3.010	Rickettsioses and other arthropod-borne diseases	80	88
3.011	Syphilis and other venereal diseases	90	99
3.012	Other spirochetal diseases	100	104
3.013	Mycoses	110	118
3.014	Helminthiases	120	129
3.015	Other infectious and parasitic diseases	130	136
3.016	Late effects of infectious and parasitic diseases	137	139
3.017	Malignant neoplasm of lip, oral cavity, and pharynx	140	149
3.018	Malignant neoplasm of digestive organs and peritoneum	150	159
3.019	Malignant neoplasm of Respiration (physiology)|respiratory and intrathoracic organs	160	165
3.020	Malignant neoplasm of bone, connective tissue, skin, and breast	170	175
3.021	Kaposi's sarcoma	176	176
3.022	Malignant neoplasm of genitourinary organs	179	189
3.023	Malignant neoplasm of other and unspecified sites	190	199
3.024	Malignant neoplasm of lymphatic and hematopoietic tissue	200	208
3.025	Neuroendocrine tumors	209	209
3.026	Benign neoplasms	210	229
3.027	Carcinoma in situ	230	234
3.028	Neoplasms of uncertain behavior	235	238
3.029	Neoplasms of unspecified nature	239	239
3.030	Disorders of thyroid gland	240	246
3.031	Diseases of other endocrine glands	249	259
3.032	Nutritional deficiencies	260	269
3.033	Other metabolic and immunity disorders	270	279
3.034	Diseases of the blood and blood-forming organs	280	289
3.035	Organic psychotic conditions	290	294
3.036	Other psychoses	295	299
3.037	Neurotic disorders	300	300
3.038	Personality disorders	301	301
3.039	Psychosexual disorders	302	302
3.040	Psychoactive substance	303	305
3.041	Other (primarily adult onset)	306	311
3.042	Mental disorders diagnosed in childhood	312	316
3.044	Inflammatory diseases of the central nervous system	320	327
3.045	Hereditary and degenerative diseases of the central nervous system	330	337

Table 6.2. Market Categorization Based on ICD9 3-Digit Code Groups (Part 2 of 2)

roup code	Disease category description	3-Digit Code Range	
3.046	Pain	338	338
3.047	Other headache syndromes	339	339
3.048	Other disorders of the central nervous system	340	349
3.049	Disorders of the peripheral nervous system	350	359
3.050	Disorders of the human eye|eye and adnexa	360	379
3.051	Diseases of the ear and mastoid process	380	389
3.052	Acute Rheumatic Fever	390	392
3.053	Chronic rheumatic heart disease	393	398
3.054	Hypertensive disease	401	405
3.055	Ischemic heart disease	410	414
3.056	Diseases of pulmonary circulation	415	417
3.057	Other forms of heart disease	420	429
3.058	Cerebrovascular disease	430	438
3.059	Diseases of arteries, arterioles, and capillaries	440	448
3.060	Diseases of veins and lymphatics, and other diseases of circulatory system	451	459
3.061	Acute respiratory infections	460	466
3.062	Other diseases of the upper respiratory tract	470	478
3.063	Pneumonia and influenza	480	488
3.064	Chronic obstructive pulmonary disease and allied conditions	490	496
3.065	Pneumoconioses and other lung diseases due to external agents	500	508
3.066	Other diseases of respiratory system	510	519
3.067	Diseases of oral cavity, salivary glands, and jaws	520	529
3.068	Diseases of esophagus, stomach, and duodenum	530	537
3.071	Noninfectious enteritis and colitis	555	558
3.072	Other diseases of intestines and peritoneum	560	569
3.073	Other diseases of digestive system	570	579
3.074	Nephritis, nephrotic syndrome, and nephrosis	580	589
3.075	Other diseases of urinary system	590	599
3.076	Diseases of male genital organs	600	608
3.077	Disorders of breast	610	611
3.078	Inflammatory disease of female pelvic organs	614	616
3.079	Other disorders of female genital tract	617	629
3.082	Complications mainly related to pregnancy	640	649
3.088	Infections of skin and subcutaneous tissue	680	686
3.089	Other inflammatory conditions of skin and subcutaneous tissue	690	698
3.090	Other diseases of skin and subcutaneous tissue	700	709
3.091	Arthropathies and related disorders	710	719
3.092	Dorsopathies	720	724
3.093	Rheumatism, excluding the back	725	729
3.114	Superficial injury	910	919
3.118	Burns	940	949

Table 6.3. Excluded Markets From Baseline Categorization

roup code	Disease category description	3-Digit Code Range	
3.069	Appendicitis	540	543
3.070	Hernia of abdominal cavity	550	553
3.080	Ectopic and molar pregnancy	630	633
3.081	Other pregnancy with abortive outcome	634	639
3.083	Normal delivery, and other indications for care in pregnancy, labor, and delivery	650	659
3.084	Complications occurring mainly in the course of labor and delivery	660	669
3.085	Complications of the puerperium	670	676
3.086	Late Effect of Complication of Pregnancy Childbirth	677	677
3.087	Other maternal and fetal complications	678	679
3.094	Osteopathies, chondropathies, and acquired musculoskeletal deformities	730	739
3.095	Congenital Anomalies	740	759
3.096	Maternal causes of perinatal morbidity and mortality	760	763
3.097	Other conditions originating in the perinatal period	764	779
3.098	Symptoms	780	789
3.099	Nonspecific abnormal findings	790	796
3.100	Ill-defined and unknown causes of morbidity and mortality	797	799
3.101	Fracture of skull	800	804
3.102	Fracture of neck and trunk	805	809
3.103	Fracture of upper limb	810	819
3.104	Fracture of lower limb	820	829
3.105	Joint dislocation|Dislocation	830	839
3.106	Sprains and strains of joints and adjacent muscles	840	848
3.107	Intracranial injury, excluding those with skull fracture	850	854
3.108	Internal injury of thorax, abdomen, and pelvis	860	869
3.109	Open wound of head, neck, and trunk	870	879
3.110	Open wound of upper limb	880	887
3.111	Open wound of lower limb	890	897
3.112	Injury to blood vessels	900	904
3.113	Late effects of injuries, poisonings, toxic effects, and other external causes	905	909
3.115	Contusion with intact skin surface	920	924
3.116	Crushing injury	925	929
3.117	Effects of foreign body entering through Body orifice	930	939
3.119	Injury to nerves and spinal cord	950	957
3.120	Certain traumatic Complication (medicine)|complications and unspecified injuries	958	959
3.121	Poisoning by drugs, medicinal and biological substances	960	979
3.122	Toxic effects of substances chiefly nonmedicinal as to source	980	989
3.123	Other and unspecified effects of external causes	990	995
3.124	Complications of surgical and medical care, not elsewhere classified	996	999
3.125	External Causes of Injury and Poisoning	E	
3.126	Supplemental Classification	V	

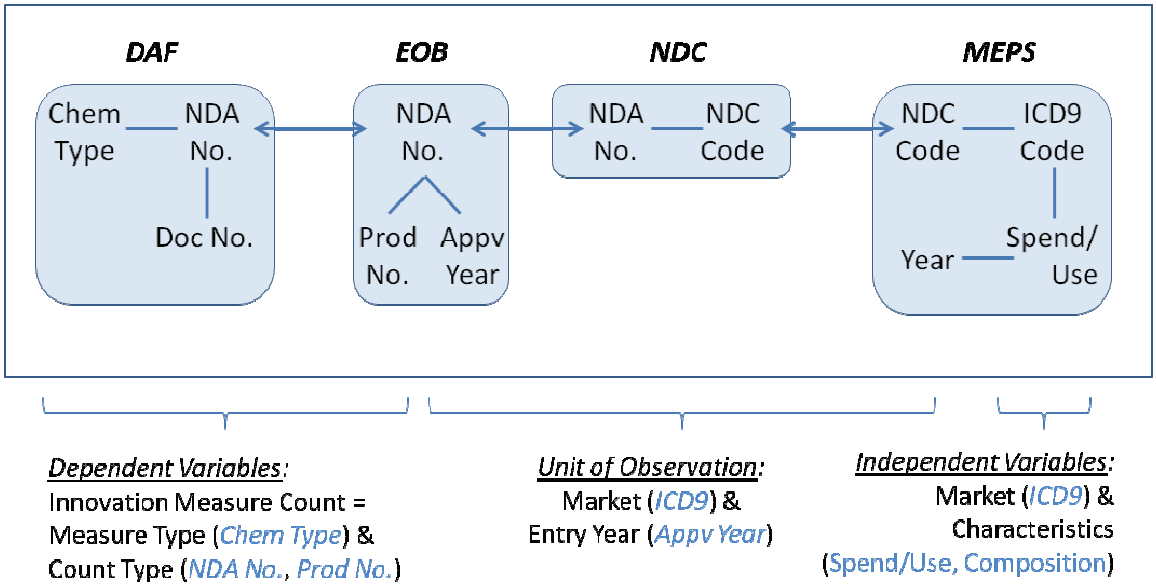


Figure 6.1. Dataset Construction Schematic

CHAPTER 7.

RESULTS

7.1 BASELINE RESULTS

Under my baseline conditions in Table 7.2 I find that a 1% increase in market size, as defined by my "treated market" construct, induces a 3.40% increase in total NDA-indication approvals in the absence of market heterogeneity controls (column I). This result, with statistical significance at the 1% level, not only aligns with the traditional Induced Innovation Hypothesis but is also consistent in magnitude with the range of indirect estimates reported by Acemgolu and Linn (2004). The inducement effect retains strong statistical significance (5% level) with only a slight decrease in magnitude to 3.27% (column V) when market size is defined by my "controlled market" construct. When market heterogeneity variables are included in my model specification, my size estimates follow the predictions from both of my testable hypotheses. Column IV shows that the coefficient on aggregate market size decreases from 3.40% to 1.98% (significant at 10% level) which is consistent with Testable Hypothesis #2. I also observe a decrease when heterogeneity controls are included in the coefficient on controlled size, from 3.27% to 2.45% (significant at 5% level). The statistically significant positive sign (at 5% level) on my RACE variable, which measures a disease market's income concentration based on white/non-white sub-groupings, indicates that an increase in market heterogeneity along race characteristics positively influences NDA-indication entry counts.[62] This is also true for my market preference heterogeneity variable, CHECKUP. However, the positive sign on the coefficients for M1 (the largest submarket) is contrary to expectation.

[62] I do not address the magnitudes of my heterogeneity estimates because interpretation is sensitive to the idiosyncrasies of my construction approach (favoring an unencumbered interpretation of the coefficient on my market size construct) and more generally because it is beyond the scope of my two main research questions for this study.

7.2 SENSITIVITY TESTING

7.2.1 ALTERING INNOVATION MEASURE TYPES

I examine whether inducement effects apply in some manner across innovation measure types. When I consider the count of approved NDA-indications associated with NDA applications for new drugs, I find that a 1% increase in market size (with disease market and time dummies) leads to a 2.85% increase in innovation entry (significant at 5% level). This is lower but not inconsistent with the 4%-6% effect reported by Aceomglu and Linn (2004). When my specification includes my full menu of market heterogeneity variables, the coefficient on market need size falls to 1.18%. The corresponding coefficients in the case of new molecular entities (chemical type = 2) are 6.49% and 4.27%.

As will be noted further along in this section, it appears that the inducement effects associated with new molecular entities is not quite always in sync with the effects associated with new drugs and all application types. It is unclear whether this is due to a lack of power in the data given the relatively few New Molecular Entities that are submitted for FDA approval and/or whether the risky nature of NME development masks IIH effects, especially when small sample sizes are involved.

7.2.2 ALTERING INNOVATION COUNT TYPES

Since my theoretical setup does not restrict the output count type that is tied to NDA approvals, I also test my predictions with two additional measures – product number counts and document number counts –associated with approved NDA-indications.

For all NDA application types, product number counts yield estimates that appear to confirm Hypothesis #1 but refute Hypothesis #2 under my baseline specification (Table 7.3). Namely, the coefficient on size goes from 2.82% (at the 5% significance level) to 3.14% (also at the 5%

significance level) with RACE and CHECKUP appearing as non-zero coefficient heterogeneity variables. This is also the case for NDA applications associated with NMEs (Table 7.9) but not with new drugs (Table 7.6).

One last alternative I consider comes from taking the broadest possible perspective on drug innovation by defining it as information generation. The measurement unit I use for this is the count of document numbers where the document code comes with an "N" prefix (i.e., documents associated with New Drug Applications). Under my baseline of all NDA application types, the coefficient on treated market size (columns I and IV in Table 7.4) decreases from 6.49% to 4.58% (significant at 1% and 5% levels, respectively) with the coefficients of CHECK (significant at 1%) and RACE supporting Hypothesis #2. This confirmatory result is even clearer for NDA applications associated with new drugs (Table 7.7). Once again, the results from NME-associated NDA applications (Table 7.10) are inconclusive.

