Regulatory Growth Theory

Danxia Xie*

Tsinghua University

December 31, 2017

Abstract

This research explores and quantifies the downside of innovations, especially the negative externality of an innovation interacting with the stock of existing innovations. Using two novel datasets, I find that the number of varieties of innovation risks is quadratic in the varieties of innovations that caused them. Based on this new empirical fact, I develop a Regulatory Growth Theory: a new growth model with innovation-induced risks and with a regulator. I model both the innovation risk generating structure and the regulator's endogenous response. This new theory can help to interpret several empirical puzzles beyond the explanatory power of existing models of innovations: (1) skyrocketing expected R&D cost per innovation and (2) exponentially increasing regulation over time. Greater expenditures on regulation and corporate R&D are required to assess the net benefit of an innovation because of "Risk Externality": negative interaction effects between innovations. The rise of regulation versus litigation, and broader implications for regulatory reform are also discussed.

*Address: Institute of Economics, Tsinghua University, China. The author's e-mail address is dxie@uchicago.edu. I am grateful to Gary Becker, Casey Mulligan, Randy Kroszner, Tom Philipson, and Eric Posner for invaluable advice. Also thank Ufuk Akcigit, Olivier Blanchard, Will Cong, Steve Davis, Jeffrey Frankel, Matt Gentzkow, Yehonatan Givati, Michael Greenstone, Lars Hansen, Zhiguo He, Chang-Tai Hsieh, Chad Jones, Greg Kaplan, John List, Bob Lucas, Joel Mokyr, Roger Myerson, Andrei Shleifer, Hugo Sonnenschein, Nancy Stokey, and Hanzhe Zhang for very helpful suggestions and discussions. An early version was presented at Econometric Society 2015 World Congress, Montreal.

"The more I learn, the more I realize how much I don't know."
— *Albert Einstein*

1 Introduction

Undoubtedly innovations are essential for our economic and knowledge growth. On the other hand, is there also a potential downside of innovations? In particular, can there be a negative consequence of an innovation interacting with existing products, that is, stock of past innovations? Is the potential negative externality increasing in the stock of past innovations?

An innovation that by itself is effective at solving a problem could cause a broader negative effect. A recent strict regulatory action on the combined use of opioids with benzodiazepines has just attracted wide public attention[1]. The FDA noticed that the emergency department visits and overdose deaths due to the combined use of opioids and benzodiazepines have tripled between 2004 to 2011. These are two types of frequently precribed medicines that have significant health benefits when used alone; however, their simutaneous administration generates a new variety of risk that is called Drug-drug interaction (DDI).

In discussing the major contributors to the 2008 Financial Crisis, Kroszner (in Kroszner and Shiller, 2011) points out that Credit Default Swap (CDS) is a valuable hedging device but its interaction with existing financial innovations could lead to "fragile interconnections" and "systemic risk" that make the system less sound. In other words, the financial innovation is useful individually but could undermine stability of the financial system.

The Great Smog of London in December 1952 killed 12,000 residents. Recent research by Wang et al (2016) suggests the major "Killer" behind the 1952 London Fog was due to the interaction between SO_2 and NO_2, through combined photochemical and aqueous processes. The authors further show the harmful chemicals in the current severe haze in China are the products from complex interactions between SO_2, NO_2,and NH_3.

Motivated by the examples above, I take a step forward to measure and quantify these innovation-induced risks, as the first main contribution of this research. I find a new empirical fact: the varieties of innovation-induced interactive risks grow much faster than the varieties of innovations (see Figure 1). I bring two novel datasets into the economic literature. One is the DrugBank, which documents detailed chemical and biological information of most existing drugs, including known theoretical DDIs that these drugs can cause. The other is the FDA's Adverse Event Reporting System (FAERS) database, which records adverse event

[1] http://www.nytimes.com/2016/09/01/health/fda-orders-stronger-warning-on-common-painkiller-sedative-mix.html

cases reported from patients. By linking and analyzing these databases, I make a pioneering effort to measure the number of varieties, dynamics and actual occurrences of risks induced by drugs. I emphasize *the varieties of risks* induced by innovations. Empirically, I find that the relationship between the number of different types of DDIs and the number of drugs generating these DDIs are best characterized by a quadratic form function as illustrated by Figure 6.

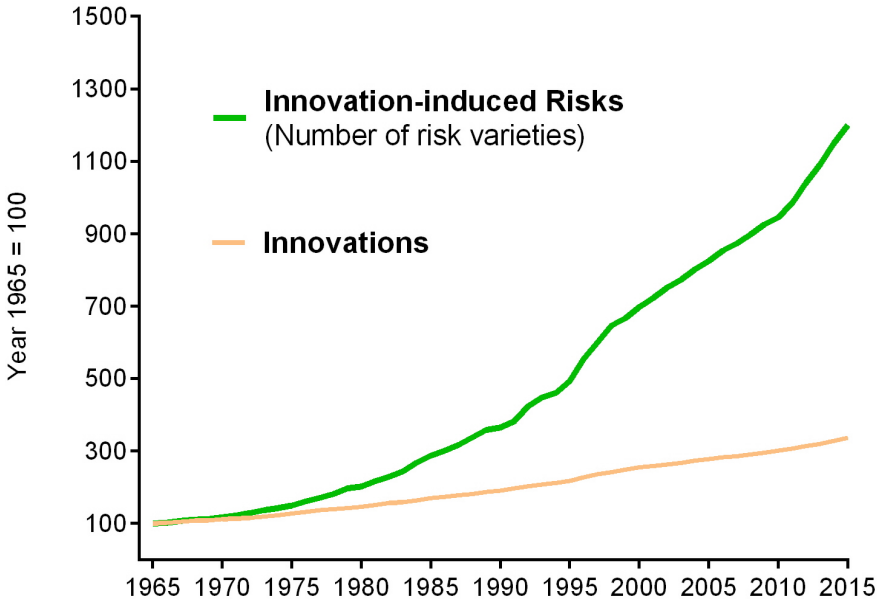


Figure 1: Varieties of Innovations vs. Varieties of Innovation-induced Risks

This new empirical fact draws parallel to *Environmental Kuznets Curve (EKC)*. *EKC* points to an $inverted-U$ relationship between growth and the quantity of known pollutants (Grossman and Krueger 1995). I explore the relationship between growth and the varieties of risks, which is revealed to be an increasing and quadratic function.

Canonical growth theories take as given the usefulness and benevolence of knowledge and innovations, but it neglects the adverse fact that technological innovations might also create negative externalities to the economy due to its direct side effects as well as complex interactions with existing technologies and environment.

As the second major contribution, I develop a new growth theory: Regulatory Growth Theory, which models both the innovation risk generating structure and process and the regulator's endogenous response. I introduce into growth theory the risk generating process which accompanies innovations, and model the testing and regulatory actions which control the macro risk structure induced by innovations. I build a model regarding the approval process for new products, reflecting an important regulatory function of the FDA on drugs

and the EPA on chemicals (per the new 2016 Lautenberg Act). I also model the interactions between regulators and innovators. Innovators will perform testing on their innovations in line with regulatory requirements and then submit the testing outcomes for regulators to review and make final approval decisions.

The implications of my theoretical model are consistent with the following two empirical puzzles that canonical growth models fail to explain:

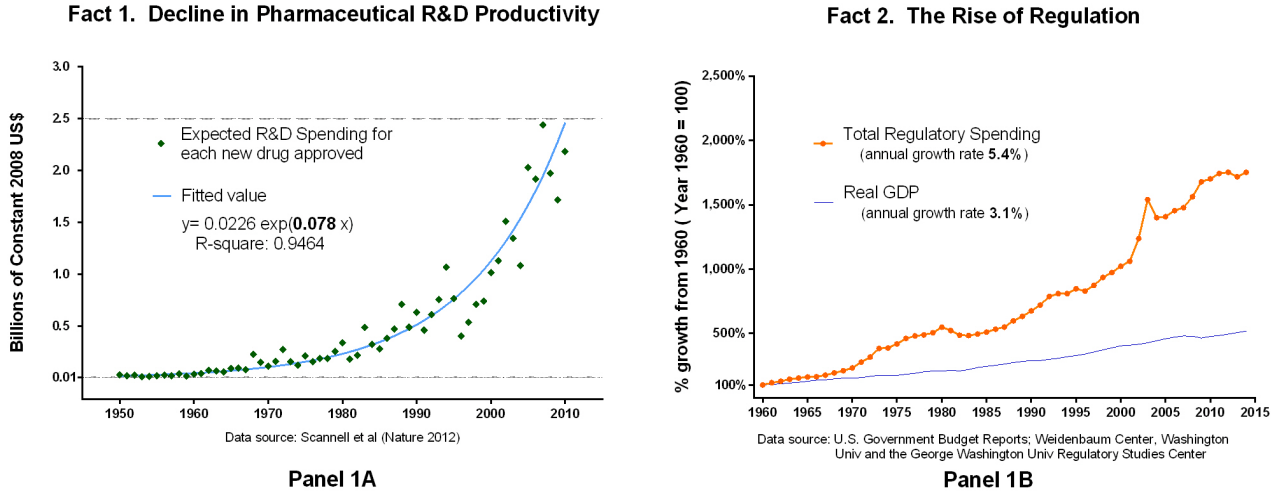


Figure 2: Empirical Puzzles

First, from 1950 to 2010, the expected R&D cost for each FDA-approved drug (NME) has skyrocketed from 20 million to almost 2.5 billion in 2008 constant US dollars, as shown by Figure 2A. The R&D spending for each successful drug has increased by more than 100 times during the last sixty years. In contrast, there is only a *five-fold* increase in GDP in the same period. This has been known as the *pharmaceutical R&D productivity crisis*.

Second, the amount of regulation and the size of the regulatory sector have been growing faster than GDP. From 1960 to 2014, the (inflation-adjusted) budget cost for federal regulatory agencies has increased by almost twenty times, while the real GDP only by five times (see Figure 2B). Since there is no role for a regulator in canonical growth models, the previous models cannot accommodate such fact.

The key channel in my theoretical model that causes the exponential growth of R&D costs and innovation-related regulation is that innovations are not only complementary in their benefits but also in their risks. The fast growth of risks due to innovations demands more regulatory resources and also reduces the ratio of "qualified" innovations.