The eIIH-confirming nature of these estimates is more clearly observable from Table 7.23, Table 7.24, Table 7.25. This is also true for the estimates obtained by using the M*HET variable, controlled market size, instead of the M variable, treated market size (Table 7.26, Table 7.27, Table 7.28).

7.2.3 ALTERING SPECIFIED VARIABLE SCOPE

As further robustness checks, I test a number of variations in the scope of my variable measures. For instance, I examine estimates derived from 1-year and 5-year time periods in addition to my baseline 3-year periods; 0-year and 5-year lags in addition to my baseline 3-year lags; moving average annual measures rather than sequential time point measures; excluding antibiotics as a market category; including orphan drugs (see Table 7.11, Table 7.14, Table 7.17); and including all disease markets that I had excluded (see Table 6.3) due to their being associated with non-

drug treatments and interventions.[63, 64] The results obtained under all of these identification variations are either inconclusive or generally consistent with the findings I report in the previous section. However, the inclusion of orphan drugs did have opposite effects on the coefficients of treated market size (decrease) and controlled market size (increase).

7.2.4 ALTERING SIZE VARIABLE

Given the possible constructs for market size that are conceptually suggested in Figure 5.1, I test C_x^v, U_N^v, and, U_x^v as substitutes for C_N^v. The empirical evidence for the traditional IIH setup is clear in all case but becomes generally mixed and inconclusive when heterogeneity variables are included.

7.2.5 ALTERING SIZE VARIABLE VALUE BASIS

In addition to drug spend, I test several additional value bases for market size, including. total healthcare spend (see Table 7.13, Table 7.16, Table 7.19), provider spend, provider + drug spend, and income. The motivation for these additional value bases is to explore the more accurate quantification of "market need." And second, in the event that drug spend suffers from time series serial correlation despite the use of lagged variables, alternative size values may serve as relevant instruments.

I do not observe any new or overwhelmingly unexpected results and in general my confirmatory baseline estimation results continue to hold under these alternatives with strongly significant results achieved with market size being measure by total healthcare spend.

7.2.6 ALTERING HETEROGENEITY VARIABLES

Next, I examine the sensitivity of my results to changes in variable construction and variable input choices. This includes testing HHI-framed measures of heterogeneity and directly substituting

[63] ICD9 group codes 3.001 to 3.016 covering ICD9 3-digit codes 001 to 139.
[64] This is motivated by A&L[2004] excluding antibiotics from their analysis in order to achieve reportable results.

alternative variables such as using FLUSHT (whether the survey respondent had received a flu shot within the past year) in place of CHECK. Such alterations do not produce any noteworthy or compellingly different results from baseline with respect to my testable hypotheses.

7.2.7 ALTERING HETEROGENEITY VARIABLE VALUE BASIS

My base measurement unit for my heterogeneity variables is income dollars (or income dollars squared, depending on the construction). So as a robustness check, I also test measurement units such as population headcount and total health care expenses. These results remain consistent with baseline estimates.

7.2.8 ALTERING ESTIMATION MODELS

I also re-run my base specifications with OLS and negative binomial regression, the latter employing three different options: pooling with robust errors, pooling with cluster-robust errors, and fixed effects.[65] Table 7.32, which provides a summery comparison of size coefficients across regression models, shows that my baseline results (coefficients and significance levels) are mostly preserved across regression models and innovation measure types. The only notable exception is how all three negative binomial models perform when the innovation measure type is defined by new molecular entities.

While the Negative Binomial, particularly with cluster-robust errors, appears to perform just as well if not better than Poisson fixed effects[66] possibly due to its ability to handle data over-dispersion, general fit statistics still favor the reporting and interpretation of Poisson results.

[65] xtnbreg command in STATA
[66] xtpoisson, fe vce(robust) command in STATA

7.3 SUMMARY OF KEY FINDINGS

1. The inducement effect of aggregate market size on approved NDA-indications for all chemical types with baseline controls is 3.40% (1% significance level) and ranges from 2.21% (NDA-indication-product counts for new molecular entities) to 6.49% (NDA-indication counts for new molecular entities) across different innovation measure types..

2. Inclusion of heterogeneity variables results in the size effect decreasing to 1.98% on all approved NDA-indications with baseline controls (10% significance level), which is confirmatory of my Research Question #2.

3. The market heterogeneity characteristic, CHECK and RACE, appear to be the most consistently and statistically significant heterogeneity constructs exerting an inducement effect in an eIIH setup.

4. The models with the best fit statistics appear to incorporate some measure of M*HET ("controlled market") as the lone variable for market size, rather than rely on distinct size and non-size variables.

5. The coefficient on size is consistently higher for "less innovative" drug innovations.

6. The inducement effect of market size is still sensitive to market size construct and innovation measure type.

7. The signs and significance of my heterogeneity coefficients vary widely according to specification and variable construction.

Table 7.1. Descriptive Statistics, Explanatory Variables

Note: All size values have been scaled down by a factor of 10^6.

Variable	Obs	Mean	Std. Dev.	Min	Max
MEPS Dataset					
Disease Market Categories	1612	3.076581	0.105719	3.001	3.9
Treated Market (Population)	1612	8057.2	13949.19	0	89126.23
Treated Market (Income)	1612	166213.6	289347.8	0	1719819
Treated Market (Drug Spend)	1612	7280.825	14362.37	0	109916.1
Treated Market (HC Spend)	1612	39368.79	70926.75	0	606045.5
Controlled Market (Population)	1612	3232.74	9951.238	0	89126.23
Controlled Market (Income)	1612	67203.74	208265.9	0	1685005
Controlled Market (Drug Spend)	1612	3197.415	10931.45	0	109916.1
Controlled Market (HC Spend)	1612	16413.74	51742.58	0	590039.8
Largest Treated Sub-market (Population)	1494	5222.531	9505.964	3.711748	69772.85
Largest Treated Sub-market (Income)	1494	106796.5	195516.8	0	1537021
Largest Treated Sub-market (Drug Spend)	1494	4619.556	9398.885	0	88928.77
Largest Treated Sub-market (HC Spend)	1494	23969.36	42571.15	0.8733848	361676
Largest Controlled Sub-market (Population)	1494	2112.76	6860.392	0	69772.85
Largest Controlled Sub-market (Income)	1494	43799.85	144091.2	0	1537021
Largest Controlled Sub-market (Drug Spend)	1494	2049.79	7282.117	0	88928.77
Largest Controlled Sub-market (HC Spend)	1494	10105.96	32142.83	0	361676
Heterogeneity (AGE)	1491	0.233894	0.296064	6.96E-09	1
Heterogeneity (RACE)	1491	0.637594	0.206717	3.96E-09	1
Heterogeneity (GENDER)	1491	0.208079	0.322358	2.04E-08	1
Heterogeneity (CHECKUP)	1488	0.405404	0.349963	3.69E-07	1
Year	1612	2002	3.742818	1996	2008
FDA Datatset					
Approved NDA Applications	316927	25523.58	21642.27	552	202379
Year	316927	1995.472	8.997143	1982	2012
ICD9 Disease Codes	293294	471.1706	257.6547	1	999
NDA Applications Per Market-Year	316927	1.015439	0.123291	1	2

Table 7.2. Poisson Fixed Effects, NDA-Indications Count for All Application Types

Dependent Variable: Count of Approved NDA-Indications for All Application Types
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0340***	0.0171*	0.0327***	0.0198*		
	(0.00839)	(0.00994)	(0.00849)	(0.0118)		
Size*Heterogeneity						
Controlled Market					0.0327**	0.0245**
					(0.0151)	(0.0119)
Largest Sub-Market		0.0263		0.0201		
		(0.0196)		(0.0211)		
Heterogeneity						
Age			0.00119	0.00102		0.00243
			(0.00603)	(0.00628)		(0.00923)
Race			0.0421**	0.0421**		0.0509
			(0.0189)	(0.0195)		(0.0482)
Gender			-0.00511	-0.00499		-0.00462
			(0.00495)	(0.00494)		(0.00840)
Checkup			0.0209*	0.0180		0.0394
			(0.0117)	(0.0120)		(0.0256)
Observations	299	299	299	299	213	213
AIC	1321.4	1322.6	1326.9	1328.4	843.4	849.0
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.3. Poisson Fixed Effects, NDA-Indication-Products Count for All Application Types

Dependent Variable: Count of Approved NDA-Indication-Products for All Application Types
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0282**	0.0335**	0.0287*	0.0314**		
	(0.0141)	(0.0149)	(0.0149)	(0.0153)		
Size*Heterogeneity						
Controlled Market					0.0279	0.0286
					(0.0193)	(0.0194)
Largest Sub-Market		-0.00787		-0.00409		
		(0.0262)		(0.0264)		
Heterogeneity						
Age			0.00200	0.00202		0.00201
			(0.00806)	(0.00803)		(0.0113)
Race			0.0223	0.0223		0.00979
			(0.0216)	(0.0214)		(0.0511)
Gender			-0.000535	-0.000566		0.00843
			(0.00967)	(0.00967)		(0.0123)
Checkup			-0.0193	-0.0187		0.00682
			(0.0174)	(0.0177)		(0.0321)
Observations	299	299	299	299	213	213
AIC	1564.1	1566.0	1570.7	1572.7	1005.1	1012.1
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on product codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.4. Poisson Fixed Effects, NDA-Indication-Documents Count for All Application Types

Dependent Variable: Count of Approved NDA-Indication-Documents for All Application Types
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0649***	0.0399**	0.0634***	0.0458**		
	(0.0150)	(0.0156)	(0.0163)	(0.0195)		
Size*Heterogeneity						
Controlled Market					0.0666**	0.0553***
					(0.0259)	(0.0190)
Largest Sub-Market		0.0363		0.0258		
		(0.0229)		(0.0239)		
Heterogeneity						
Age			-0.00436	-0.00451		0.000545
			(0.00679)	(0.00695)		(0.00849)
Race			0.0195	0.0194		-0.00210
			(0.0241)	(0.0248)		(0.0384)
Gender			-0.00338	-0.00325		-0.00752
			(0.00402)	(0.00414)		(0.00684)
Checkup			0.0442***	0.0404***		0.0734***
			(0.0148)	(0.0151)		(0.0270)
Observations	299	299	299	299	213	213
AIC	1332.3	1332.9	1336.3	1337.6	853.3	855.9
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on N-type document codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.5. Poisson Fixed Effects, NDA-Indications Count for New Drugs

Dependent Variable: Count of Approved NDA-Indications for New Drugs
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0285**	0.00645	0.0267**	0.0118		
	(0.0126)	(0.0128)	(0.0135)	(0.0157)		
Size*Heterogeneity						
Controlled Market					0.0358***	0.0244**
					(0.0138)	(0.0103)
Largest Sub-Market		0.0342**		0.0233		
		(0.0156)		(0.0163)		
Heterogeneity						
Age			0.000113	-0.0000878		0.00172
			(0.00628)	(0.00645)		(0.0107)
Race			0.0118	0.0119		0.0336
			(0.0165)	(0.0170)		(0.0438)
Gender			-0.00271	-0.00256		-0.00169
			(0.00476)	(0.00476)		(0.00859)
Checkup			0.0427***	0.0394***		0.0764**
			(0.0147)	(0.0147)		(0.0324)
Observations	299	299	299	299	213	213
AIC	1292.9	1293.8	1297.4	1298.9	826.7	830.0
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.6. Poisson Fixed Effects, NDA-Indication-Products Count for New Drugs

Dependent Variable: Count of Approved NDA-Indication-Products for New Drugs
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size: disease spend						
log M(disease-treated)	0.0264*	0.0147	0.0274	0.0198		
	(0.0158)	(0.0191)	(0.0171)	(0.0220)		
Size*Heterogeneity						
Controlled Market					0.0484***	0.0439***
					(0.0147)	(0.0131)
Largest Sub-Market		0.0174		0.0113		
		(0.0209)		(0.0220)		
Heterogeneity						
Age			-0.000371	-0.000437		-0.00103
			(0.00657)	(0.00667)		(0.0116)
Race			0.00486	0.00477		0.0121
			(0.0185)	(0.0185)		(0.0465)
Gender			0.00226	0.00233		0.0152
			(0.00904)	(0.00900)		(0.0132)
Checkup			0.0254	0.0239		0.0695**
			(0.0161)	(0.0163)		(0.0328)
Observations	299	299	299	299	213	213
AIC	1479.1	1480.6	1485.3	1487.1	956.4	958.1
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on product codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.7. Poisson Fixed Effects, NDA-Indication-Documents Count for New Drugs