As the third major contribution, I put forward a new *knowledge theory of regulation*: new varieties of risks are continuously created by innovations, and the main purpose and

function of regulation is to discover and control these new risks. This paper therefore fits in the recent literature which tries to explain the root and the rise of regulation (e.g. Mulligan and Shleifer 2005, Shleifer 2012), but I have different explanations. Discovering new varieties of risks generated by technological innovations are becoming more costly and important than regulating known risks. Science, technology, and social science knowledge tell us what we can do, i.e. through innovations and new products, as well asd the knowledge of risks and what we cannot do, which build the foundation of modern regulation. In this sense, the modern regulatory sector is an institutional setup representing and executing human knowledge about the negative side of human-made technologies and related activities.

FDA has regulated the drug and food industry for more than a century since the 1906 Legislation. The establishment of the CFPB (Consumer Financial Protection Bureau) in 2011 represents the latest efforts in detecting, disclosing and preventing potential risks in financial products, as a response to the wide blame on financial innovations as a cause of the Subprime Crisis and Great Recession. On June 22, 2016, the Lautenberg Chemical Safety Act was just signed into law, which endowed the EPA with the new power to review and approve any new chemical product. Besides the FDA, the newly established CFPB together with the EPA augmented by the 2016 Lautenberg Act allude to an analogous *qualification process* of regulation which inspires the theoretical model developed in this research.

There are several interesting and crucial features that can only be derived from my theory. There will be a divergence between the *General Knowledge*, and the *Qualified Knowledge*. The number of patents represent the *General Knowledge*, while the qualified innovations (regulator-approved innovations) representing the *Qualified Knowledge* which can provide us net benefits. Macro risk structure due to complex interaction effects between innovations in use can make this divergence grow larger, given effective regulation (see Figure 13). The total human knowledge (*General Knowledge*) can keep growing fast but the GDP growth can lag much behind it owing to rapid expansion of the varieties of new risks.

The rest of this paper is organized as follows. Section 2 presents our empirical measurement of interactive risks induced by drugs. Section 3 builds the Regulatory Growth Theory that models the innovation risks and a regulator. Section 4 discusses the implications for corporate R&D, regulation, and potential regulatory reform proposals. Section 5 concludes.

The Literature

Becker and Murphy (1992) points to the increasing coordination cost due to the deepening of division of labor, and discusses its implications in a growth framework.

Romer (1986,1990) starts the literature on endogenous growth, which emphasizes the benefit of knowledge spillover. Potential hazards of innovation is largely omitted by the

literature. However, the spillover of "innovation" can also have widespread adverse effects. Jones (2016) takes a first step forward to also consider potential risk of innovations, and models life-saving innovations.

Weitzman (1998) proposes a "Recombinant growth" model, which shares some features with this research. However, there are several essential differences. Weitzman (1998) does not deal with adverse effects of innovations. The unexpected adverse effects from combinations creates daunting complex interactions in an autonomous and hidden way, and distinguish this research from Weitzman's. After inventing and adopting some new technologies, we are actually forced to play a blind game with Mother Nature, who secretly generates all possible innovation-induced risks behind us.

In environmental research, interactions between different pollutants are called synergistic effects. List and Mason (1999) analyzes a dynamic game for the optimal choice of central and local regulation based on the synergistic effects between different pollutants.

In contrast to the literature of Environmental Macroeconomics (e.g. Acemoglu et al 2012, Golosov et al 2014) which commonly focus on one or several varieties of known pollutants or risks, this research provides a general framework for analyzing risk varieties dynamically generated by continuous innovations in the economy. Discovering new types of risks are an essential part of our framework, while the existing literature is limited to certain known types of risks.

There is a recent literature on Uncertainty shocks and policy uncertainty, pioneered by Bloom (2009), and Baker, Bloom and Davis (2012). This research is complementary to this research line by trying to offer an economic explanation for the origin and rise of uncertainty over the last several decades.

Barro (2006, 2009) starts the literature of research on rare disasters. The Subprime Crisis advances new interests in tail risk measurement and modeling. However, this literature generally assumes the rare disasters are exogenous. This research proposes a new way to generate tail risk with endogenous complex risks.

Shleifer (2012) documents the rise of regulation relative to litigation. In comparison to the theories advanced in Shleifer (2012) and the classical Capture Theory by Stigler (1971), this research is relatively close to Pigou (1924): but my model integrates the explicit externality generating process with innovation and growth. I emphasize the public good nature of discovering new varieties of risks.

2 Measuring Innovation-induced Risks

In this section I measure the interactive risks induced by innovations, using the DrugBank and FDA FAERS databases. I characterize and derive the relationship between the varieties of interactive risks caused by drugs (i.e. Drug-drug Interactions) and the varieties of drugs.

2.1 Prevalence and Regulation of Drug-drug interactions (DDI)

Bjorkman et al (2002) compile a large dataset of six European countries and find out that up to **46%** of all patients had encountered at least one potential DDIs, **10%** among which were severe ones. Moreover, the DDI occurance has been rising quickly. Guthrie et al (2015) show that serious DDIs more than doubled in 15 years from 1995 to 2010: **13.1%** of adult patients encountered at least one DDI in 2010, while **5.8%** of adult patients did in 1995.

Huang and Lesko (2004) points out "serious Drug-drug interactions have contributed to half of the recent U.S. market withdrawals and also recent nonapprovals of a few new molecular entities. ... In addition to drug-drug interactions, drug–dietary supplement and drug–citrus fruit interactions, among others, are emerging as important issues to consider in the evaluation of new drug candidates."

2.2 Data Description

2.2.1 The DrugBank Database

DrugBank is a comprehensive database that includes detailed chemical and biological information of most existing drugs in the world. It is deemed as the gold standard in many aspects by Pharmacy researchers. It covers all FDA approved small molecule and biotech drugs (NMEs). In addition, DrugBank documents known DDIs for its covered drugs. These DDI information comes from drug labels, clinical trials, and postmarketing surveillance.

It has standard classification system for drugs based on their molecular structure. This can help to solve the challenging problem of duplicate drug names (many different names correspond to the same drug chemical molecule).

I use the latest DrugBank Version 5.0.1 for this research.

2.2.2 The FDA's FAERS Database

The FDA's Adverse Event Reporting System (FAERS) records the reported adverse events and medical errors[2]. FAERS is a crucial part of the post-marketing surveilance infrastructure. The author also gets the full historical time series statistics for the Adverse Events Reports by direct data request to the FDA[3], shown as in Figure 3. The fitted value for the adverse events reporting is close to an exponential curve.

The number and types of risks due to innovations grow much faster than GDP and innovations. This empirical fact is new by itself: I use the drug adverse events reported to the FDA. Figure 3 shows the annual number of adverse events per thousand people. Adverse event reports per capita has increased more than 100 times in the last decades.

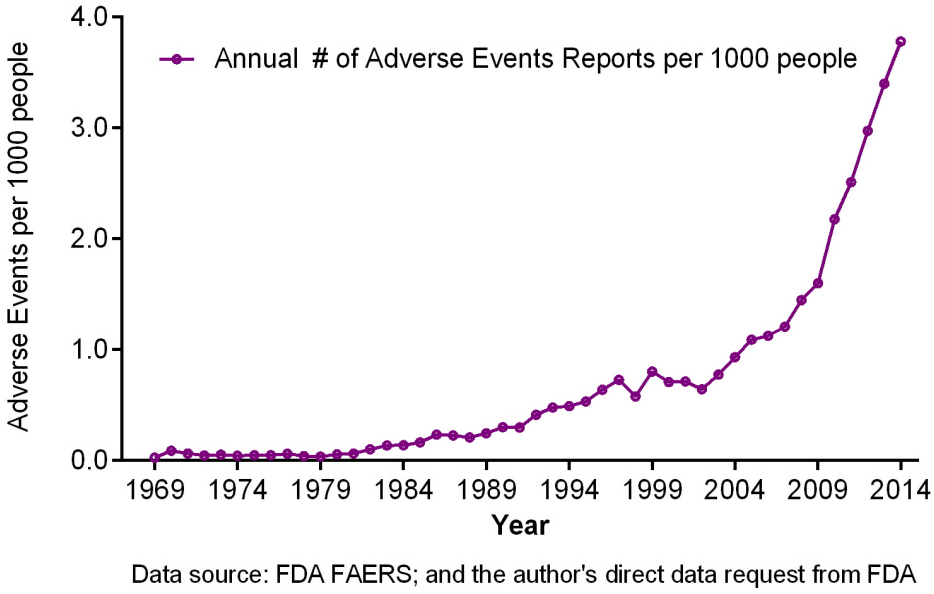


Figure 3: The Growth of Drug Adverse Events Reported

FAERS database includes detailed reports for each adverse event entered by the FDA from 2004 to the most recent quarter. For each adverse event case report, all the drugs that the patient was taking are recorded. This is the basis for identifying DDIs from each adverse event case.

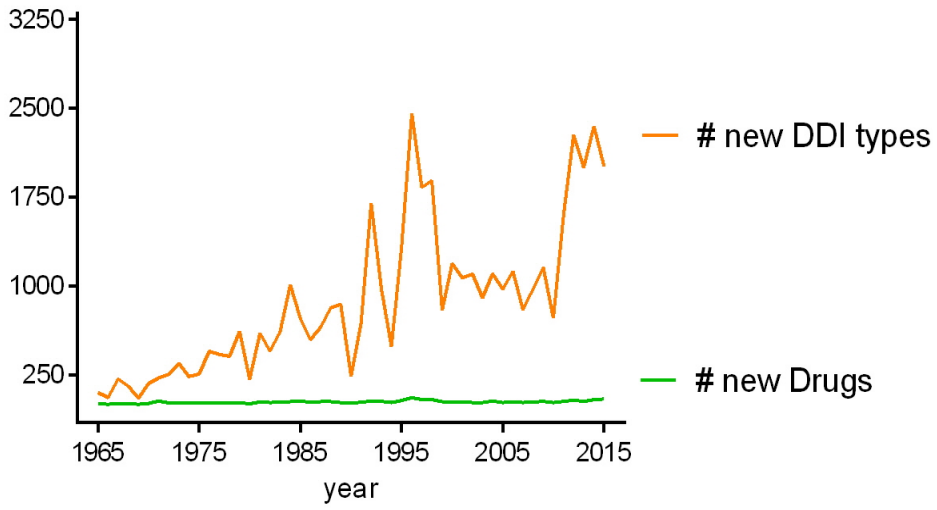
[2]Detailed data description is provided in Appendix C.

[3]The author is grateful for the generous help of the FDA staff.

2.3 The Dynamics of Incremental DDIs

DrugBank documents DDIs for each FDA approved NME. I link the Drugbank's DDIs with the FDA approved NMEs for each year. Figure 4 displays the annual number of NMEs approved by FDA, in comparison with the new DDIs generated by the new NMEs. That is, the upper curve in Figure 4 shows the incremental DDIs that are directly attributable to the new NMEs approved in that year.

Figure 4: New DDI types v.s. New Drugs (NME) in each year



2.4 The Varieties of DDIs and the Varieties of Drugs

In the introduction section, Figure 1 shows how the number of DDI types grow with the number of drugs. During the last five decades, the number of DDI types have increased by 12 times whereas the total number of NMEs only 3.4 times. DDI types grow at a much higher speed.

We want to estimate a function form of DDI types and drugs: $DDI = f(drugs)$. Various specifications have been tried. Figure 5 uses a linear function form.

Figure 6 adopts a quadratic function form, and can fits the data much better than the linear form.

We can empirically derive a quadratic form function (1) :

$$DDI = 0.0172 \cdot (NME)^2 + 0.7618 \cdot NME - 1236.8 \tag{1}$$

the high R^2 indicates (1) can approximate the data of DDI types and NMEs quite well.

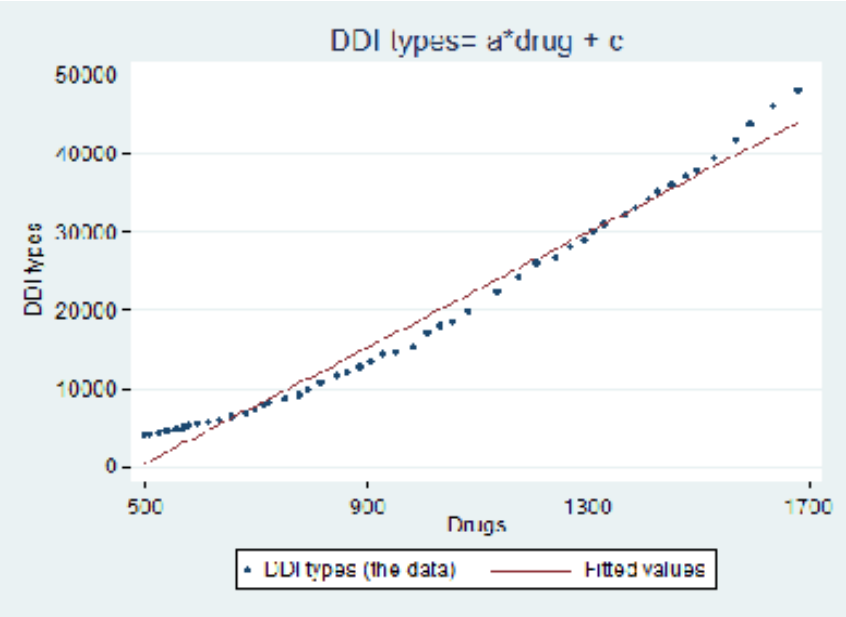


Figure 5: Linear Specification

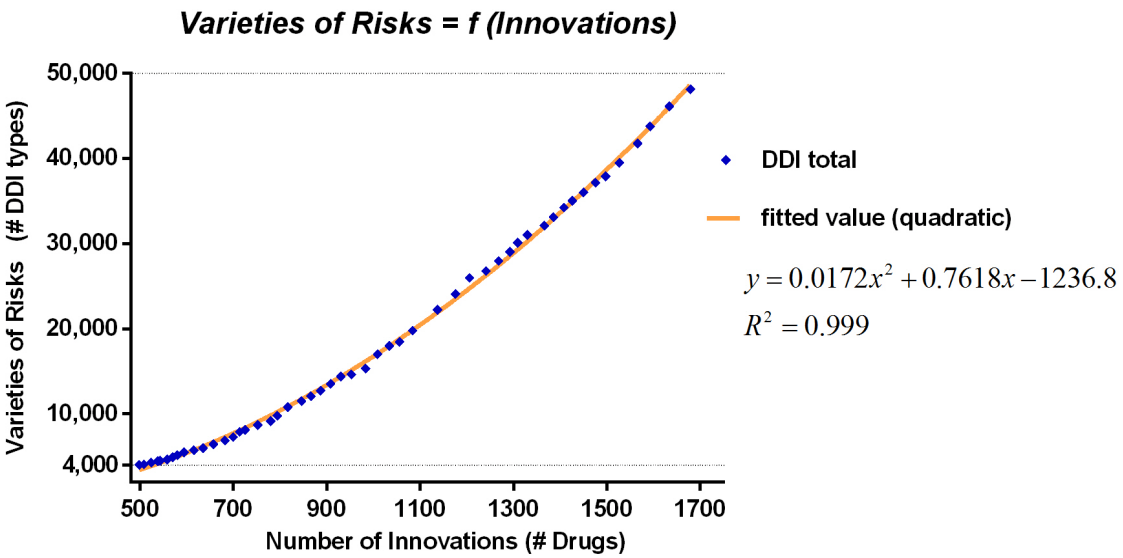


Figure 6: Varieties of Innovation-induced Risks as a Function of Innovations

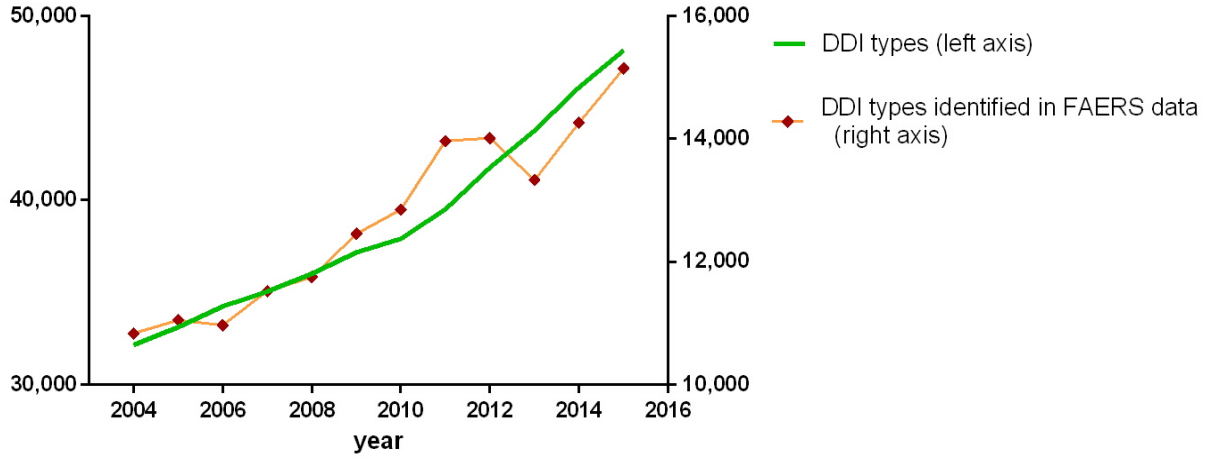
2.5 Real DDIs Identified from the Adverse Events Database

More importantly, I also want to count the DDIs occurring in reality. For this purpose, I link the FDA's FAERS database with the DrugBank database. I use the drug names and theoretical DDIs documented in the DrugBank to match and identify the cases of DDIs reported to the FAERS. Each adverse event in the FAERS records detailed information for the drugs used by the patient, as well as the patient's demographic information. If a patient took several drugs simultaneously, the corresponding adverse event report is supposed to document all the drug names (though some drugs might be omitted for reporting).

Our *identification strategy* is to use each theoretical DDI from the DrugBank to match real DDI in each FAERS adverse event. Our purpose is to find all DDI occurances in the real adverse events data. In the DrugBank, the number of all types of theoretical DDIs for the FDA approved drugs is close to 50,000. The FDA's FAERS has recorded up to 7 million adverse events since 2004. Linking and matching these two database brings us a formidable computational challenge[4]. I have designed an efficient algorithm to reduce the computing time.

Figure 7 shows the real DDI types identified from the FAERS data. In general, there are one third of the theoretical DDIs that can be identified from the actual FAERS database. This ratio of one third is relatively constant over the period 2004-2015.

Figure 7: Theoretical DDI types and Real DDI types identified in FAERS Database



This result also implies that a significant portion of the theoretical DDI combinations are actually prescribed and used together in the real life. DDIs can impose substantial cost. The recent Black box warning on the DDI of opioids and benzodiazepines by the FDA highlights this challenge.

[4]Here I must thank our supercomputer Acropolis at UChicago.

3 The Model

Safety and efficacy information of innovative products is costly to acquire and verify. Consumers delegate this task to a group of experts: the regulator. The regulator reviews and evaluates the safety and efficacy information for new products provided by the innovators. The objective of the regulator is to accurately choose the useful and safe products. According to the preference of consumers, regulators require the innovative firms to provide testing information for their innovations. Then the regulator verify the testing information provided by the firms. They compare the benefit and cost of each innovation based on the testing information and decide whether to approve it. The regulator in this model resembles the FDA, and I have a detailed description of this regulatory regime in Appendix A.

3.1 Consumer Preference

There is one representative consumer in the economy. Her instantaneous utility is represented by $u_t(C_t - \tilde{D}_t) = \frac{\left(C_t - \tilde{D}_t\right)^{1-\gamma}}{1-\gamma}$. It is composed of two parts: consuming the final goods generates utility C_t as well as damage (or disutility) $\tilde{D}_t$ to the consumer.What really matters for consumer is the net util $C_t - \tilde{D}_t$. At time t, consumer only consume one type of final goods.

The infinite-horizon expected utility for the representative consumer is,

$$EU = E_0 \sum_{t=0}^{\infty} \beta^t \frac{\left(C_t - \tilde{D}_t\right)^{1-\gamma}}{1-\gamma} \tag{2}$$

3.2 Final Goods Production

At any time t, there is a unique final goods Y_t, which is produced with a range of intermediate products and labor. Production of this final goods is represented by an aggregate production function (3) :

$$Y_t = \frac{1}{\alpha} l_t^{1-\alpha} \cdot \sum_{i=1}^{M_t} (x_{i,t})^{\alpha} \tag{3}$$

where l_t is labor input, M_t is the number of varieties of intermediate products used to produce the final goods. x_i is the quantity of intermediate product i used in aggregate production. Intermediate product is produced directly from the final good and will fully depreciate after use.