Dependent Variable: Count of Approved NDA-Indication-Documents for New Drugs
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0501**	0.0191	0.0478**	0.0274		
	(0.0207)	(0.0177)	(0.0234)	(0.0229)		
Size*Heterogeneity						
Controlled Market					0.0628***	0.0474***
					(0.0199)	(0.0116)
Largest Sub-Market		0.0466***		0.0311*		
		(0.0178)		(0.0165)		
Heterogeneity						
Age			-0.00224	-0.00245		0.00264
			(0.00593)	(0.00604)		(0.00813)
Race			0.00653	0.00680		-0.00334
			(0.0242)	(0.0251)		(0.0431)
Gender			-0.00101	-0.000802		-0.00315
			(0.00439)	(0.00447)		(0.00660)
Checkup			0.0650***	0.0605***		0.115***
			(0.0191)	(0.0191)		(0.0332)
Observations	299	299	299	299	213	213
AIC	1270.3	1270.5	1272.2	1273.4	818.5	817.2
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001
Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on N-type document codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.8. Poisson Fixed Effects, NDA-Indications Count for New Molecular Entities

Dependent Variable: Count of Approved NDA-Indications for New Molecular Entities
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0649	0.0517	0.0467	0.0427		
	(0.0601)	(0.0633)	(0.0505)	(0.0576)		
Size*Heterogeneity						
Controlled Market					0.0517	0.0133
					(0.0580)	(0.0456)
Largest Sub-Market		0.0194		0.00631		
		(0.0383)		(0.0393)		
Heterogeneity						
Age			-0.00580	-0.00585		-0.0140
			(0.0159)	(0.0159)		(0.0254)
Race			0.0829	0.0834		0.0788
			(0.0545)	(0.0548)		(0.101)
Gender			0.00423	0.00425		-0.0118
			(0.0157)	(0.0157)		(0.0195)
Checkup			0.0730*	0.0721		0.160
			(0.0434)	(0.0446)		(0.107)
Observations	276	276	276	276	204	204
AIC	833.7	835.6	840.1	842.1	563.1	568.3
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.9. Poisson Fixed Effects, NDA-Indication-Products Count for New Molecular Entities

Dependent Variable: Count of Approved NDA-Indication-Products for New Molecular Entities
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0221	0.00657	0.0120	0.00331		
	(0.0655)	(0.0753)	(0.0616)	(0.0720)		
Size*Heterogeneity						
Controlled Market					0.0808	0.0420
					(0.0543)	(0.0502)
Largest Sub-Market		0.0208		0.0123		
		(0.0512)		(0.0522)		
Heterogeneity						
Age			-0.0177	-0.0178		-0.0268
			(0.0162)	(0.0162)		(0.0233)
Race			0.0543	0.0550		0.0784
			(0.0890)	(0.0900)		(0.131)
Gender			0.00840	0.00841		0.00756
			(0.0135)	(0.0135)		(0.0203)
Checkup			0.0706	0.0691		0.220**
			(0.0480)	(0.0486)		(0.0915)
Observations	276	276	276	276	204	204
AIC	1023.0	1024.9	1028.6	1030.6	706.3	706.3
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on product codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.10. Poisson Fixed Effects, NDA-Indication-Documents Count for New Molecular Entities

Dependent Variable: Count of Approved NDA-Indication-Documents for New Molecular Entities
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	-0.0849	-0.124	-0.0870*	-0.111		
	(0.0592)	(0.0778)	(0.0491)	(0.0676)		
Size*Heterogeneity						
Controlled Market					0.0375	0.0351
					(0.0540)	(0.0513)
Largest Sub-Market		0.0481		0.0307		
		(0.0449)		(0.0447)		
Heterogeneity						
Age			-0.00389	-0.00416		-0.0155
			(0.0167)	(0.0166)		(0.0183)
Race			0.101	0.103		0.0468
			(0.106)	(0.105)		(0.0929)
Gender			0.0413**	0.0411**		0.0169
			(0.0197)	(0.0199)		(0.0199)
Checkup			0.0839	0.0804		0.0374
			(0.0550)	(0.0561)		(0.0797)
Observations	262	262	262	262	193	193
AIC	768.2	770.0	772.0	773.9	512.0	519.4
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on N-type document codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.11. Poisson Fixed Effects, NDA-Indications Count for All Application Types, With Orphan Drugs

Dependent Variable: Count of Approved NDA-Indications for All Application Types, With Orphan Drugs
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(VII)	(VIII)	(IX)	(X)	(XI)	(XII)
Size						
Treated Market	0.0344***	0.0200**	0.0338***	0.0231**		
	(0.00815)	(0.00925)	(0.00842)	(0.0114)		
Size*Heterogeneity						
Controlled Market					0.0310**	0.0230**
					(0.0136)	(0.0110)
Largest Sub-Market		0.0225		0.0168		
		(0.0205)		(0.0224)		
Heterogeneity						
Age			0.000641	0.000497		0.00207
			(0.00637)	(0.00661)		(0.00931)
Race			0.0427**	0.0428**		0.0619
			(0.0192)	(0.0197)		(0.0491)
Gender			-0.00381	-0.00370		-0.00339
			(0.00474)	(0.00472)		(0.00805)
Checkup			0.0199*	0.0175		0.0380
			(0.0110)	(0.0115)		(0.0250)
Observations	299	299	299	299	213	213
AIC	1325.5	1326.9	1331.2	1332.9	844.9	850.5
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	include	include	include	include	include	include

* significant at p=0.1; ** at p=0.05; *** at p=0.001
Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.12. Poisson Fixed Effects, NDA-Indications Count for All Application Types, With Full ICD9

Dependent Variable: Count of Approved NDA-Indications for All Application Types, With Full ICD9
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0352***	0.0223**	0.0334***	0.0237*		
	(0.00832)	(0.0114)	(0.00830)	(0.0124)		
Size*Heterogeneity						
Controlled Market					0.0307**	0.0210*
					(0.0139)	(0.0111)
Largest Sub-Market		0.0201		0.0154		
		(0.0196)		(0.0207)		
Heterogeneity						
Age			0.00242	0.00228		0.00112
			(0.00592)	(0.00612)		(0.00887)
Race			0.0429**	0.0434**		0.0598
			(0.0177)	(0.0181)		(0.0411)
Gender			-0.00413	-0.00404		-0.00417
			(0.00503)	(0.00502)		(0.00824)
Checkup			0.0188*	0.0168		0.0414*
			(0.0111)	(0.0114)		(0.0248)
Observations	339	339	339	339	243	243
AIC	1462.1	1463.6	1467.6	1469.3	934.9	940.2
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001
Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.13. Poisson Fixed Effects, NDA-Indications Count for All Application Types, HC Spend

Dependent Variable: Count of Approved NDA-Indications for All Application Types
Dependent Variable Basis: Health Care Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0448***	0.0262*	0.0455***	0.0327***		
	(0.0130)	(0.0136)	(0.0119)	(0.0126)		
Size*Heterogeneity						
Controlled Market					0.0376**	0.0264*
					(0.0154)	(0.0145)
Largest Sub-Market		0.0247		0.0171		
		(0.0172)		(0.0170)		
Heterogeneity						
Age			0.000610	0.000589		0.00161
			(0.00604)	(0.00624)		(0.00934)
Race			0.0467**	0.0456**		0.0517
			(0.0200)	(0.0203)		(0.0484)
Gender			-0.00664	-0.00601		-0.00558
			(0.00507)	(0.00505)		(0.00835)
Checkup			0.0190	0.0171		0.0400
			(0.0118)	(0.0118)		(0.0253)
Observations	299	299	299	299	213	213
AIC	1321.2	1322.4	1326.4	1328.0	843.7	849.2
Size basis	health care spend	health care spend	health care spend	health care spend		
Size*Het basis		income		income	health care spend, provider visits, non-work days	health care spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.14. Poisson Fixed Effects, NDA-Indications Count for New Drugs, With Orphan Drugs

Dependent Variable: Count of Approved NDA-Indications for Drugs, With Orphan Drugs
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(VII)	(VIII)	(IX)	(X)	(XI)	(XII)
Size						
Treated Market	0.0286***	0.00885	0.0276**	0.0141		
	(0.0109)	(0.0121)	(0.0126)	(0.0150)		
Size*Heterogeneity						
Controlled Market					0.0322**	0.0211*
					(0.0127)	(0.0108)
Largest Sub-Market		0.0310*		0.0214		
		(0.0160)		(0.0173)		
Heterogeneity						
Age			-0.000381	-0.000571		0.00149
			(0.00646)	(0.00666)		(0.0109)
Race			0.0133	0.0135		0.0457
			(0.0172)	(0.0176)		(0.0441)
Gender			-0.00171	-0.00157		-0.000850
			(0.00456)	(0.00455)		(0.00822)
Checkup			0.0387***	0.0357**		0.0734**
			(0.0139)	(0.0141)		(0.0321)
Observations	299	299	299	299	213	213
AIC	1295.5	1296.6	1300.7	1302.2	827.5	830.9
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	include	include	include	include	include	include

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.15. Poisson Fixed Effects, NDA-Indications Count for New Drugs, With Full ICD9

Dependent Variable: Count of Approved NDA-Indications for New Drugs, With Full ICD9
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0272**	0.0109	0.0245**	0.0142		
	(0.0118)	(0.0136)	(0.0125)	(0.0156)		
Size*Heterogeneity						
Controlled Market					0.0319**	0.0191*
					(0.0131)	(0.0115)
Largest Sub-Market		0.0256		0.0165		
		(0.0157)		(0.0161)		
Heterogeneity						
Age			0.00148	0.00132		0.000353
			(0.00617)	(0.00630)		(0.0103)
Race			0.0107	0.0112		0.0371
			(0.0161)	(0.0163)		(0.0384)
Gender			-0.00218	-0.00208		-0.00213
			(0.00482)	(0.00482)		(0.00844)
Checkup			0.0389***	0.0369***		0.0737**
			(0.0139)	(0.0140)		(0.0314)
Observations	339	339	339	339	243	243
AIC	1429.2	1430.5	1434.0	1435.7	915.2	918.6
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.16. Poisson Fixed Effects, NDA-Indications Count for New Drugs, HC Spend

Dependent Variable: Count of Approved NDA-Indications for New Drugs, HC Spend
Dependent Variable Basis: Health Care Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0393***	0.0163	0.0363***	0.0207		
	(0.0132)	(0.0166)	(0.0139)	(0.0163)		
Size*Heterogeneity						
Controlled Market					0.0490***	0.0330**
					(0.0175)	(0.0163)
Largest Sub-Market		0.0307**		0.0210		
		(0.0154)		(0.0144)		
Heterogeneity						
Age			-0.000311	-0.000356		0.000739
			(0.00629)	(0.00644)		(0.0108)
Race			0.0155	0.0142		0.0331
			(0.0168)	(0.0171)		(0.0445)
Gender			-0.00398	-0.00320		-0.00259
			(0.00476)	(0.00479)		(0.00851)
Checkup			0.0411***	0.0388***		0.0759**
			(0.0149)	(0.0147)		(0.0322)
Observations	299	299	299	299	213	213
AIC	1292.6	1293.6	1297.2	1298.8	826.4	829.9
Size basis	health care spend	health care spend	health care spend	health care spend		
Size*Het basis		income		income	health care spend, provider visits, non-work days	health care spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.17. Poisson Fixed Effects, NDA-Indications Count for NMEs, With Orphan Drugs

Dependent Variable: Count of Approved NDA-Indications for New Molecular Entities, With Orphan Drugs
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(VII)	(VIII)	(IX)	(X)	(XI)	(XII)
Size						
Treated Market	0.0474	0.0385	0.0264	0.0281		
	(0.0597)	(0.0631)	(0.0499)	(0.0570)		
Size*Heterogeneity						
Controlled Market					0.0359	-0.000856
					(0.0566)	(0.0451)
Largest Sub-Market		0.0128		-0.00255		
		(0.0381)		(0.0396)		
Heterogeneity						
Age			-0.00613	-0.00610		-0.0159
			(0.0165)	(0.0165)		(0.0247)
Race			0.0914	0.0912		0.115
			(0.0608)	(0.0610)		(0.102)
Gender			0.00368	0.00367		-0.0110
			(0.0151)	(0.0151)		(0.0192)
Checkup			0.0813*	0.0817*		0.163
			(0.0441)	(0.0453)		(0.105)
Observations	276	276	276	276	204	204
AIC	838.9	840.9	844.9	846.9	564.7	569.6
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	include	include	include	include	include	include

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.18. Poisson Fixed Effects, NDA-Indications Count for NMEs, With Full ICD9

Dependent Variable: Count of Approved NDA-Indications for New Molecular Entities, With Full ICD9
Dependent Variable Basis: Drug Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0765	0.0582	0.0570	0.0467		
	(0.0557)	(0.0585)	(0.0464)	(0.0536)		
Size*Heterogeneity						
Controlled Market					0.0555	0.0152
					(0.0541)	(0.0420)
Largest Sub-Market		0.0274		0.0166		
		(0.0370)		(0.0382)		
Heterogeneity						
Age			-0.00532	-0.00549		-0.0116
			(0.0153)	(0.0154)		(0.0249)
Race			0.0770	0.0787		0.0637
			(0.0483)	(0.0489)		(0.0844)
Gender			0.00447	0.00451		-0.0119
			(0.0157)	(0.0158)		(0.0195)
Checkup			0.0703*	0.0680		0.150
			(0.0411)	(0.0422)		(0.1000)
Observations	304	304	304	304	226	226
AIC	893.0	894.9	899.5	901.4	604.3	609.7
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.19. Poisson Fixed Effects, NDA-Indications Count for New Molecular Entities, HC Spend

Dependent Variable: Count of Approved NDA-Indications for New Molecular Entities
Dependent Variable Basis: Health Care Spend
Regression: Poisson with Fixed Effect Controls (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.135**	0.137**	0.121**	0.133**		
	(0.0621)	(0.0665)	(0.0579)	(0.0641)		
Size*Heterogeneity						
Controlled Market					0.101	0.0676
					(0.0674)	(0.0555)
Largest Sub-Market		-0.00262		-0.0173		
		(0.0407)		(0.0388)		
Heterogeneity						
Age			-0.00723	-0.00718		-0.0151
			(0.0156)	(0.0155)		(0.0247)
Race			0.0975*	0.0975*		0.0896
			(0.0551)	(0.0551)		(0.103)
Gender			0.00135	0.000759		-0.0119
			(0.0155)	(0.0151)		(0.0198)
Checkup			0.0652	0.0679		0.147
			(0.0436)	(0.0448)		(0.105)
Observations	276	276	276	276	204	204
AIC	832.7	834.7	839.2	841.2	562.4	567.9
Size basis	health care spend	health care spend	health care spend	health care spend		
Size*Het basis		income		income	health care spend, provider visits, non-work days	health care spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 8.

Table 7.20. Negative Binomial Pooled, NDA-Indications Count for All Application Types

Dependent Variable: Count of Approved NDA-Indications for All Application Types
Dependent Variable Basis: Drug Spend
Regression: Negative Binomial Pooled (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0344***	0.0200*	0.0338***	0.0231*		
	(0.0101)	(0.0115)	(0.0103)	(0.0128)		
Size*Heterogeneity						
Controlled Market					0.0310***	0.0230***
					(0.0103)	(0.00853)
Largest Sub-Market		0.0225		0.0168		
		(0.0168)		(0.0179)		
Heterogeneity						
Age			0.000641	0.000497		0.00207
			(0.00470)	(0.00482)		(0.00690)
Race			0.0427***	0.0428***		0.0619*
			(0.0160)	(0.0161)		(0.0366)
Gender			-0.00381	-0.00370		-0.00339
			(0.00382)	(0.00378)		(0.00636)
Checkup			0.0199*	0.0175		0.0380*
			(0.0105)	(0.0109)		(0.0208)
Observations	300	300	300	300	217	217
AIC	2054.9	2054.3	2060.5	2062.2	1522.0	1521.6
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White robust standard errors are reported in parentheses. Model is estimated with STATA nbreg option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 7.

Table 7.21. Negative Binomial Pooled, NDA-Indications Count for New Drugs

Dependent Variable: Count of Approved NDA-Indications for Drugs
Dependent Variable Basis: Drug Spend
Regression: Negative Binomial Pooled (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0286***	0.00885	0.0276**	0.0141		
	(0.0107)	(0.0105)	(0.0110)	(0.0127)		
Size*Heterogeneity						
Controlled Market					0.0322***	0.0211**
					(0.0103)	(0.00881)
Largest Sub-Market		0.0310**		0.0214		
		(0.0135)		(0.0146)		
Heterogeneity						
Age			-0.000381	-0.000574		0.00149
			(0.00507)	(0.00516)		(0.00806)
Race			0.0133	0.0135		0.0457
			(0.0165)	(0.0167)		(0.0353)
Gender			-0.00171	-0.00157		-0.000851
			(0.00376)	(0.00374)		(0.00646)
Checkup			0.0387***	0.0357***		0.0734***
			(0.0120)	(0.0121)		(0.0259)
Observations	300	300	300	300	217	217
AIC	2011.1	2012.2	2018.3	2021.8	1489.4	1496.8
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White robust standard errors are reported in parentheses. Model is estimated with STATA nbreg option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 7.

Table 7.22. Negative Binomial Pooled, NDA-Indications Count for New Molecular Entities

Dependent Variable: Count of Approved NDA-Indications for New Molecular Entities
Dependent Variable Basis: Drug Spend
Regression: Negative Binomial Pooled (1996-2011)

	(I)	(II)	(III)	(IV)	(V)	(VI)
Size						
Treated Market	0.0474	0.0385	0.0265	0.0281		
	(0.0500)	(0.0514)	(0.0445)	(0.0479)		
Size*Heterogeneity						
Controlled Market					0.0359	-0.000856
					(0.0450)	(0.0383)
Largest Sub-Market		0.0128		-0.00255		
		(0.0347)		(0.0360)		
Heterogeneity						
Age			-0.00613	-0.00610		-0.0159
			(0.0137)	(0.0137)		(0.0213)
Race			0.0914*	0.0912*		0.115
			(0.0520)	(0.0519)		(0.0944)
Gender			0.00368	0.00367		-0.0110
			(0.0119)	(0.0119)		(0.0148)
Checkup			0.0814*	0.0817*		0.163*
			(0.0434)	(0.0443)		(0.0892)
Observations	276	276	276	276	205	205
AIC	1402.5	1404.5	1408.5	1410.5	1090.8	1097.7
Size basis	drug spend	drug spend	drug spend	drug spend		
Size*Het basis		income		income	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis			income	income		income
Orphan drugs	exclude	exclude	exclude	exclude	exclude	exclude

* significant at p=0.1; ** at p=0.05; *** at p=0.001
Notes: Huber-White robust standard errors are reported in parentheses. Model is estimated with STATA nbreg option. Dependent count variable is based on NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Market size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Heterogeneity constructs are unit-free concentration measures. All specifications include disease market and time period dummies. Details in Chapter 7.

Table 7.23. Summary of Poisson Fixed Effects, Base Specification for All Application Types

Dependent Variable: Counts for All Application Types
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

	NDA-Indications		NDA-Indication-Products		NDA-Indication-Documents	
	(I)	(IV)	(I)	(IV)	(I)	(IV)
Size						
Treated Market	0.0340***	0.0198*	0.0282**	0.0314**	0.0649***	0.0458**
	(0.00839)	(0.0118)	(0.0141)	(0.0153)	(0.0150)	(0.0195)
Size*Heterogeneity						
Largest Sub-Market		0.0201		-0.00409		0.0258
		(0.0211)		(0.0264)		(0.0239)
Heterogeneity						
Age		0.00102		0.00202		-0.00451
		(0.00628)		(0.00803)		(0.00695)
Race		0.0421**		0.0223		0.0194
		(0.0195)		(0.0214)		(0.0248)
Gender		-0.00499		-0.000566		-0.00325
		(0.00494)		(0.00967)		(0.00414)
Checkup		0.0180		-0.0187		0.0404***
		(0.0120)		(0.0177)		(0.0151)
Observations	299	299	299	299	299	299
AIC	1321.4	1328.4	1564.1	1572.7	1332.3	1337.6
Size basis	drug spend	drug spend	drug spend	drug spend	drug spend	drug spend
Size*Het basis		income		income		income
Het basis		income		income		income

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is either based on raw counts, product codes or N-type document codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Size*Heterogeneity and Heterogeneity constructs are unit-free concentration measures based on income. All specifications include disease market and time period dummies. Details in Chapter 7.

Table 7.24. Summary of Poisson Fixed Effects, Base Specification for New Drugs

Dependent Variable: Counts for New Drugs
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

	NDA-Indications		NDA-Indication-Products		NDA-Indication-Documents	
	(I)	(IV)	(I)	(IV)	(I)	(IV)
Size						
Treated Market	0.0285**	0.0118	0.0264*	0.0198	0.0501**	0.0274
	(0.0126)	(0.0157)	(0.0158)	(0.0220)	(0.0207)	(0.0229)
Size*Heterogeneity						
Largest Sub-Market		0.0233		0.0113		0.0311*
		(0.0163)		(0.0220)		(0.0165)
Heterogeneity						
Age		-0.0000878		-0.000437		-0.00245
		(0.00645)		(0.00667)		(0.00604)
Race		0.0119		0.00477		0.00680
		(0.0170)		(0.0185)		(0.0251)
Gender		-0.00256		0.00233		-0.000802
		(0.00476)		(0.00900)		(0.00447)
Checkup		0.0394***		0.0239		0.0605***
		(0.0147)		(0.0163)		(0.0191)
Observations	299	299	299	299	299	299
AIC	1292.9	1298.9	1479.1	1487.1	1270.3	1273.4
Size basis	drug spend	drug spend	drug spend	drug spend	drug spend	drug spend
Size*Het basis		income		income		income
Het basis		income		income		income

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is either based on raw counts, product codes or N-type document codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Size*Heterogeneity and Heterogeneity constructs are unit-free concentration measures based on income. All specifications include disease market and time period dummies. Details in Chapter 7.

Table 7.25. Summary of Poisson Fixed Effects, Base Specification for New Molecular Entities

Dependent Variable: Counts for New Molecular Entities
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

	NDA-Indications		NDA-Indication-Products		NDA-Indication-Documents	
	(I)	(IV)	(I)	(IV)	(I)	(IV)
Size						
Treated Market	0.0649	0.0427	0.0221	0.00331	-0.0849	-0.111
	(0.0601)	(0.0576)	(0.0655)	(0.0720)	(0.0592)	(0.0676)
Size*Heterogeneity						
Largest Sub-Market		0.00631		0.0123		0.0307
		(0.0393)		(0.0522)		(0.0447)
Heterogeneity						
Age		-0.00585		-0.0178		-0.00416
		(0.0159)		(0.0162)		(0.0166)
Race		0.0834		0.0550		0.103
		(0.0548)		(0.0900)		(0.105)
Gender		0.00425		0.00841		0.0411**
		(0.0157)		(0.0135)		(0.0199)
Checkup		0.0721		0.0691		0.0804
		(0.0446)		(0.0486)		(0.0561)
Observations	276	276	276	276	262	262
AIC	833.7	842.1	1023.0	1030.6	768.2	773.9
Size basis	drug spend	drug spend	drug spend	drug spend	drug spend	drug spend
Size*Het basis		income		income		income
Het basis		income		income		income

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is either based on raw counts, product codes or N-type document codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Size*Heterogeneity and Heterogeneity constructs are unit-free concentration measures based on income. All specifications include disease market and time period dummies. Details in Chapter 7.

Table 7.26. Summary of Poisson Fixed Effects, Alternative Specification for All Application Types

Dependent Variable: Counts for All Application Types
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

	NDA-Indications		NDA-Indication-Products		NDA-Indication-Documents	
	(V)	(VI)	(V)	(VI)	(V)	(VI)
Size*Heterogeneity						
Controlled Market	0.0327**	0.0245**	0.0279	0.0286	0.0666**	0.0553***
	(0.0151)	(0.0119)	(0.0193)	(0.0194)	(0.0259)	(0.0190)
Heterogeneity						
Age		0.00243		0.00201		0.000545
		(0.00923)		(0.0113)		(0.00849)
Race		0.0509		0.00979		-0.00210
		(0.0482)		(0.0511)		(0.0384)
Gender		-0.00462		0.00843		-0.00752
		(0.00840)		(0.0123)		(0.00684)
Checkup		0.0394		0.00682		0.0734***
		(0.0256)		(0.0321)		(0.0270)
Observations	213	213	213	213	213	213
AIC	843.4	849.0	1005.1	1012.1	853.3	855.9
Size*Het basis	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis		income		income		income

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is either based on raw counts, product codes or N-type document codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Size*Heterogeneity constructs are based on drug spend, provider visits, and missed work days. Heterogeneity constructs are unit-free concentration measures based on income. All specifications include disease market and time period dummies. Details in Chapter 7.