The final goods is produced under perfect competition. At any time t, given intermediate

product price $p_{i,t}$ and wage w_t, a final goods producer's maximization problem is (4),

$$\max_{l_t,[x_{i,t}]_{i\in[0,M_t]}} \frac{1}{\alpha} l_t^{1-\alpha} \cdot \sum_{i=1}^{M_t} (x_{i,t})^{\alpha} - \sum_{i=1}^{M_t} p_{i,t} x_{i,t} - w_t l_t \tag{4}$$

3.3 Generation of Risk Structure and Damage

When consuming the final goods to get utility C_t, consumer also bears a damage $\tilde{D}_t$. Damage is calculated as the aggregate adverse effects caused by all innovation-induced risks. The risk structure is created by the interactions between different intermediate goods (e.g. the Drug-drug interactions). These interactions happen automatically. Empirical findings from Section 3 point to a quadratic form relationship (1) between innovations and their induced risk types.

Higher-order (> 2) interactive risks are not ruled out in theory, but in this research I stick to our main empirical evidence[5]. Notice that the measured DDI types and real occurrences are the outcome after FDA's qualification process. The number of risk types and occurrences have been significantly reduced by FDA's requirements and rejections (e.g. the Thalidomide case).

3.3.1 Macro Risk Matrix

I use a $2-$*dimensional* Macro Risk Matrix to represent various types of risks due to interactions between intermediate products[6]. Here I adopt a standard index system for the matrix elements. Intermediate product i has uncertain interactive side effect with j, which is represented by potential damage $\tilde{d}_{ij}$. The Macro Technology Matrix Ξ_M with M intermediate products is represented as below:

$$\Xi_M = \begin{bmatrix} \tilde{d}_{11} & \tilde{d}_{12} & \cdot & \cdot & \tilde{d}_{1,M-1} & \tilde{d}_{1,M} \\ \tilde{d}_{21} & \tilde{d}_{22} & \cdot & \cdot & \tilde{d}_{2,M-1} & \tilde{d}_{2,M} \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \tilde{d}_{M-1,1} & \tilde{d}_{M-1,2} & \cdot & \cdot & \tilde{d}_{M-1,,M-1} & \tilde{d}_{M-1,,M} \\ \tilde{d}_{M,1} & \tilde{d}_{M,2} & \cdot & \cdot & \tilde{d}_{M,M-1} & \tilde{d}_{M,M} \end{bmatrix}$$

which is a $2-$*dimensional* random matrix. Each element $\tilde{d}_{ij}$ is a random variable, and has the following properties,

[5] Appendix E also provides some real cases for Higher-order (> 2) DDIs.

[6] Appendix E presents a generalized Higher-order (> 2) *Macro Risk Tensor* representation with random tensor.

1. Symmetry: $\tilde{d}_{ij} = \tilde{d}_{ji}$

2. $\tilde{d}_{ii}$ denotes the side effect of intermediate i itself

3. Matrix elements are independent **but not** necessarily identically distributed

4. The distribution of any matrix element is unknown ex ante

Different matrix element follows disparate distributions. In fact, this is an important cause of complexity. When the number of matrix elements grow, I can not easily infer the probability distribution of new elements from existing ones.

$\tilde{d}_{ij}$ will either be 1 (with side effect) or 0 (without side effect) :

$$\tilde{d}_{ij} = \left\{ \begin{array}{lcl} 1 & : & \text{i and j has adverse side effect with Probability } q_{ij} \\ 0 & : & \text{i and j has no side effect with Probability } 1 - q_{ij} \end{array} \right\}$$

$\tilde{d}_{ij}$ follows a Bernoulli distribution with parameter q_{ij} : $\tilde{d}_{ij} \sim Bernoulli(q_{ij})$.

3.3.2 Aggregate Risk and Aggregate Damage

I define *aggregate risk* as the total number of elements with value 1 in the Macro Risk Matrix. Aggregate risk is denoted by D_t, calculated as the following:

$$D_t = \frac{1}{2} \sum_{i=1}^{M_t} \sum_{j=1}^{M_t} \tilde{d}_{ij} \tag{5}$$

The *aggregate damage* is calculated according to the Macro Risk Matrix by equation (6),

$$\tilde{D}_t = \frac{1}{2} \sum_{i=1}^{M_t} \sum_{j=1}^{M_t} x_i x_j \cdot \tilde{d}_{ij} \tag{6}$$

which quantifies the real damage with the actual intermediate product usage.

3.4 Intermediates Producer (Stage 1): R&D and Patenting

Each *qualified intermediate product* is produced by one innovative intermediate producer. A potential intermediate producer firstly needs to successfully invent an *intermediate product candidate,* by hiring researchers to conduct R&D. If R&D succeeds, the firm owns the full Intellectual Property of the *intermediate product candidate.* The patent will belong to the firm forever. If the *intermediate product candidate* is approved by the regulator, it becomes a *qualified intermediate product.* An *intermediate product candidate* cannot be produced until it becomes a *qualified intermediate product.* Similarly, final goods can only be produced from *qualified intermediate products.*

ΔE_t new varieties of *intermediate product candidates* will be invented with human capital input h_t :

$$\Delta E_t = E_{t+1} - E_t = (\lambda E_t) \cdot h_t \tag{7}$$

Here I assume the arrival rate of the number of *intermediate product candidates* follow a poisson process. λ is a parameter for R&D efficiency. Eqn (7) implies knowledge spillover effect because the aggregate R&D efficiency λE_t is augmented by E_t.

3.5 The Regulator

The regulator requires intermediates producers to test their new intermediate candidates. Clinical trials requirements for drugs exemplifies this. Intermediates producers need to submit testing information in the form of new product applications, e.g. *NDAs* (New Drug Applications) to FDA, and *PMNs* (Premanufacture Notices) to EPA according to the Lautenberg Act. Then the regulator reviews and verifies these applications. According to the submitted information, the regulator will decide whether the applications can satisfy the standards and be qualified for a final approval.

3.5.1 Requiring, Reviewing and Verifying Testing Information

For a new intermediate product candidate k, the regulator requires the firm to test its benefit b_k, as well as all the risks $\tilde{d}_{kj}, (j = 1, ...M_t)$. Firm can do either *effective testing* or *faked testing*. I assume,

Assumption 1 (Effective testing) *After effective testing, the random variable $\tilde{d}_{kj}$ will be revealed to be a constant number $d_{kj} \in \{0, 1\}$; After faked testing, there is no more information acquired for $\tilde{d}_{kj}$.*

To guarantee firms conduct effective testing,the regulator will review and verify the testing information provided by firms. For a new intermediate candidate k, the regulator needs to verify the information set $I_t = \left\{b_k, \tilde{d}_{k1}, \tilde{d}_{k2}, ..., \tilde{d}_{k,M_t}\right\}$. Applications with faked testing results will be dismissed immediately.

I make additional assumptions:

Assumption 2 *With unit labor cost ω to review each element in set I_t, testing results can be accurately verified by the regulator.*

Assumption 3 *According to the legislative mandates, regulator will review and verify all testing information in the new product applications.*

Labor needed for reviewing and verifying testing information constitutes the main regulatory staff with size z_t. According to the three assumptions in this subsection, to accurately review ΔE_t new product applications at t will demand a regulatory staff size[7] :

$$z_t = \omega\left(1 + M_t\right) \cdot \Delta E_t \tag{8}$$

3.5.2 The Decision Rule for Approval

The regulator follows a simple decision rule (9)[8] to approve an application: only approving a new product when the benefit is larger than the sum of risks:

$$approve \;\; \text{iff} \;\; \left(b_k > \sum_{j=1}^{M_t} d_{kj}\right) \tag{9}$$

According to the decision rule (9), the number of newly approved drugs at time t is ΔM_t :

$$\Delta M_t = \sum\nolimits_{i=1}^{\Delta E_t} \left[\mathbf{1}_{\left\{b_k > \sum_{j=1}^{M_t} \tilde{d}_{kj}\right\}}\right] \tag{10}$$

To characterize the relation between ΔM_t and ΔE_t, I define a function Q_t as below:

Definition 1 *The Qualified Innovation Ratio Q_t is defined as (11),*

$$Q_t = \frac{new\ drugs\ approved\ at\ t}{new\ drug\ patents\ issued\ at\ t} = \frac{\Delta M_t}{\Delta E_t} \tag{11}$$

Q_t maps the number of newly issued patents ΔE_t to the number of newly approved (or qualified) products ΔM_t at time t. The puzzling fact of a sharply declining Q_t for drugs over time was presented at the very beginning of this paper.

3.5.3 Risk Generating and a Binomial Distribution

Each new drug k has a probability q_{kj} of interacting with any existing drugs j. Our finding in the empirical section shows that q_{kj} is quite constant. Moreover, these probabilities are independent from each other. Then I use q to approximate q_{kj}.

Therefore the sum of risks $\sum_{j=1}^{M_t} \tilde{d}_{kj}$ caused by drug k (when the number of varieties of existing drugs is M_t) follows a Binomial distribution (12),

$$\sum\nolimits_{j=1}^{M_t} \tilde{d}_{kj} \sim B(M_t, q) \tag{12}$$

[7] Later I will omit the "1" in (8) for convenience.

[8] This simple decision rule might not be optimal. I can extend this to a generalized optimal decision rule.

3.5.4 Probability of Approval and Qualified Innovation Ratio Q_t

Because I mainly investigate the dynamics of innovation-induced risks, for simplicity I assume the benefit of a new drug is relatively constant $b_k \approx b$. Then the decision rule for approval (9) implies that the probability of approving a drug at time t is equal to a Binomial CDF function $F(b; M_t, q)$:

$$F(b; M_t, q) = \Pr(\textstyle\sum_{j=1}^{M_t} \tilde{d}_{kj} < b) \tag{13}$$

The Qualified Innovation Ratio Q_t should be determined by the probability of approving a drug, so I have:

$$Q_t = F(b; M_t, q) \tag{14}$$

With this setup, Q_t is simply equal to the Binomial CDF function $F(b; M_t, q)$. Moreover, the number of approved drugs at time t will be:

$$\Delta M_t = F(b; M_t, q) \cdot \Delta E_t \tag{15}$$

3.6 Intermediates Producer (Stage 2): Testing, Application and Production

The innovative intermediates producers will conform to the requirements of the regulator to test the newly invented intermediate candidates. According to the testing results, firm will decide whether to submit an application. If they submit an application and the application gets approved, the firm will produce the intermediate product and sell to the final goods producers.