Table 7.27. Summary of Poisson Fixed Effects, Alternative Specification for New Drugs

Dependent Variable: Counts for New Drugs
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

	NDA-Indications		NDA-Indication-Products		NDA-Indication-Documents	
	(V)	(VI)	(V)	(VI)	(V)	(VI)
Size*Heterogeneity						
Controlled Market	0.0358***	0.0244**	0.0484***	0.0439***	0.0628***	0.0474***
	(0.0138)	(0.0103)	(0.0147)	(0.0131)	(0.0199)	(0.0116)
Heterogeneity						
Age		0.00172		-0.00103		0.00264
		(0.0107)		(0.0116)		(0.00813)
Race		0.0336		0.0121		-0.00334
		(0.0438)		(0.0465)		(0.0431)
Gender		-0.00169		0.0152		-0.00315
		(0.00859)		(0.0132)		(0.00660)
Checkup		0.0764**		0.0695**		0.115***
		(0.0324)		(0.0328)		(0.0332)
Observations	213	213	213	213	213	213
AIC	826.7	830.0	956.4	958.1	818.5	817.2
Size*Het basis	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis		income		income		income

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is either based on raw counts, product codes or N-type document codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Size*Heterogeneity constructs are based on drug spend, provider visits, and missed work days. Heterogeneity constructs are unit-free concentration measures based on income. All specifications include disease market and time period dummies. Details in Chapter 7.

Table 7.28. Summary of Poisson Fixed Effects, Alternative Specification for NMEs

Dependent Variable: Counts for New Molecular Entities
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

	NDA-Indications		NDA-Indication-Products		NDA-Indication-Documents	
	(V)	(VI)	(V)	(VI)	(V)	(VI)
Size*Heterogeneity						
Controlled Market	0.0517	0.0133	0.0808	0.0420	0.0375	0.0351
	(0.0580)	(0.0456)	(0.0543)	(0.0502)	(0.0540)	(0.0513)
Heterogeneity						
Age		-0.0140		-0.0268		-0.0155
		(0.0254)		(0.0233)		(0.0183)
Race		0.0788		0.0784		0.0468
		(0.101)		(0.131)		(0.0929)
Gender		-0.0118		0.00756		0.0169
		(0.0195)		(0.0203)		(0.0199)
Checkup		0.160		0.220**		0.0374
		(0.107)		(0.0915)		(0.0797)
Observations	204	204	204	204	193	193
AIC	563.1	568.3	706.3	706.3	512.0	519.4
Size*Het basis	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days	drug spend, provider visits, non-work days
Het basis		income		income		income

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Huber-White cluster-robust standard errors are reported in parentheses. Model is estimated with STATA xtpoisson with fe option. Dependent count variable is either based on raw counts, product codes or N-type document codes associated with NDA-indication approvals by ICD9-defined disease market groupings. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Size variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. Size*Heterogeneity constructs are based on drug spend, provider visits, and missed work days. Heterogeneity constructs are unit-free concentration measures based on income. All specifications include disease market and time period dummies. Details in Chapter 7.

Table 7.29. Summary of Size Coefficients for All Application Types, Poisson Fixed Effects

Dependent Variable: Counts for All Application Types
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

Regression Dataset	NDA-Indications		NDA-Indication-Products		NDA-Indication-Documents	
Size = "Treated Market"						
	(I)	(IV)	(I)	(IV)	(I)	(IV)
A. Drug Spend	0.0340***	0.0198*	0.0282**	0.0314**	0.0649***	0.0458**
	(0.00839)	(0.0118)	(0.0141)	(0.0153)	(0.0150)	(0.0195)
B. Drug Spend + Orphans	0.0352***	0.0258**	0.0298**	0.0381**	0.0610***	0.0445**
	(0.00803)	(0.0115)	(0.0146)	(0.0156)	(0.0133)	(0.0176)
C. Drug Spend + Full ICD9	0.0352***	0.0237*	0.0294**	0.0351**	0.0630***	0.0445**
	(0.00832)	(0.0124)	(0.0137)	(0.0162)	(0.0140)	(0.0176)
D. Health Care Spend	0.0448***	0.0327***	0.0430***	0.0533**	0.0730***	0.0480***
	(0.0130)	(0.0126)	(0.0167)	(0.0219)	(0.0159)	(0.0169)
Size*Heterogeneity = "Controlled Market"						
	(V)	(VI)	(V)	(VI)	(V)	(VI)
A. Drug Spend	0.0327**	0.0245**	0.0279	0.0286	0.0666**	0.0553***
	(0.0151)	(0.0119)	(0.0193)	(0.0194)	(0.0259)	(0.0190)
B. Drug Spend + Orphans	0.0282**	0.0188*	0.0246	0.0242	0.0588***	0.0468***
	(0.0127)	(0.0104)	(0.0173)	(0.0175)	(0.0208)	(0.0155)
C. Drug Spend + Full ICD9	0.0307**	0.0210*	0.0251	0.0248	0.0608***	0.0482***
	(0.0139)	(0.0111)	(0.0174)	(0.0175)	(0.0221)	(0.0163)
D. Health Care Spend	0.0376**	0.0264*	0.0438**	0.0429*	0.0788***	0.0649***
	(0.0154)	(0.0145)	(0.0213)	(0.0222)	(0.0204)	(0.0162)

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Cluster-robust standard errors are reported in parentheses. The four regression datasets refer to: (a) baseline; (b) baseline including orphan drugs; (c) baseline including full set of ICD9 groupings; (d) baseline with size measured by health care spend. "Treated market" represents total drug or health care spend. "Controlled market" represents spend for patients whose condition appears controlled as indicated by provider visits and missed work days. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. Details in Chapter 7.

Table 7.30. Summary of Size Coefficients for New Drugs, Poisson Fixed Effects

Dependent Variable: Counts for New Drugs
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

Regression Dataset	NDA-Indications		NDA-Indication-Products		NDA-Indication-Documents	
Size = "Treated Market"						
	(I)	(IV)	(I)	(IV)	(I)	(IV)
A. Drug Spend	0.0285**	0.0118	0.0264*	0.0198	0.0501**	0.0274
	(0.0126)	(0.0157)	(0.0158)	(0.0220)	(0.0207)	(0.0229)
B. Drug Spend + Orphans	0.0286***	0.0141	0.0251*	0.0207	0.0491**	0.0294
	(0.0109)	(0.0150)	(0.0141)	(0.0201)	(0.0200)	(0.0236)
C. Drug Spend + Full ICD9	0.0272**	0.0142	0.0234	0.0211	0.0470**	0.0280
	(0.0118)	(0.0156)	(0.0145)	(0.0209)	(0.0191)	(0.0219)
D. Health Care Spend	0.0393***	0.0207	0.0347**	0.0251	0.0513**	0.0159
	(0.0132)	(0.0163)	(0.0161)	(0.0208)	(0.0203)	(0.0209)
Size*Heterogeneity = "Controlled Market"						
	(V)	(VI)	(V)	(VI)	(V)	(VI)
A. Drug Spend	0.0358***	0.0244**	0.0484***	0.0439***	0.0628***	0.0474***
	(0.0138)	(0.0103)	(0.0147)	(0.0131)	(0.0199)	(0.0116)
B. Drug Spend + Orphans	0.0322**	0.0211*	0.0454***	0.0408***	0.0602***	0.0451***
	(0.0127)	(0.0108)	(0.0142)	(0.0132)	(0.0188)	(0.0113)
C. Drug Spend + Full ICD9	0.0319**	0.0191*	0.0407***	0.0346**	0.0564***	0.0399***
	(0.0131)	(0.0115)	(0.0140)	(0.0142)	(0.0172)	(0.0120)
D. Health Care Spend	0.0490***	0.0330**	0.0693***	0.0597***	0.0793***	0.0578***
	(0.0175)	(0.0163)	(0.0192)	(0.0191)	(0.0189)	(0.0170)

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Cluster-robust standard errors are reported in parentheses. The four regression datasets refer to: (a) baseline; (b) baseline including orphan drugs; (c) baseline including full set of ICD9 groupings; (d) baseline with size measured by health care spend. "Treated market" represents total drug or health care spend. "Controlled market" represents spend for patients whose condition appears controlled as indicated by provider visits and missed work days. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. Details in Chapter 7.

Table 7.31. Summary of Size Coefficients for New Molecular Entities, Poisson Fixed Effects

Dependent Variable: Counts for New Molecular Entities
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

Regression Dataset	NDA-Indications		NDA-Indication-Products		NDA-Indication-Documents	
Size = "Treated Market"						
	(I)	(IV)	(I)	(IV)	(I)	(IV)
A. Drug Spend	0.0649	0.0427	0.0221	0.00331	-0.0849	-0.111
	(0.0601)	(0.0576)	(0.0655)	(0.0720)	(0.0592)	(0.0676)
B. Drug Spend + Orphans	0.0474	0.0281	0.00247	-0.00734	-0.128*	-0.168**
	(0.0597)	(0.0570)	(0.0643)	(0.0697)	(0.0682)	(0.0788)
C. Drug Spend + Full ICD9	0.0765	0.0467	0.0358	0.0147	-0.0711	-0.0985*
	(0.0557)	(0.0536)	(0.0601)	(0.0667)	(0.0534)	(0.0584)
D. Health Care Spend	0.135**	0.133**	0.0395	0.0243	-0.0450	-0.0872
	(0.0621)	(0.0641)	(0.0626)	(0.0628)	(0.0674)	(0.0606)
Size*Heterogeneity = "Controlled Market"						
	(V)	(VI)	(V)	(VI)	(V)	(VI)
A. Drug Spend	0.0517	0.0133	0.0808	0.0420	0.0375	0.0351
	(0.0580)	(0.0456)	(0.0543)	(0.0502)	(0.0540)	(0.0513)
B. Drug Spend + Orphans	0.0359	-0.000856	0.0656	0.0279	-0.0237	-0.0225
	(0.0566)	(0.0451)	(0.0542)	(0.0502)	(0.0576)	(0.0549)
C. Drug Spend + Full ICD9	0.0555	0.0152	0.0838*	0.0429	0.0302	0.0265
	(0.0541)	(0.0420)	(0.0504)	(0.0471)	(0.0489)	(0.0472)
D. Health Care Spend	0.101	0.0676	0.105	0.0665	0.0185	0.0124
	(0.0674)	(0.0555)	(0.0650)	(0.0593)	(0.0496)	(0.0460)

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Cluster-robust standard errors are reported in parentheses. The four regression datasets refer to: (a) baseline; (b) baseline including orphan drugs; (c) baseline including full set of ICD9 groupings; (d) baseline with size measured by health care spend. "Treated market" represents total drug or health care spend. "Controlled market" represents spend for patients whose condition appears controlled as indicated by provider visits and missed work days. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. Details in Chapter 7.

Table 7.32. Summary of Size Coefficients, Base Specification Across Regression Models

Dependent Variable: Counts of NDA-Indications
Dependent Variable Basis: Drug Spend
Regression: Poisson Fixed Effects (1996-2011)

	NDA-Indication Counts					
Regression Model	For All Application Types		For New Molecular Entities		For New Drugs	
Treated Market	(I)	(IV)	(I)	(IV)	(I)	(IV)
Poisson FE, cluster	0.0340***	0.0198*	0.0649	0.0427	0.0285**	0.0118
	(0.00839)	(0.0118)	(0.0601)	(0.0576)	(0.0126)	(0.0157)
Neg Bin, robust	0.0344***	0.0231*	0.0474	0.0281	0.0286***	0.0141
	(0.0101)	(0.0128)	(0.0500)	(0.0479)	(0.0107)	(0.0127)
Neg Bin, cluster	0.0344***	0.0231**	0.0474	0.0281	0.0286***	0.0141
	(0.00820)	(0.0115)	(0.0601)	(0.0574)	(0.0110)	(0.0151)
Neg Bin FE	0.0365	0.0242	0.0366	0.0308	0.0310	0.0162
	(0.0233)	(0.0303)	(0.0927)	(0.111)	(0.0259)	(0.0331)
Controlled Market	(V)	(VI)	(V)	(VI)	(V)	(VI)
Poisson FE, cluster	0.0327**	0.0245**	0.0517	0.0133	0.0358***	0.0244**
	(0.0151)	(0.0119)	(0.0580)	(0.0456)	(0.0138)	(0.0103)
Neg Bin, robust	0.0310***	0.0230***	0.0359	-0.000856	0.0322***	0.0211**
	(0.0103)	(0.00853)	(0.0450)	(0.0383)	(0.0103)	(0.00881)
Neg Bin, cluster	0.0310**	0.0230**	0.0359	-0.000856	0.0322**	0.0211*
	(0.0137)	(0.0111)	(0.0570)	(0.0454)	(0.0128)	(0.0109)
Neg Bin FE	0.0345	0.0257	0.0490	-0.0169	0.0347	0.0240
	(0.0254)	(0.0259)	(0.0847)	(0.0868)	(0.0282)	(0.0282)

* significant at p=0.1; ** at p=0.05; *** at p=0.001

Notes: Standard errors are reported in parentheses. Model estimates are presented according to STATA regression commands in far-left column. Columns are labeled by dependent count measure associated with NDA approvals (including CDER-approved BLAs). Treated market represents drug spend by ICD9-defined disease market groupings. Controlled market represents drug spend for that portion of patients whose disease appear clinically controlled by drug treatment as defined by provider visits and missed work days cutoff statistics. Double-counting occurs for NDAs linked with multiple ICD9 codes in MEPS. All explanatory variables are calculated as logs measures. Size and Size*Heterogeneity variables are scaled measures of drug spending using three-year time periods and with a three-year lag of market size. All specifications include disease market and time period dummies. Details in Chapter 7.

CHAPTER 8.

DISCUSSION

8.1 DISCUSSION OF HYPOTHESES AND PREDICTIONS

Using Poisson count panel regression with a traditional IIH setup I find with strong statistical significance that a 1% increase in market size generally produces a 2%-6% increase in drug innovation output which is consistent with previously reported estimates. With an extended "Induced Innovation Hypothesis" (eIIH) setup where I attempt to account for market composition characteristics, I find preliminary but still confirmatory empirical evidence of the influence of both market size and market heterogeneity on innovation introduction rates. Specifically, I obtain coefficient estimates (with mixed statistical significance) in the 1%-4% range across innovation measure and innovation count types. Of note, the CHECKUP and RACE heterogeneity variables achieve statistical significance most consistently and with a positive sign supporting theoretical predictions. My results are relatively robust to changes in specification (e.g., choice of market heterogeneity variables and their constructs) and identification. While I was unable to convincingly show that inducement increases with heterogeneity but my evidence still suggests that non-size characteristics of market heterogeneity are possible omitted variables from prior IIH studies.

There are several additional observations of note. First, I observe that my size coefficients are generally significant when estimated alone and then lose some/all significance with addition of heterogeneity variables.[67] This may be indicative that there is a correlation between size and heterogeneity that could be confounding estimates.

[67] (despite an increase in R-squared with my OLS results and decrease in AIC/BIC goodness-of-fit test statistics with my Poisson results)

With regard to the reduction in the coefficient of market size with market heterogeneity included in model specification (Research Question #2), I am unable to test directly for significance given my maximum-likelihood identification strategy based on the Stata regression command xtpoisson. However, for indicative purposes, I employ two approaches based on using the -suest- and -khb- commands in Stata. The former is a post-estimation command which combines estimation results and allows for coefficient testing across models. However, -suest- could only work in the context of GLM regression (with log link and Poisson distribution). The latter command, -khb-, applies the KHB method[68] to compare the estimated coefficients between two nested non-linear probability models. As with -suest-, -khb- tests models of the GLM family but unfortunately is only experimental for Poisson estimation. By employing altered specification and identification strategies, I am able to use these commands to provide somewhat indicative evidence of the reduction in market size coefficient with the addition of market heterogeneity variables. I am cautious in trying to interpret this result as anything more than the fact that the specification with market heterogeneity generates empirical estimates that are more theoretically consistent than specifications without market heterogeneity.

Another observation of interest are the coefficient signs I obtain when using document count as my innovation entry measurement unit. My theoretical setup does not differentiate between innovation production and innovation activity. Instead, I follow the traditional IIH setup of relying on the presumption that attrition rates do not vary systematically by disease markets/sub-markets. This is why getting negative estimates for size with the document count measure is unexpected. It is inconsistent with innovation productivity being a proportionate downstream result of innovation activity. However, the negative coefficients on size in the full specification model may simply be reflecting the large extent to which innovation productivity (new entry) and innovation activity (“N” prefix documents) are correlated.

[68] Karlson et al. (2011)

It is noteworthy that alternative M*HET variables, particularly my controlled market construct, $C_N(v)$, support an eIIH setup as well as, if not better than, total drug spend. As alluded to earlier, this could be an indication that health care spend may be useful as an instrument in this context for drug spend if there are potential endogeneity issues between drug spend and innovation output have been under-addressed. The usefulness of the health care spend measure could also be indicating the merits of distinguishing market "unmet need" from market need size. This latter concept is also supported by the significant results I achieve with my M*HET variables.

8.2 THREATS TO VALIDITY

There are multiple possible threats to validity to consider.

From a simple data sourcing perspective, my results are susceptible to the weaknesses of the data generating process within MEPS such as the biases in how ICD9 codes are matched to survey answers on disease conditions, and the associated under-reporting issues likely with household representative self-reporting. Also, there is some unfortunate information loss in MEPS reporting its ICD9 variable as a 3-digit code instead of the 5-digit code that was originally recorded.

My research is also sensitive to data sufficiency concerns. My dataset examines a 15-year time period but given that it can take firms 5-10 years or longer to bring a drug compound to market, my dataset may not have enough longitudinal observations to distinguish inducement effects beyond that of basic market size. In future extensions of this research, I hope to increase my statistical power by adding surrogate observations such as pre-approval innovation rate data (e.g., drug compound counts in clinical trials).

Another set of validity threats involve my approach to dataset construction. First, the idiosyncrasies of my NDA-indication construct for measuring innovation counts may have confounding effects. Second, my reliance on using NDC 9-digit codes as my linking variable to

assign disease categories to my dependent variable dataset assumes there is no significant bias towards bigger (i.e., better-selling) drugs in the completeness of NDC coding in MEPS. Third, there is some arbitrariness in creating and using disease categorization based on ICD9 3-digit (versus 4-digit or 5-digit) codes to define my market categories.

A further set of threats to my results is the idiosyncrasies of how disease market categories get to be associated with my dependent and explanatory variables in my dataset. As mentioned earlier in this section, ambiguity can arise because of how disease conditions are reported by survey respondents and then coded by survey administrators. Further ambiguity arises when a single disease may have different ways of being reported/recorded as one or more 3-digit ICD9 codes. Also causing possible ambiguity is the practice of off-label prescribing which would explain how a drug that has only ever been approved for a single disease indication could be associated with multiple ICD9 disease codes in MEPS reporting.

Threats are also presented by the identification assumptions I make which may not rest on sufficient grounding. For example, my independence assumption between my DIS and PHYS heterogeneity variables may be more plausible for some disease conditions (e.g. infectious diseases) than for others (e.g. hereditary diseases). Also, I may inadvertently invoke endogeneity issues with my inclusion of DIS heterogeneity variables.

It is still possible that not controlling for number of compounds already in the market means that my use of lagged sales to measure market size is potentially biased since the more drugs already serving the market, the less the potential for new drugs.[69]

Additional threats include insufficient management of data dispersion; sub-optimally parameterized market heterogeneity measures; time-sensitive or disease market-sensitive probability of R&D success.

[69] Controls could include the number of on-patent compounds/formulations and number of generics with some consideration of their age, e.g., limiting to molecules approved since say 1960.

Finally, there may be merit to considering the role of market size growth instead of or in addition to absolute market size.

8.3 Study Limitations

There are several study limitations deserving of mention. First is my reliance on the MEPS data. As a result, my research period could only cover the specific 16-year time period from 1996 to 2011. Also, the MEPS data is left censored because the limited survey sample sizes results in the under-reporting of less prevalent and orphan diseases and drugs.

Next, I encountered substantive matching attrition in constructing my dataset. For instance, 13,848 out of 18,066 NDA applications were not associated with any chemical type coding in the Drugs@FDA database. I further encountered not insignificant attrition when linking NDC product codes with NDA numbers, especially for new molecular entities (my dataset contained 491 out of the 767 NMEs available for my time period).

CHAPTER 9.

FUTURE RESEARCH AND CONCLUSION

9.1 FUTURE RESEARCH

There are a number of ways to further refine and investigate the merits of an eIIH. For instance, a more comprehensive understanding of drug innovation entry may eventually require a fuller specification that includes for each market some measure(s) of drug stock quality (e.g., number of non-generic drugs, number of generic drugs, number of on-patent molecules/formulations, number of non-generic drugs approved since 1960, average age of drugs available) as well as of potential growth in a market (e.g., using a proxy such as the inverse of the number of drugs already in the market) since the more drugs (and/or drug products) already in the marke the greater the incremental benefit a new drug (and/or drug product) will have to provide to justify reimbursement and use.[70]

My research may also benefit from testing additional empirical constructs of market heterogeneity, including "directional" measures (especially for inherently ordered characteristics such as age) that could provide interpretative value in understanding and identifying those subpopulations that are under- (or over-) served.

Since the policy implications of my expected results are potentially quite broad-ranging, another extension of my research effort here would be to test how well an eIIH model can explain historical exogenous changes in market exclusivity (e.g. Waxman-Hatch), R&D tax credits (e.g. Orphan Drug Act), technology transfer restrictions (e.g. Bayh-Dole), etc. A particularly interesting policy initiative to study surrounds the effort to better address the biopharmaceutical needs of diverse sub-populations. For example, Section 115 of The Food and Drug Modernization Act of

[70] Special thanks to Patricia Danzon for raising these issues.

1997 requires the inclusion of women and minorities in clinical drug trials. In theory, this policy intervention could have either dis-incentivized drug innovation (e.g. by raising clinical development costs), incentivized drug innovation (e.g. by allowing firms to better differentiate their drugs for FDA approval and payer acceptance) or had no net impact (e.g. due to offsetting effects). Whether and how this FDA intervention and other diversity-driven regulatory measures have affected drug innovation are empirically addressable questions.

Also worthy of investigation for its policy implications might be my testing of additional measurement units of innovation entry such as counts of product strengths and counts of dosage forms. Furthermore, prospectively understanding the role of market preference characteristics in drug innovation could inform current debate in both investment and health care communities on the coming "revolution" in pharmacaogenomics and personalized medicines. The promise of pharmacogenomics, which studies the relationship between a patient's genetic makeup and his/her pharmacological response to a drug, is to eventually enable person-specific drug therapy.

To provide a more precise foundation for analyzing these policy issues, it may be worthwhile to revisit my theoretical setup to better understand the explanatory power of the levels of market size and market heterogeneity in inducing innovation versus the change in levels of market size and market heterogeneity.[71]

Finally, it would not be unreasonable to consider that my model setup and methodology may be generalized to examine demand-side determinants of new product innovation and innovativeness in technology markets beyond pharmaceuticals.

[71] Special thanks to Mark Pauly for raising this issue as food for thought.

9.2 CONCLUSIONS

1. Research Question #1: For a given market size, will the number of new drugs (and/or products associated with drug approvals) introduced be higher the more heterogeneously, or non-homogeneously, composed the population? I find evidence, with varying statistical significance, that output rates associated with drug innovation are influenced by market heterogeneity but not always in line with theoretical predictions.

2. Research Question #2: Does accounting for market heterogeneity produce market size estimates that are more consistent with theoretical predictions? I confirm that drug innovation rates are increasing in market size (with strong statistical significance) when controlling for market heterogeneity. The available statistical evidence also indicates that the magnitude of this size effect is more consistent with theoretical predictions. Thus, by overlooking market composition heterogeneity, prior empirical research likely over-estimated the effect of market size due to omitted variable bias.

3. My research results suggest an extended IIH may be able to provide a more theoretically consistent and informative inducement model than the traditional IIH across different innovation count measures. This could provide policy-makers with improved levers and strategies (e.g., setting FDA resourcing priorities) to incentivize drug innovation that targets under-served as well as un-served populations.

4. This study provides further empirical evidence that new drug product introductions across innovation measures and count types (e.g., me-too drugs) are economic responses of firms to market need/demand.

5. Given the sensitivity of my results to variations in specification as well as measurement constructs, follow-on research is warranted to better understand which market characteristics can induce which innovation count measures.

CHAPTER 10.

APPENDIX

10.1 INTUITION FOR SUPPLY-SIDE INDUCEMENT

Let M denote the size of a given market and let K_a denote the expected cost of a successful product innovation project where a is the number of product innovation attempts per project and a successful project produces one new product entry. If the nature of the product innovation process is such that product innovation attempts are independently and identically distributed – the probability of success for an attempt being denoted by p – then we can calculate $\mathrm{E}[\mathrm{K}_a] = \frac{F+a\cdot C}{\tau_a}$, where F is the fixed cost of the project, C is the marginal cost of each attempt, and $\tau_a = 1 - (1-p)^a$. So successful product innovation (i.e. product entry) is given by $\mathrm{N}_a = \frac{M}{\mathrm{E}[\mathrm{K}_a]} = \frac{M\cdot\tau_a}{F+a\cdot C}$. Now consider two markets with equal market size, M, where the structural attributes of one market only allow for $a = 1$ projects (one product innovation attempt per project) while the structural attributes of the other market only allow for $a = 2$ projects (two product innovation attempts per project). Then $\frac{\mathrm{N}_2}{\mathrm{N}_1} = \frac{\mathrm{E}[\mathrm{K}_1]}{\mathrm{E}[\mathrm{K}_2]} = \frac{\frac{F+C}{\tau_1}}{\frac{F+2\cdot C}{\tau_2}} = \frac{p(2-p)}{p}\cdot\frac{F+C}{F+2\cdot C} = (2-p)\cdot\left(1-\frac{1}{\frac{F}{C}+2}\right)$, which implies that $\mathrm{N}_2 \gtrless \mathrm{N}_1$ if and only if $\frac{F}{c} \gtrless \frac{p}{1-p}$. In other words, entry may increase or decrease in a depending on the relationship between the project's fixed-to-variable-cost ratio ($\frac{F}{c}$) and the attempt success odds $\left(\frac{p}{1-p}\right)$.[72]

[72] Referring to DiMasi et al. (2004) to estimate that F=$366M, C=$170M, p=0.125, and so deduce that the FVCR (2.15) is greater than the success odds (0.14), our prediction is that entry increases with the number of attempts in the case of pharmaceuticals. If the number of attempts possible per project is correlated with market size, this result suggests that prior empirical studies of induced pharmaceutical innovation (e.g. Acemoglu & Linn (2004)) predicated on a simple flow-through model of innovation (equivalent to the one-attempt-per-project case) may have yielded biased results by not controlling for number of attempts.