3.6.1 Testing

The firm will test the required set $I_t = \left\{ b_k, \tilde{d}_{k1}, \tilde{d}_{k2}, ..., \tilde{d}_{k,M_t} \right\}$. Firm can conduct either *effective testing* or *faked testing*. Assuming conducting effective testing for each item in I_t costs the firm c units of labor, whereas faked testing costs 0 labor. The firm can choose the total number of items κ for effective testing. The total labor hired by the firm for testing is denoted by n_t :

$$n_t = c \cdot \kappa \tag{16}$$

Then the intermediate producer submits the testing results of all their new intermediate candidates to the Regulator.

3.6.2 Production after Approval

If the new intermediate product is approved by the regulator, the innovative firm can produce the new intermediate input. I assume that one unit of any intermediate input is produced by 1 unit of final goods. Innovative firm monopolizes the production of the new products it just invented. Each intermediate product firm chooses the optimal quantity $x_{i,t}$ to maximize the profit flow $\pi_{i,t}$:

$$\max_{x_{i,t}} \pi_{i,t} = p_{i,t} x_{i,t} - x_{i,t} \tag{17}$$

where $p_{i,t}$ is equal to the marginal productivity of intermediate product i in final goods production.

Then the Net Present Value (NPV) of a qualified innovation approved at t is:

$$V_{i,t} = \sum_{\tau=t+1}^{\infty} \frac{\pi_{i,\tau}}{\prod_{s=t+1}^{\tau} (1 + r_s)} \tag{18}$$

I assume the entry into R&D sector is free. The NPV discounted by the Qualified Innovation Ratio Q_t should be equal to the sum of R&D, testing cost, and the regulatory staff's compensation[9]. This gives the Research-arbitrage equation (19),

$$Q_t \Delta E_t \cdot V_{i,t} \leq w_t \left(h_t + n_t + z_t\right) \tag{19}$$

If "$<$" happens in (19), there will be no R&D.

3.7 Resource Constraints

Resource constraint in the final goods sector is,

$$C_t + X_t \leq Y_t \tag{20}$$

I assume away population growth. At any time, consumers inelastically supply labor at constant quantity L. The labor market clears at any time t:

$$l_t + h_t + n_t + z_t \leq L \tag{21}$$

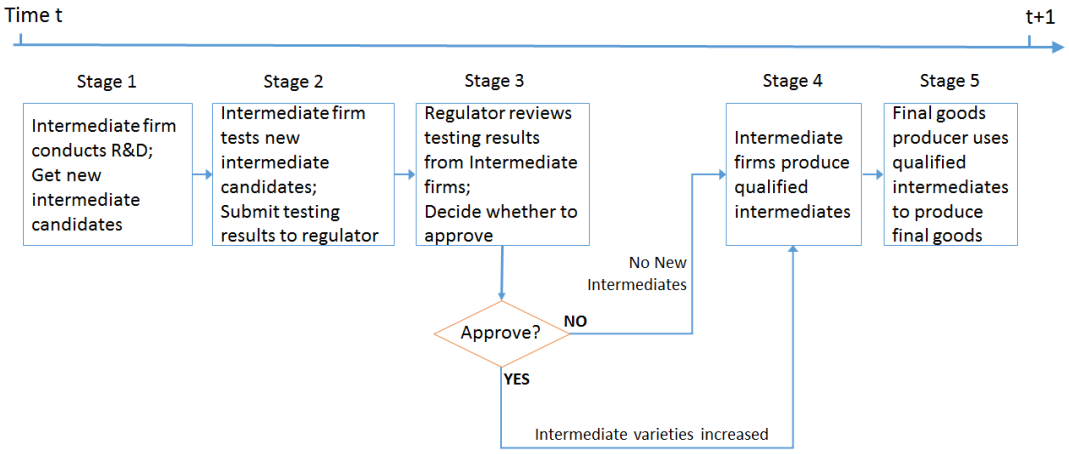
[9] According to The Prescription Drug User Fee Act (PDUFA), since 1992, the FDA has been authorized to collect fees from drug companies to fund the new drug approval process. The 2016 Lautenberg Act also granted the EPA similar authority to collect fees to finance the approval process for new chemicals. That is, though the FDA and EPA are independent, fees for reviewing new products are funded by the applicants.

where l_t represents labor for final goods production, $h_t + n_t$ is the total labor hired by intermediate producers, and z_t is the staff hired by the regulator.

3.8 The Timeline and Evolution of Macro Risk Matrix

The Timeline is illustrated by (8).

Figure 8: The Timeline



After new intermediate products are invented and finally approved by the regulator, the **Macro Risk Matrix** Ξ_{M_t} evolves, as the following,

$$\Xi_{M_{t+1}} = \begin{bmatrix} & & \tilde{d}_{1,M_t+1} & \tilde{d}_{1,M_t+2} & \cdot & \tilde{d}_{1,M_{t+1}} \\ & \Xi_{M_t} & \tilde{d}_{2,M_t+1} & \tilde{d}_{2,M_t+2} & & \tilde{d}_{2,M_{t+1}} \\ & & \cdot & \cdot & & \cdot \\ & & \tilde{d}_{M_t,M_t+1} & \tilde{d}_{M_t,M_t+2} & & \tilde{d}_{M,M_{t+1}} \\ \tilde{d}_{M_t+1,1}, \tilde{d}_{M_t+1,2}, ..., \tilde{d}_{M_t+1,M_t} & & \tilde{d}_{M_t+1,M_t+1} & \tilde{d}_{M_t+1,M_t+2} & \cdot & \tilde{d}_{M_t+1,M_{t+1}} \\ \tilde{d}_{M_t+2,1}, \tilde{d}_{M_t+2,2}, ..., \tilde{d}_{M_t+2,M} & & \tilde{d}_{M_t+2,M_t+1} & \tilde{d}_{M_t+2,M_t+2} & \cdot & \tilde{d}_{M_t+2,M_{t+1}} \\ \cdot & & \cdot & \cdot & \cdot & \cdot \\ \tilde{d}_{M_{t+1},1}, \tilde{d}_{M_{t+1},2}, ..., \tilde{d}_{M_{t+1},M_t} & & \tilde{d}_{M_{t+1},M_t+1} & \tilde{d}_{M_{t+1},M_t+2} & \cdot & \tilde{d}_{M_{t+1},M_{t+1}} \end{bmatrix} \downarrow$$

From t to $t+1$,after new R&D investment, the random matrix grows from Ξ_{M_t} to $\Xi_{M_{t+1}} = \Xi_{M_t+\Delta M_t}$.

The incremental risk ΔD_t would be:

$$\Delta D_t = \sum_{i=1}^{\triangle M_t} \sum_{j=1}^{M_t} \tilde{d}_{ij} \tag{22}$$

Notice the incremental risk is proportional to the number of existing intermediate products.

After the intermediates grow large enough, the expected value of any untested patent can be negative because the aggregate adverse effects become so large.

Testing can help to find the shrinking share of patents with positive net value.

3.9 Optimal Growth

The objective of the allocation problem is to optimally allocate resources between final good production and R&D activity. In detail, the optimal allocation of resource is to choose the time paths $\left\{C_t, \{x_{i,t}\}_{i\in[1,M_t]}, h_t, n_t, l_t\right\}$ that maximizes the sum of the discounted net utility, solving the following problem (23) :

$$\max_{\left\{h_t,n_t,l_t,C_t,\ [x_{i,t}]_{i\in[1,M_t]}\right\}} \sum_{t=0}^{\infty}\beta^t \frac{\left(C_t-\tilde{D}_t\right)^{1-\gamma}}{1-\gamma} \tag{23}$$

$$\tilde{D}_t = \frac{X_t \cdot D_t}{M_t} \tag{24}$$

$$X_t = \sum_{i=1}^{M_t} x_{i,t} \tag{25}$$

$$\frac{\Delta E_t}{E_t} = \lambda h_t \tag{26}$$

$$\frac{\Delta M_t}{\Delta E_t} = Q_t = F(b, M_t, q) \tag{27}$$

$$\Delta D_t = \Delta M_t \times \left[\int_0^b \nu \cdot f(\nu, M_t, q) d\nu\right] \tag{28}$$

$$n_t = c \cdot \Delta E_t \times M_t \tag{29}$$

$$C_t + X_t = \frac{1}{\alpha} l_t^{1-\alpha} \cdot \sum_{i=1}^{M_t} (x_{i,t})^{\alpha} \tag{30}$$

$$l_t + h_t + n_t = L \tag{31}$$

where X_t is the total quantify of intermediate products, l_t denotes labor for final goods production. Intermediate producer hires h_t researchers to conduct R&D to get new products candidates, and hire additional n_t researchers to conduct testing regarding the intermediate product candidates. For the optimal allocation problem, I do not need regulator to review testing results.

$F(b, M_t, q)$ denotes a Binomial CDF, equal to the Qualified Innovation Ratio Q_t, or the probability of approval. The Binomial PDF $f(\nu, M_t, q)$ represents the probability of getting exactly ν interactions in M_t trials, with q as the probability of a single interaction between

intermediates. Therefore $\int_0^b \nu \cdot f(\nu, M_t, q)d\nu$ calculates the average number of adverse effects that a new intermediate candidate will interact with all M_t existing intermediates at time t.

3.9.1 The Static Allocation Problem at Time t

It is better to firstly solve the static allocation problem at time t. This can simplify the grand optimization problem (23) by reducing the number of variables. At time t, the optimal $x_{i,t}$ can be chosen to maximize the main component of instantaneous utility $C_t - \tilde{D}_t$. I know that $C_t - \tilde{D}_t = \frac{1}{\alpha} l_t^{1-\alpha} \cdot \sum_{i=1}^{M_t} (x_{i,t})^{\alpha} - \sum_{i=1}^{M_t} x_{i,t} - \frac{X_t \cdot D_t}{M_t}$.

For simplicity of calculation, I make the following assumption:

Assumption 4 *At any time t, all existing intermediate products will be used at the same quantity:* $x_{i,t} = x_t$.