10.2 INTUITION FOR GENERAL INDUCEMENT

Consider two disease categories G_1 and G_2 with respective sizes M_1 and M_2 (without loss of generality, say $M_1 \geq M_2$). If G_1 and G_2 are sufficiently independent in their characteristics mixes, I describe them as being two differently homogeneous markets. If G_1 and G_2 share sufficient commonalities or dependencies in their characteristics mixes, I describe them as being two differently homogeneous or additively separable sub-markets of one larger heterogeneous market.[73] Figure 10.1 visually represents M_1 and M_2 on the x-axis and y-axis, respectively.

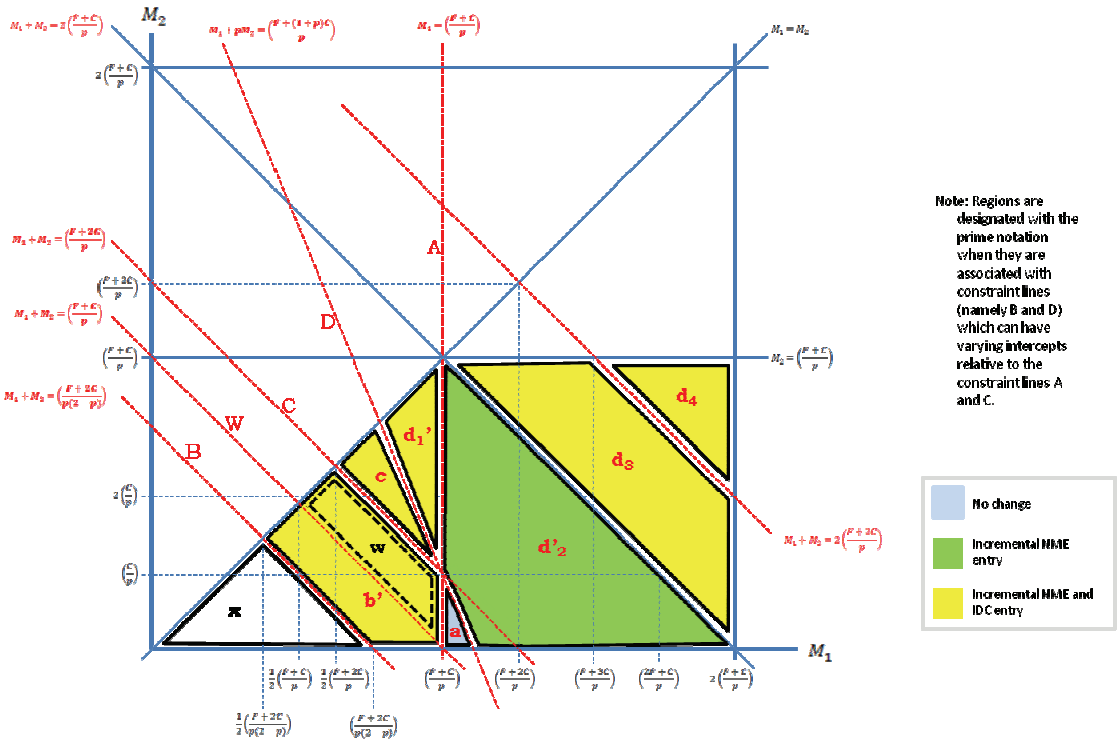


Figure 10.1: Intuition for General Inducement Effects

[73] Within this context, by "additively separable" I have the more strict definition of MECE (mutually exclusive and collectively exhaustive) in mind.

Strategy	E[Revenue]	E[Cost]	$M_1 + M_2 \geq$ Constraint	Region	no HET	with HET		HET Effect on Entry	
					E[# NMEs]	E[# NMEs]	E[# IDCs]	E[# NMEs]	E[# IDCs]
B	$p(2-p)M$ $=[1-(1-p)^2]M$	$F+2C$	$\frac{F+2C}{p(2-p)}$	**b'**	0	1	$\frac{2}{2-p}$	+1	$+\frac{p}{2-p}$
W	pM	$F+C$	$\frac{F+C}{p}$	**w**	0	1	1	+1	+1
A	pM_1	$F+C$	$\frac{F+C}{p}$	**a**	1	1	1		
C	pM $=p(M_1+M_2)$	$F+2C$	$\frac{F+2C}{p}$	**c**	0	1	$\frac{2}{2-p}$	+1	$+\frac{p}{2-p}$
D	$p(M_1+pM_2)$	$F+(1+p)C$	$\frac{F+(1+p)C}{p(M_1+pM_2)}$	$\mathbf{d'_1}$	0	1	$1+p$	+1	$+(1+p)$
				$\mathbf{d'_2}$	1	1	$1+p$		$+p$
				$\mathbf{d_3}$	1	2	2	+1	+1
				$\mathbf{d_4}$	1	2	$2(1+p)$	+1	$+(1+2p)$

Figure 10.2. Potential inducement effects of heterogeneity (from Figure 10.1)

Notes: Strategy A is the base scenario posited by the traditional Induced Innovation Hypothesis. E[# NMEs] refers to the expected number of new molecular entities; IDC refers to new approved indications

Consider the case where $M_1 < \frac{F+C}{p}$, which refers to the region bounded on the right side by constraint line A. This region is in fact also bounded above by the constraint line $M_1 = M_2$ because our setup assumes $M_1 \geq M_2$. Now when G_1 and G_2 are separately homogeneous groups, neither is large enough to incent or support innovation product entry. In other words, there is no new drug product entry when $\{M_1, M_2\}$ are located within the general triangular area composed by regions **x**, **b′**, **c**, and $\mathbf{d_1'}$.

However, when G_1 and G_2 are approached as differently homogeneous sub-groups of one larger heterogeneous group, they together can incent or support innovation product entry due to the possible sharing of fixed costs of entry for intra-firm projects. There are three such fixed-cost sharing strategies for the firm and these can give rise to the constraint lines C, D, and W in Figure 10.1. The first strategy – applicable to projects at market size combinations to the right of constraint line C (i.e., for $M_1 + M_2 \geq \frac{F+2C}{p}$) – is when simultaneous attempts are made with

each drug development project (i.e., for each new drug molecule candidate) to enter G_1 and G_2.[74] The second strategy – applicable to projects at market size combinations to the right of constraint line D (i.e., for $M_1 + pM_2 \geq \frac{F+(1+p)C}{p}$) – is when sequential attempts are made with each drug development project to enter G_1 and G_2 (i.e., an initial clinical trial is conducted for G_1 and, if successful, then an additional clinical is conducted for G_2). The third strategy – applicable to projects at market size combinations to the right of constraint line W (i.e., for $M_1 + M_2 \geq \frac{F+C}{p}$) – is when attempts are made with each drug development project to enter G_1 and G_2 but where G_1 and G_2 are treated as one joint group by firms and regulators, perhaps intentionally to create a market of sufficient size to offset the expected costs of entry. For completeness, it is worth noting that this last strategy is dominated – either partially or wholly – by the more dominant strategy applicable to drug development projects at market size combinations to the right of constraint line B (i.e., for $M_1 + M_2 \geq \frac{F+2C}{p(2-p)}$). This occurs when attempts are made with each drug development project to simultaneously enter G_1 and G_2 but where labeling approval in only one of the sub-groups ensures off-label use in (and therefore sales from) the other sub-group. The rationale here is that physicians are willing to use the closest alternative(s) in a situation where there are limited drug options. While the intercept of constraint line B may vary, note that the configuration shown in Figure 10.1 – where B appears as a lower bound relative to W – is reflective of empirical observation.[75] Also note that region $\mathbf{d_1'}$ is representatively distinct from region **c** because strategy D dominates strategy C – while both strategies yield the equivalent

[74] This is the same scenario as described in section 2a above.

[75] If the intercepts for B are greater than the intercepts for W depending on the values of p, F, and C, then **w** and **b′** will actually be distinct regions rather than **w** being a subset of **b′**. This occurs when $\frac{p}{1-p} > \frac{F}{C}$ but as already mentioned this is not empirically consistent with real-world observations.

inducement result with respect to new product entry, strategy D's effect on the number of indication approvals $(1 + p)$ is greater than strategy C's effect $(\frac{p}{2-p})$.[76]

Therefore, for the case of $M_1 < \frac{F+C}{p}$, when drug development projects can exploit G_1 and G_2 as separately homogeneous sub-groups rather than as one joint homogeneous group, the expected number of new product entries (i.e., new drug molecules) in the region composed of $\mathbf{b'}$ (inclusive of $\mathbf{w}$), $\mathbf{c}$, and $\mathbf{d_1'}$ increases from 0 to 1, while the expected number of new indication approvals increases from 0 to either $(\frac{p}{2-p})$ or $(1 + p)$.

Next, consider the alternative case of $\frac{F+C}{p} \leq M_1 < \frac{F+2C}{p}$, which is shown in Figure 10.1 as the region bounded on the left side by constraint line A and from above by the setup constraint of $M_2 < \frac{F+C}{p}$.[77] When G_1 and G_2 are separately homogeneous groups, the expected number of new product entries for projects targeting both groups is 1 because G_1 – and only G_1 – is large enough to incent or support innovation product entry regardless of firm strategy. However, when G_1 and G_2 are approached as differently homogeneous sub-groups, firms can pursue strategy D (as is described in the preceding sub-case of $M_1 < \frac{F+C}{p}$ and which dominates strategy C in the currently considered region) in order to exploit intra-project sharing of the fixed costs of entering G_1 and G_2. This then allows for incremental product entry in terms of both the expected number (i.e., 1) of new product entries as well as the expected number (i.e., 1) of new approved indications. In fact, the two additional threshold constraints, represented by $M_1 + M_2 \geq 2\left(\frac{F+C}{p}\right)$ and $M_1 + M_2 \geq$

[76] This holds because $\frac{p}{2-p} < (1 + p)$ if and only if, which is true.

[77] It is straightforward to see that all cases of the form $\frac{F+j\cdot C}{p} \leq M_1 < \frac{F+(j+1)\cdot C}{p}$ and $\frac{F+g\cdot C}{p} \leq M_2 < \frac{F+(g+1)\cdot C}{p}$ reduce to this case of *j*=1, *g*=0.

$2\left(\frac{F+2C}{p}\right)$, enable greater leverage in the cost sharing and thus produce greater inducement effects on new product entry on $\mathbf{d_4}$ versus $\mathbf{d_3}$ and on $\mathbf{d_3}$ versus $\mathbf{d_2'}$.[78]

So for the alternative case of $\frac{F+C}{p} \leq M_1 < \frac{F+2C}{p}$, when drug development projects can exploit G_1 and G_2 as separately homogeneous sub-groups rather than as one joint homogeneous group, the expected number of new product entries (i.e., new drug molecules) in the region composed of $\mathbf{d_3}$ and $\mathbf{d_4}$ increases from 1 to 2, while the expected number of new indication approvals increases from 1 to either $(1+p)$, 2, or $2(1+p)$ for regions $\mathbf{d_2'}$, $\mathbf{d_3}$, and $\mathbf{d_4}$, respectively.

10.3 Drug Development Phases

Preclinical ("Phase 0"): Preclinical research programs have separate setup costs for different pharmacological mechanism-of-action strategies and since the number of potential compounds to be generated and tested can vary across programs, so this phase exhibits a non-CRS cost structure. And since only a specified number of compounds ("leads") will become candidates for phase I trials, this phase exhibits quota flow attrition.

Phase I: Phase I trials serve to test the basic safety of new compounds in man. Since results are binary (safe or not safe), any drug compound entering and passing any test during this phase will move into Phase II. Also, in general, compounds only need to be tested once. This describes a hurdle attrition flow and constant returns-to-scale structure.

Phase II: When a compound enters this phase, the firm conducts one or more trials in order to determine a trial design which will maximize the compound's chance of both passing-through to Phase III testing and achieving FDA approvable results in Phase III testing. Given the costs involved at this stage, generally only one compound is selected for Phase III.

[78] Real-world cases of such inducement effects include R&D phenomena known as "indication expansion" and "drug re-purposing."

Phase III: Any drug compound entering and passing any test during this phase will be presented for FDA approval. This means hurdle flow attrition is in effect. Each trial can be (and often is) designed to test multiple clinical endpoints in multiple subpopulations based on Phase II outcomes, so the non-CRS cost structure applies.

Market ("Phase IV"): Drug compounds are launched into the marketplace once they have received FDA approval. Drug prescription choice is determined by treatment need along the three dimensions of safety, (i.e. no severe adverse events), efficacy, and tolerability (i.e. mild-or-moderate adverse events acceptable to patient).

10.4 Backup Calculations for Symmetric Oligopoly Equilibrium Model

For a given disease market of size *d*, the representative firm chooses x, P, τ_3 and φ, to solve

$$\max \pi(P, \tau_3, \varphi;\ n, \delta, t, c, F_i, C_i, p_i) = E[Revenue] - E[Costs]$$

$$= p_3 \tau_3 (P - c) x(P, \varphi; n, \bar{P}, \bar{\varphi}) - \left[F_0 + \frac{C_1}{p_1} + r_2 C_2 + \tau_3 C_3\right].$$

One first-order condition (FOC#1) that can now be solved is

$$\frac{\partial \pi(P, \tau_3, \varphi)}{\partial P} = 0$$

$$= p_3 \tau_3 [x + (P - c)x']$$

$$= p_3 \tau_3 \left\{ \frac{\delta(1-\varphi)}{n} \left[1 + n\left(\frac{\bar{P}-P}{t}\right)\left(1 + \frac{\frac{\bar{\varphi}}{2}}{\delta(1-\bar{\varphi})}\right) + \frac{\bar{\varphi}\left(1-\frac{\bar{\varphi}}{2}\right)}{\delta(1-\bar{\varphi})^2}\right] + (P - c)\left[(1 - \varphi)\left(\frac{-1}{t}\right)\left(\delta + \frac{\bar{\varphi}}{2(1-\bar{\varphi})}\right)\right]\right\}$$

$$= \mathrm{p}_3\tau_3(1-\varphi)\frac{\delta}{n}\left[1+n\left(\frac{\bar{P}+c-2P}{t}\right)\left(1+\frac{\frac{\bar{\varphi}}{2}}{\delta(1-\bar{\varphi})}\right)+\frac{\bar{\varphi}\left(1-\frac{\bar{\varphi}}{2}\right)}{\delta(1-\bar{\varphi})^2}\right],$$

which implies

$$P=\frac{\bar{P}+c}{2}+\frac{t}{2n}\frac{\left[1+\frac{\bar{\varphi}\left(1-\frac{\bar{\varphi}}{2}\right)}{\delta(1-\bar{\varphi})^2}\right]}{\left[1+\frac{\frac{\bar{\varphi}}{2}}{\delta(1-\bar{\varphi})}\right]}=\frac{\bar{P}+c}{2}+\frac{t}{2n}\left[1+\frac{1}{(1-\bar{\varphi})[\frac{2\delta(1-\bar{\varphi})}{\bar{\varphi}}+1]}\right].$$

Setting $\bar{P}=P$ and $\bar{\varphi}=\varphi$ for the symmetric oligopoly equilibrium case thus gives the profit-maximizing solution for P,

$$\boxed{P=c+\frac{t}{n}\left[1+\frac{1}{(1-\varphi)[\frac{2\delta(1-\varphi)}{\varphi}+1]}\right]}. \qquad (*1)$$

Note I can derive the following hypotheses regarding P, all of which are consistent with basic economic intuition:

$$\frac{\partial P}{\partial c}=1>0;$$

$$\frac{\partial P}{\partial t}=\frac{1}{n}\left[1+\frac{1}{(1-\varphi)[\frac{2\delta(1-\varphi)}{\varphi}+1]}\right]>0;$$

$$\frac{\partial P}{\partial \varphi}=sgn|\,\varphi^2(1-2\delta)+2\delta=\,sgn|\,\varphi^2+2\delta(1-\varphi^2)>0;$$

$$\frac{\partial P}{\partial n}=-\frac{t}{n^2}\left[1+\frac{1}{(1-\varphi)[\frac{2\delta(1-\varphi)}{\varphi}+1]}\right]<0;\text{ and}$$

$$\frac{\partial P}{\partial \delta}=\frac{t}{n(1-\varphi)}\frac{-\frac{2(1-\varphi)}{\varphi}}{\left[\frac{2\delta(1-\varphi)}{\varphi}+1\right]^2}=-\frac{2t}{n\varphi\left[\frac{2\delta(1-\varphi)}{\varphi}+1\right]^2}<0.$$

Another first-order condition (FOC#2) that can be solved is

$$\frac{\partial \pi(P,\tau_3,\varphi)}{\partial r_2} = 0$$

$$= p_3(P-c)x\tau_3' - C_2 - C_3\tau_3'$$

$$= \tau_3'[p_3(P-c)x - C_3] - C_2.$$

Now since $\tau_3' = -(1-p_2)^{r_2}\ln(1-p_2) = -(1-\tau_3)\ln(1-p_2)$ and by setting $\bar{P} = P$ and $\bar{\varphi} = \varphi$ for the symmetric oligopoly equilibrium case as well as substituting for $(P-c)$ from (*1), I get

$$0 = \tau_3'[p_3(P-c)x - C_3] - C_2$$

$$= -(1-\tau_3)\ln(1-p_2)\left\{p_3\frac{t}{n}\left[1+\frac{1}{(1-\varphi)\left[\frac{2\delta(1-\varphi)}{\varphi}+1\right]}\right]\frac{\delta(1-\varphi)}{n}\left[1+\frac{\varphi\left(1-\frac{\varphi}{2}\right)}{\delta(1-\varphi)^2}\right] - C_3\right\} - C_2.$$

This allows me to deduce the profit-maximizing solution for τ_3 (and therefore r_2) as being

$$\tau_3 = 1 + \frac{C_2}{\ln(1-p_2)}\frac{1}{\frac{\delta t p_3(1-\varphi)}{n^2}\left[1+\frac{1}{(1-\varphi)\left[\frac{2\delta(1-\varphi)}{\varphi}+1\right]}\right]\left[1+\frac{\varphi\left(1-\frac{\varphi}{2}\right)}{\delta(1-\varphi)^2}\right]-C_3}$$

$$\boxed{= 1 + \frac{C_2}{\ln(1-p_2)\left[\frac{t p_3\left[(2\delta-1)(1-\varphi)^2+1\right]^2}{2n^2(1-\varphi)^2[(2\delta-1)(1-\varphi)+1]}-C_3\right]}}. \qquad (*2)$$

Note that $\tau_3 < 1$ which implies that $\left[\frac{t p_3\left[(2\delta-1)(1-\varphi)^2+1\right]^2}{2n^2(1-\varphi)^2[(2\delta-1)(1-\varphi)+1]} - C_3\right] > 0$. Thus, I can derive the following hypotheses regarding τ_3, all of which are consistent with basic economic intuition:

$$\frac{\partial \tau_3}{\partial C_2} = \frac{1}{\ln(1-p_2)\left[\frac{t p_3\left[(2\delta-1)(1-\varphi)^2+1\right]^2}{2n^2(1-\varphi)^2[(2\delta-1)(1-\varphi)+1]}-C_3\right]} < 0;$$

$$\frac{\partial \tau_3}{\partial C_3} = \frac{-C_2(-\ln(1-p_2))}{\left\{\ln(1-p_2)\left[\frac{t p_3\left[(2\delta-1)(1-\varphi)^2+1\right]^2}{2n^2(1-\varphi)^2[(2\delta-1)(1-\varphi)+1]}-C_3\right]\right\}^2} < 0;$$

$$\frac{\partial \tau_3}{\partial p_2} = \frac{C_2}{\left[\frac{t p_3[(2\delta-1)(1-\varphi)^2+1]^2}{2n^2(1-\varphi)^2[(2\delta-1)(1-\varphi)+1]} - C_3\right]} \frac{-1}{(1-p_2)[\ln(1-p_2)]^2} < 0;$$

$$sgn\left|\frac{\partial \tau_3}{\partial p_3}\right. = sgn\left|\frac{\partial \tau_3}{\partial t}\right. > 0;$$

$$sgn\left|\frac{\partial \tau_3}{\partial \delta}\right. = sgn\frac{\partial}{\partial \delta}\left|\frac{[(2\delta-1)(1-\varphi)^2+1]^2}{[(2\delta-1)(1-\varphi)+1]}\right. = (2\delta-1)(1-\varphi)^2 + (1-2\varphi) \gtrless 0.$$

Furthermore, since τ_3 is a function of r_2 and $\frac{\partial r_2}{\partial \tau_3} = \frac{-1}{(1-\tau_3)\ln(1-p_2)} > 0$, these comparative static for τ_3 hold correspondingly for r_2.

10.5 Backup Calculations for Monopolistically Competitive Equilibrium Model

Building further on the equations derived under symmetric oligopolistic competition, we exploit the fact that firm profits goes to zero with the free entry-exit condition of monopolistic competition. This free-entry condition (FEC) is given by

$$\pi(P, \tau_3, \varphi, n) = 0$$

$$= p_3\tau_3(P-c)x(P, \tau_3, \varphi) - \left[F_0 + \frac{C_1}{p_1} + r_2C_2 + \tau_3C_3\right]$$

$$= \tau_3[p_3(P-c)x - C_3] - r_2C_2 - \left[F_0 + \frac{C_1}{p_1}\right]. \qquad (*3)$$

From FOC#2,

$$[p_3(P-c)x - C_3] = \frac{C_2}{(\frac{\partial \tau_3}{\partial r_2})} = \frac{C_2}{-(1-\tau_3)\ln(1-p_2)}. \qquad (*4)$$

Substituting $r_2 = \frac{\ln(1-\tau_3)}{\ln(1-p_2)}$ and (*4) into (*3) gives

$$0 = \tau_3\left[\frac{C_2}{-(1-\tau_3)\ln(1-p_2)}\right] - \left[\frac{\ln(1-\tau_3)}{\ln(1-p_2)}\right]C_2 - \left[F_0 + \frac{C_1}{p_1}\right]$$

$$= \frac{C_2}{-\ln(1-p_2)}\left[\ln(1-\tau_3) + \frac{\tau_3}{1-\tau_3}\right] - \left[F_0 + \frac{C_1}{p_1}\right],$$

which implies

$$\frac{-\ln(1-p_2)}{C_2}\left[F_0 + \frac{C_1}{p_1}\right] = \ln(1-\tau_3) + \frac{\tau_3}{1-\tau_3} = \ln(1-\tau_3) + \frac{1}{1-\tau_3} - 1.$$

Setting $K = 1 - \frac{\ln(1-p_2)}{C_2}\left[F_0 + \frac{C_1}{p_1}\right]$ and rearranging gives

$$e^{-\ln(1-\tau_3)} = -\ln(1-\tau_3) + K,$$

which can then be solved using the Lambert function[79] to give

$$\ln(1-\tau_3) = W(-e^{-K}) + K,$$

or

$$\tau_3 = 1 - e^{W(-e^{-K})+K}. \qquad . \qquad (*5)$$

Therefore, rearranging (*2) and substituting from (*5) enables me to express innovation entry in terms of only exogenous variables:

$$n^2 = \left[\frac{t p_3\left[(2\delta-1)(1-\varphi)^2+1\right]^2}{2(1-\varphi)^2[(2\delta-1)(1-\varphi)+1]\left[C_3 - \frac{C_2}{e^{W(-e^{-K})+K}\ln(1-p_2)}\right]}\right],$$

or equivalently,

[79] For $p^{ay+b} = cy + d$, where $p > 0$ and $a, c \neq 0$, then y can be solved as $y = -\frac{W\left(-\frac{a\ln(p)}{c}p^{b-\frac{ad}{c}}\right)}{a\ln(p)} - \frac{d}{c}$, where W is the Lambert function.

$$n = \left[\left(\delta - \frac{1}{2}\right)(1-\varphi) + \frac{1}{2(1-\varphi)}\right] \sqrt{\frac{tp_3}{\left[\left(\delta - \frac{1}{2}\right)(1-\varphi) + \frac{1}{2}\right]\left[C_3 - \frac{C_2}{(1-\tau_3)\ln(1-p_2)}\right]}}, \qquad (*6)$$

where τ_3 is a function of F_0, C_1, C_2, p_1, and p_2.

CHAPTER 11.

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