Then the optimal x_t^* is calculated from the following optimization:

$$\underset{x_t}{max} M_t \left(\frac{1}{\alpha} l_t^{1-\alpha} \cdot x_t^{\alpha} - x_t - x_t \cdot \frac{D_t}{M_t} \right) \tag{32}$$

I can solve (32) to get x_t^* :

$$x_t^* = l_t \left(1 + \frac{D_t}{M_t} \right)^{\frac{1}{\alpha - 1}} \tag{33}$$

With the solution x_t^* *above*, I can represent the time t instantaneous utility u_t without $x_{i,t}$:

$$u_t = \underbrace{\frac{1-\alpha}{\alpha} \cdot M_t \cdot \underbrace{\frac{1}{\left(1 + \frac{D_t}{M_t}\right)^{\frac{\alpha}{1-\alpha}}}}_{risk\ discount\ factor}}_{risk\ discounted\ TFP} \cdot l_t \tag{34}$$

3.9.2 Necessary Condition for Growth to Start

From the instantaneous utility (34) , I can see the part labeled as *Risk discount factor* will determine how useful an extra innovation is to the consumer. The order of D_t relative to M_t is determinant.

If D_t is a linear function of M_t, e.g. $D_t = s \cdot M_t$, then u_t can be represented by a function form $u_t = A \cdot M_t \cdot l_t$, where A is a constant. *Risk discounted TFP* in (34) is linear in M_t. Instantaneous utility is linear in the number of varieties of innovations, then the dynamics of (23) resembles a classical variety expansion endogenous growth model.

But in another case, if $\alpha = 0.6$, and $D_t = M_t^2$, $u_t \approx \frac{1-\alpha}{\alpha} \frac{1}{\sqrt{M_t}} l_t$. So the highest instantaneous utility is $u_0 \approx \frac{1-\alpha}{\alpha} \frac{1}{\sqrt{M_0}} L$. There will be no growth from $t = 0$.

I can derive a more general result as below:

Proposition 1 *There will be no growth from the beginning iff* $D_t = O(M_t^\sigma)$ *and* $\sigma \geq \frac{1}{\alpha}$.

When $D_t = O(M_t^\sigma)$ *and* $\sigma \geq \frac{1}{\alpha}$,the *Risk discounted TFP* is a decreasing function of M_t. A larger M_t will reduce utility. No R&D and growth will happen from the beginning.

This results imply when the damage grows too fast relative to the varieties of innovations, there should be no innovation and variety increase in the first place. The condition also depends on the capital share α. A high capital share will amplify the damage so that the condition for non-growth can be more easily satisfied.

Our empirical work finds a quadratic relationship: $DDIs = f(drugs)$ in the function form of (1).In this case, D_t is quadratic function of M_t, $D_t = M_t^2, \sigma = 2$. I normally take $\alpha = 0.3$ in Macroeconomics.$\sigma = 2 < \frac{1}{0.3} = \frac{1}{\alpha}$. The condition for non-growth is not satisfied according to Proposition 1. In fact, we have $u_t = \frac{1-\alpha}{\alpha} \cdot M_t \cdot l_t \cdot \frac{1}{(1+M_t)^{\frac{3}{7}}}$, which can be simplified to:

$$u_t \approx \frac{7}{3} \cdot M_t^{\frac{4}{7}} \cdot l_t \tag{35}$$

Then a larger number of intermediates varieties is beneficial and growth will happen at $t = 0$.

3.9.3 Revised Optimization Problem

I move on to the dynamic optimization problem.

Labor devoted to testing is $n_t = c \cdot \Delta E_t \times M_t$. Because $\Delta E_t = \lambda h_t E_t$, I can get the representation of n_t in h_t :

$$n_t = c\lambda M_t E_t \cdot h_t \tag{36}$$

This also gives us the ratio between R&D staff and testing staff.

From $n_t + h_t + l_t = L$, I can derive the representation of h_t in l_t :

$$h_t = \frac{L - l_t}{1 + c\lambda M_t E_t} \tag{37}$$

With the results derived in the last subsection, I get a simplified optimization problem:

$$\max_{\{l_t\}} \sum_{t=0}^{\infty} \beta^t \cdot \frac{\left[M_t \cdot l_t \left(1 + \frac{D_t}{M_t} \right)^{\frac{\alpha}{\alpha-1}} \right]^{1-\gamma}}{1-\gamma} \tag{38}$$

$$\Delta E_t = \lambda \frac{L - l_t}{1 + c\lambda M_t E_t} E_t \tag{39}$$

$$\Delta M_t = F(b, M_t, q) \cdot \Delta E_t \tag{40}$$

$$\Delta D_t = \Delta M_t \times \left[\int_0^b \nu \cdot f(\nu, M_t, q) d\nu \right] \tag{41}$$

Now there is only one control variable $\{l_t\}$, together with three state variables:

E_t : the total patented innovations;
M_t : the total qualified innovations;
D_t : aggregate risk (corresponding to theoretical DDIs).

I can set up the following Lagrangian to solve (38)

$$\mathcal{L} = \sum_{t=0}^{\infty} \left\{ \begin{array}{c} \beta^t \cdot \frac{\left[M_t \cdot l_t \left(1 + \frac{D_t}{M_t} \right)^{\frac{\alpha}{\alpha - 1}} \right]^{1-\gamma}}{1-\gamma} \\ + \mu_t \cdot \left[E_{t+1} - E_t - \lambda \frac{L - l_t}{1 + c\lambda M_t E_t} E_t \right] \\ + \xi_t \cdot \left[M_{t+1} - M_t - F(b, M_t, q) \cdot \lambda \frac{L - l_t}{1 + c\lambda M_t E_t} E_t \right] \\ + \varphi_t \cdot \left[D_{t+1} - D_t - F(b, M_t, q) \cdot \lambda \frac{L - l_t}{1 + c\lambda M_t E_t} E_t \cdot \left(\int_0^b \nu \cdot f(\nu, M_t, q) d\nu \right) \right] \end{array} \right\} \tag{42}$$

where the costate variables μ_t, ξ_t, φ_t represent the shadow prices of an additional patent, a qualified innovation, and risk respectively.

From four sets of first order conditions for $l_t, \mu_t, \xi_t, \varphi_t$, together with three $LOMs$ for E_t, M_t, D_t, I can get a system of seven ODEs for (42), which are put in the Appendix.

Proposition 2 *Growth stops at a threshold $\bar{M}$. At the steady state, innovation stops.*

In our model, additional new innovations will increase testing cost as well as reduce qualified innovation ratio for the future. In contrast, the canonical endogenous growth models will have an expanding choice set over time. For example, in the Romer model, $E_{t+1} - E_t = \lambda l_t \cdot E_t < \lambda L \cdot E_t$. The choice set for E_{t+1} keeps expanding proportional to E_t, therefore growth will never stop.

There will be a $\bar{M}$, where the expected cost of innovation will be less than the expected benefit of introducing an additional innovation. This results in a steady state where R&D stops. I analyze the existence of such a threshold as follows.

Although it becomes more difficult for an innovation candidate to qualify for approval as the pool of qualified innovations enlarges, there is always a positive probability of qualificaton since $F(b, M_t, q) > 0$. The question of whether R&D stops depend on the total expected cost of R&D and testing.

At time t, the labor cost of inventing and obtaining a patent is $\frac{1}{\lambda E_t}$,and the cost of testing a new innovation candidate is $c \cdot M_t$. The probability of the patent being qualified to market is $F(b, M_t, q)$. So the expected total cost of successfully increasing a new qualified innovation is $\frac{\frac{1}{\lambda E_t}+cM_t}{F(b,M_t,q)}$.

At the steady state, all labor is allocated to production of the aggregate good: $l_t = L$. There will be a switching at the threshold.

3.10 Equilibrium Growth

In this section, I will characterize the Equilibrium Growth Path of the model.

The Equilibrium Definition

An equilibrium of this model is an allocation, such that,

(1) Consumers make their optimal choices between consumption and savings $[C_t, S_t]_{t=0}^{\infty}$ taking interest rate as given;

(2) Final goods producers choose the quantity of labor $[l_t]_{t=0}^{\infty}$ and quantities of each intermediate products $\left[\{x_{i,t}\}_{i\in[0,M_t]}\right]_{t=0}^{\infty}$ to maximize their profit, taking the wage rate and intermediate price as given;

(3) Each intermediate producer with a qualifed intermediate product maximizes its profit by choosing optimal price and quantities $\left[\{p_{i,t}, x_{i,t}\}_{i\in[0,M_t]}\right]_{t=0}^{\infty}$ to supply, taking the interest rate as given;

(4) Taking as given wage rate and the price of a qualified intermediate product, a potential intermediate producer chooses the quantity of researchers $[h_t]_{t=0}^{\infty}$ to hire, the quantities of effective testing which is equivalent to proportionally choosing the size of their testing staff $[n_t]_{t=0}^{\infty}$, and submit to regulator the applications of all their new intermediate product candidates; free entry condition will determine the path of varieties of intermediate product candidates $[E_t]_{t=0}^{\infty}$;

(5) The regulator reviews and verified all testing results in the new product applications, and charges the firms a fee to hire regulatory staff with size $[z_t]_{t=0}^{\infty}$, which is proportional to the workload of reviewal and verification. The regulator immediately dismisses any application with faked testing results, and then decide whether to approve an application according to a decision rule (9). Regulator's decisions determine the path of varieties of qualified intermediates $[M_t]_{t=0}^{\infty}$;

(6) Markets clear to determine interest rate and wage rate $[r_t, w_t]_{t=0}^{\infty}$

The regulator reviews and verifies all testing results in new intermediate product applicaitons. All applications with faked testing results will be rejected. Then the only equilibrium

path left in the game is that potential intermediate producers only conduct effective testing and tell true testing outcomes to the regulator, therefore removing all other inefficient equilibrium paths.

3.10.1 Consumer Optimization

Similar to the canonical growth model, I can solve and get the growth rate of (net) consumption,

$$g_t = \frac{\Delta\left(C_t - \tilde{D}_t\right)}{C_t - \tilde{D}_t} = \frac{r_t - \rho}{\gamma} \tag{43}$$

where $\tilde{D}_t$ follows (24).

3.10.2 Equilibrium Factor Prices

The price of intermediate product i is equal to its marginal productivity in final good production (3) :

$$p_{i,t} = x_{i,t}^{\alpha-1} \cdot l_t^{1-\alpha}$$

Wage is equal to marginal productivity of labor in final good production (3) :

$$w_t = \frac{1-\alpha}{\alpha} l_t^{-\alpha} \cdot \sum_{i=1}^{M_t} \left(x_{i,t}\right)^{\alpha}$$

Intermediate producer will choose the optimal output $x_{i,t}$ to maximize profit, solving problem (9) :

$$x_{i,t} = \alpha^{\frac{1}{1-\alpha}} \cdot l_t \tag{44}$$

and the intermediate product $i\prime s$ profit at t will be:

$$\pi_{i,t} = \frac{1-\alpha}{\alpha} \alpha^{\frac{1}{1-\alpha}} \cdot l_t \tag{45}$$

the profit is proportional to the final goods production labor l_t.

Applying the solution $x_{i,t}$ in (44) can further simplify $p_{i,t}$ and w_t :

$$w_t = \frac{1-\alpha}{\alpha} \alpha^{\frac{\alpha}{1-\alpha}} \cdot M_t \tag{46}$$

wage is proportional to the varieties of innovations.

$$p_{i,t} = \frac{1}{\alpha} \tag{47}$$

the intermediate product price is constant over time.

3.10.3 R&D Expenditure in Equilibrium

The Research-arbitrage equation (19) implies:

$$Q_t \Delta E_t \cdot \sum_{\tau=t+1}^{\infty} \frac{\pi_{i,\tau}}{\prod_{s=t+1}^{\tau} [1+r_s]} \leq w_t \left(h_t + n_t + z_t\right) \tag{48}$$

Entry into the R&D sector is free, so the total R&D expenditure at t should be equal to the present value of $Q_t \Delta E_t$ qualified innovations generated at t, which is the sum of the discounted profits from time t on.

By substituting (8), (36),and (46) into (48), we can get

$$\sum_{\tau=t}^{\infty} \frac{1}{[1+r(\tau)]^{\tau-t}} \pi_{i,\tau} \leq \underbrace{\frac{\frac{1-\alpha}{\alpha} \alpha^{\frac{\alpha}{1-\alpha}} M_t \left[1 + (c+\omega)\, \lambda E_t M_t\right]}{\lambda E_t \cdot F(b, M_t, q)}}_{ERC} \tag{49}$$

Definition 2 *The Expected R&D Cost* (ERC). *The RHS of* (49) *denotes the* Expected R&D Cost (ERC) *: the expected expenditure that an innovative firm needs to spend to get a qualified innovation successfully.*

In the following proposition, I give a lower bound for the Expected R&D Cost in the limit.

Proposition 3 *The Expected R&D Cost (ERC) has a lower bound* $\underline{ERC}$ *:* $ERC \geq \underline{ERC}$, *and* $O(\underline{ERC}) = M_t^2 \cdot e^{2q^2 \cdot M_t}$.

This proposition gives us an amazing result: in the limit, the Expected R&D Cost grows faster even than exponential. The exponential component comes from the reciprocal of the qualified innovation ratio.

3.10.4 The Steady State

This subsection discuss the steady state of the decentralized equilibrium.

Proposition 4 *There exists a threshold* $\hat{M}$ *as the upper limit of this economic system. R&D and growth stops when the threshold* $\hat{M}$ *is reached. A larger labor force L can lead to a higher threshold* $\hat{M}$.

The proof is put in Appendix B. Within this economic setup, there is an upper limit $\frac{L}{\rho}$ for the value of a qualifed patent. Innovators can only earn the monopolistic profit to this limit. The average R&D cost is an increasing function of the varieties of innovations.

This proposition implies that the R&D cost can grow to be so high as to fully stymie R&D in the end.

3.10.5 Two Externalities

There are two externalities in the decentralized model.

The externality of *knowledge spillover:* new knowledge can reduce the cost of future R&D cost $\frac{1}{\lambda E_t}$. This traditional source of externality will discourge private R&D investment due to the public good nature of knowledge.

The externality of *risk spillover:* the cost of testing any new innovation candidate is cM_t, which increases with the number of existing qualified innovations. The Qualified Innovation Ratio of later innovations will be reduced due to risk spillover of early innovations. This is the type of negative externality we measure and demonstrate in Section 2.

3.11 Comparison with Romer Model

Eqn (50) makes a decomposition of the Expected R&D Cost (ERC). We can see there are three factors contributing to this puzzling escalation of expected R&D cost. Firstly, wage rate grows proportional to M_t. Secondly, testing cost grows with M_t after cancelling out the knowledge spillover benefit λE_t in the denominator. This includes the testing expenditure that innovative firms directly spend, and regulatory cost that regulators charge firms for reviewing their new product applications. Thirdly, the declining Qualified Innovation Ratio due to the innovation-induced risk structure.

$$ERC_t = \frac{\underbrace{\frac{1-\alpha}{\alpha}\alpha^{\frac{\alpha}{1-\alpha}}M_t}_{wage} \times \left[1 + \underbrace{c \cdot \lambda E_t \cdot M_t}_{firm's\ testing\ cost} + \underbrace{\omega \cdot \lambda E_t \cdot M_t}_{regulatory\ cost}\right]}{\underbrace{\lambda E_t}_{knowledge\ spillover} \times \underbrace{F(b, M_t, q)}_{Qualified\ Innovation\ Ratio}} \tag{50}$$

This has a sharp contrast with the canonical endogenous growth model (Romer style).

The Romer model has the following ERC representation:

$$ERC_{Romer,\,t} = \frac{\underbrace{\frac{1-\alpha}{\alpha}\alpha^{\frac{\alpha}{1-\alpha}}M_t}_{wage} \times \left[1 + \underbrace{0}_{testing\ cost} + \underbrace{0}_{regulatory\ cost}\right]}{\underbrace{\lambda M_t}_{knowledge\ spillover} \times \underbrace{1}_{Qualified\ Innovation\ Ratio}} \tag{51}$$

Canonical endogenous growth model does not have the qualification process, and so does not distinguish between M_t and E_t. We can see from (51), the knowledge spillover effect in the denominator can exactly cancel out the wage rate increase in the nominator. Though wage rate increases proportionally to the knowledge growth rate, the R&D productivity grows at the same rate due to knowledge spillover. Moreover, there is no testing cost in the Romer model. Therefore, this results in a neat solution (52) for ERC :

$$ERC_{Romer,\,t} = \frac{1}{\lambda}\frac{1-\alpha}{\alpha}\alpha^{\frac{\alpha}{1-\alpha}} \tag{52}$$

The Expected R&D Cost *keeps constant over time in the canonical endogenous growth model*. This is a crucial feature behind the canonical endogenous growth model. However, empirical evidence in the following subsection contradicts this prediction very firmly. The comparison between (50) and (51) illustrates a key difference between this regulatory growth model and the canonical endogenous growth model.

3.12 Simulation and Quantitive Results

In this section, I provide some numerical results for the problem (38) . This is challenging due to the $3-dimensional$ structure of the state space, which is exploding. I have designed an efficient algorithm to conquer this.

The following Figure (9) displays the evolution of states $(E, M, D)_t$ using a well-designed Value Function Iteration algorithm. Figure (9) shows the optimal growth path, evolving from initial state $(E, M, D)_0$ to $(E, M, D)_t$.

The qualifed innovations M_t is a concave function of the number of patents E_t. Innovation finally reaches a steady state and growth stops. Risk varieties D_t is initially a convex function of the number of patents and switches to a concave function at a higher level.

Definition 3 *The reachable set of states* Θ *from initial state* $(E, M, D)_0$: $\Theta = \{(E, M, D)_i |$ *there is a feasible transition path from* $(E, M, D)_0$ *to* $(E, M, D)_i\}$.

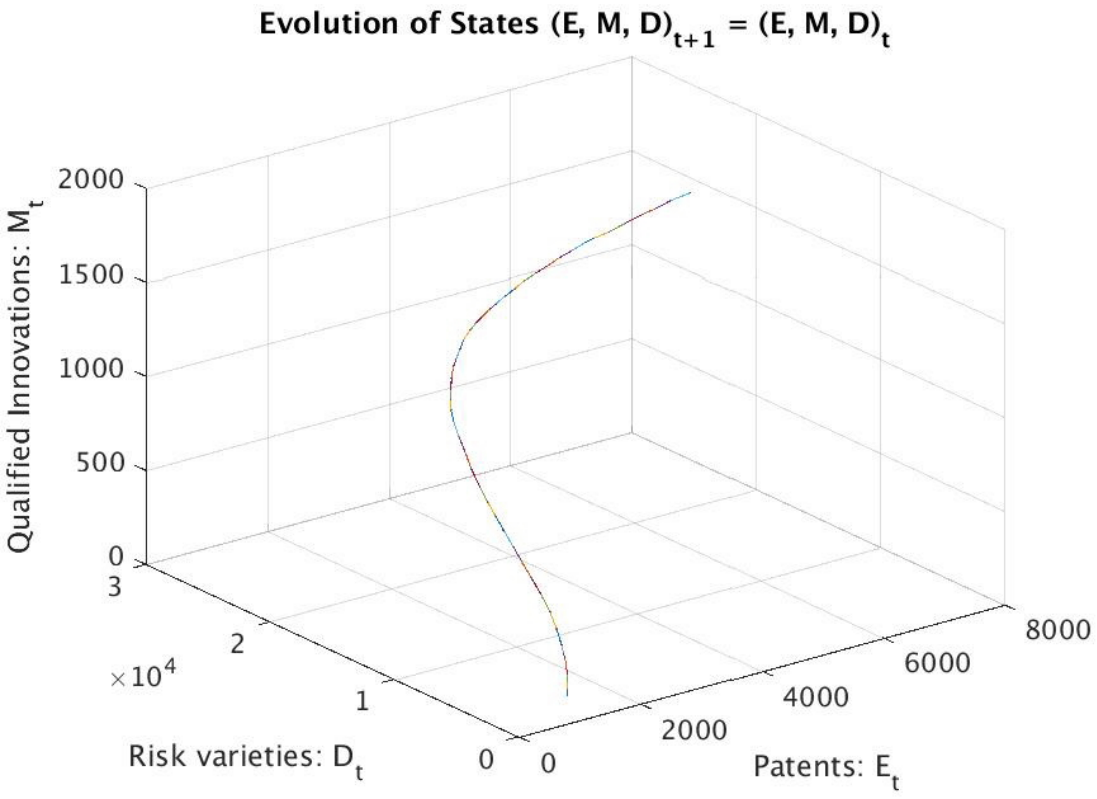


Figure 9: State Evolution

Although the whole state space is huge, the reachable set of states from $(E, M, D)_0$ is relatively small. As the first step, our algorithm recursively calculate the reachable set of states Θ for the initial state $(E, M, D)_0$. The first step of the algorithm stops until no new state is added into Θ.

Moreover, for each state $(E, M, D)_i$ in Θ, there exists a State Transition Set Ψ_i :

Definition 4 *State Transition Set* Ψ_i *from state* $(E, M, D)_i$: $\Psi_i = \{(E, M, D)_j |$ *there is a feasible direct transition from* $(E, M, D)_i$ *to* $(E, M, D)_j\}$.

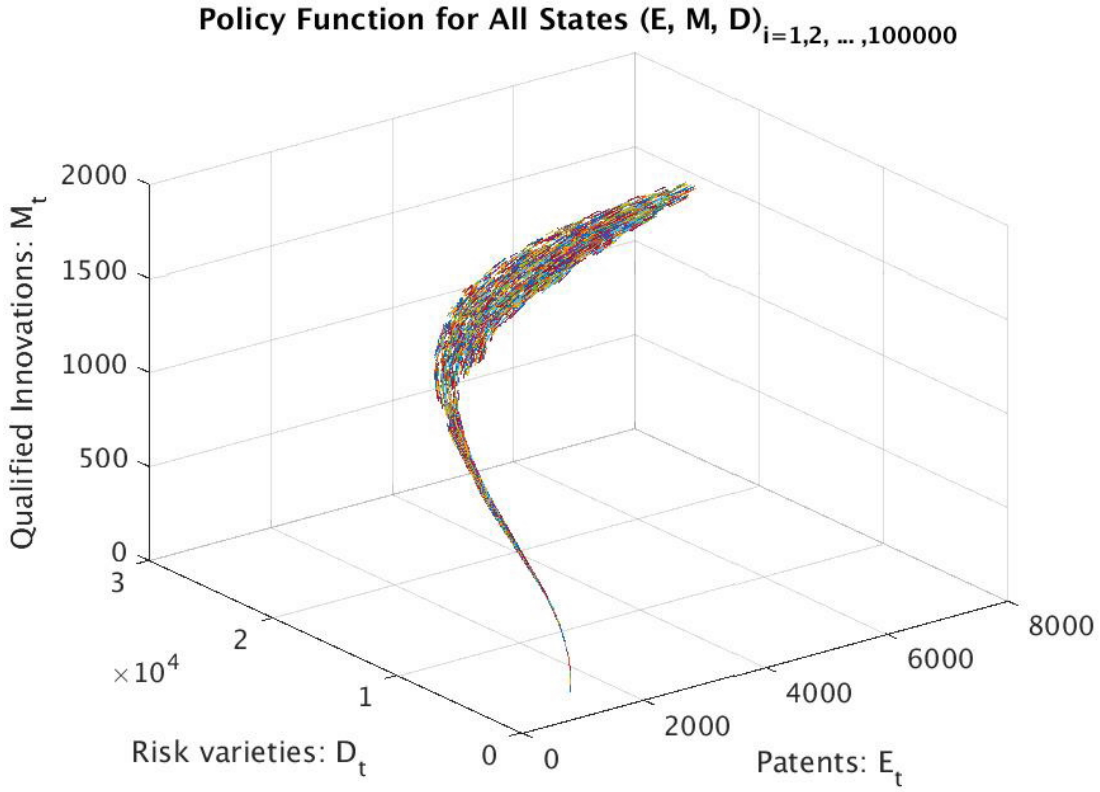


Figure 10: The Policy Function

Therefore, as the second step of our algorithm, value function iteration for each state i in Θ is based on its specific State Transition Set Ψ_i :

$$V_i = \max_{j \in \Psi_i} \{u(c_j) + \beta \cdot V_j\} \tag{53}$$

Ψ_i for each state is small. With this algorithm, I derive and depict a specific form of the policy function shown in Figure (10). In Figure (10) , from each state $i \in \Theta$, I draw a line from state i to state j, $j = P(i)$, where $P(i)$ is the policy function.

As we can see, although the whole $3-dimensional$ state space is huge, the reachable set from the initial state is only a small slice of the full space.

4 Implications for R&D and Regulation

In this section, we discuss the implications of our theoretical model for regulation, and provide additional empirical evidence. There will be greater expenditures on regulation and compliance. Then we analyze the current regulatory regimes and discuss a proposal for future regulatory reform.

4.1 The Composition of Regulation

A direct implication of our new empirical fact in Section 2 and new theory in Section 3 is that regulation will not only grow fast but also become more and more risk-oriented.

Resources spent on regulations have grown significantly during the last several decades. The long-run trend of regulatory spending is displayed by Figure 2B. When regulatory spending is decomposed into categories (see Figure 11), we can see an obvious trend. The rise of regulation is mainly caused by the disproportionate increase in the social and economic risk regulations. This offers support for our previous argument and model that the fast growing new varieties of risks are the main driving force of regulation growth.

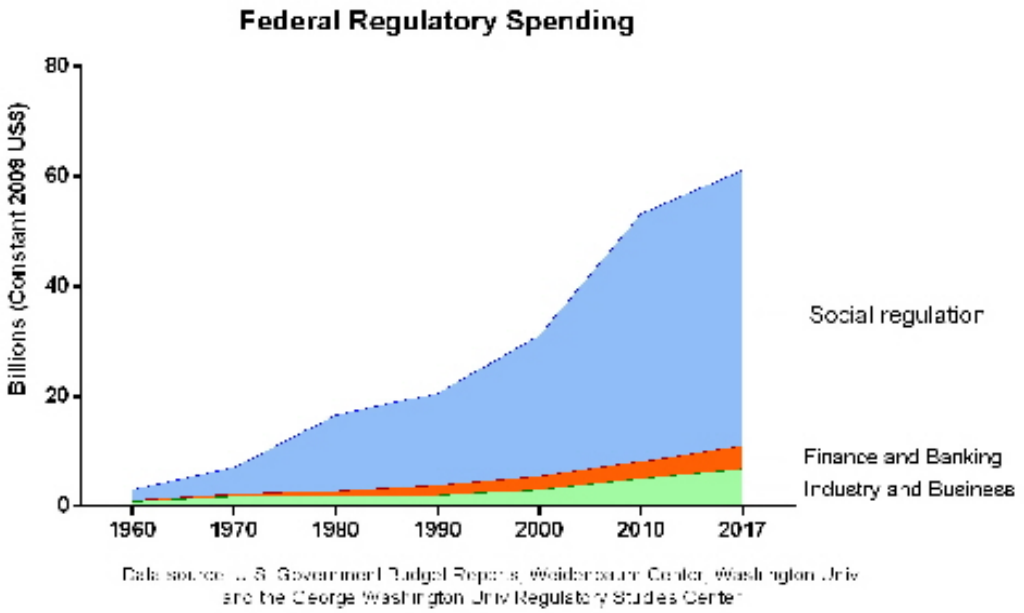


Figure 11: Decomposed Budget of Federal Regulatory Agencies (Inflation adjusted)

Moreover, traditional economic regulation, illustrated as "Industry and Business regulation" in Figure 11, stays relatively stagnant. In the traditional view of economists, regulators mainly deal with inefficiencies attributable to monopoly. In contrast, social regulations cope

with Safety, Health, and Environmental issues, with an aim to identifying, controlling and removing the risks induced by technologies. In the same sense, the purpose of Finance and Banking regulation is also to identify and control the risks in the financial and economic system. Therefore, I propose to group the Social Regulation, and Finance and Banking regulation into one grand category: the Social and Economic Risk regulations (or *abbr. Risk regulations*).

4.2 Statistics for the Interactive Risk Generating Process

From the FAERS and Drugbank datasets, I estimated that each new drug k has a probability q_{kj} of interacting with any existing drugs j. Our statistics shows that q_{kj} is quite constant around 3.5%[10]. Moreover, these probabilities are independent from each other. Then I use q to approximate q_kj :

$$q_{kj} \approx 3.5\% = q \tag{54}$$

This reflects the interactive risk generating process behind innovations. Innovation-induced risks demand the increase in regulatory expenditures to assess the NET benefits of an innovation, that is, interactions of drugs for health, and systemic risk in the financial system.

4.3 Pharmaceutical R&D

4.3.1 Skyrocketing Expected R&D Spending for New Drugs

As an important empirical puzzle, Figure (2A) shows, from 1950 to 2010, the expected R&D spending for each FDA-approved drug has increased by more than 100 times, in contrast to a $5-fold$ increase in real GDP. This is also an important factor contributing to the fast increase in health care expenditure.

The canonical endogenous growth model obviously fails to explain this fact. Nevertheless, this Pharmaceutical R&D Productivity puzzle is consistent with the prediction of our Proposition 4: the Expected R&D Cost (ERC) for each successful innovation grow faster even than an exponential function of the number of existing innovations.

According to the Regulatory Growth Theory proposed in Section 3, the rise of ERC mainly comes from two sources: the decline in Qualified Innovation Ratio, and the rise of

[10] Admittedly, this statistics comes from the data of approved drugs. I do not have data for the unapproved drugs. It can be reasonably conjectured the interaction probability between unapproved drugs and approved drugs will be higher than 3.5%.

testing cost. Following subsection discusses the cost of clinical trials. Qualified Innovation Ratio will be discussed in the next subsection.

4.3.2 Clinical Trials as Increasing Share of R&D Cost

The decomposition of ERC of our model points to three major contributors to this huge increase. Besides the declining Qualified Innovation Ratio, I will provide further evidence on the rise in testing (e.g. clinical trials) cost.

As documented by various Pharmaceutical Industry report[11], clinical trials has been growing to make up a major share of the total R&D cost for drugs.

Table 1. 2014 R&D by Function, PhRMA Member Companies

Function	**Million US$**	**Share**
Pre-Human/Pre-Clinical	11,272.7	21.2%
Phase I	4,722.0	8.9%
Phase II	5,697.8	10.7%
Phase III	15,264.4	28.7%
Approval	2,717.7	5.1%
Phase IV	8,827.0	16.6%
Uncategorized	4,751.5	8.9%
TOTAL R&D	**53,253.2**	**100.0%**
Phase I,II,III,IV, Approval	**37,228.9**	**70.0%**

Source: Pharmaceutical Research and Manufacturers of America
PhRMA Annual Membership Survey 2016.

Table 1 shows that clinical trials plus approval now take up 70% of all R&D expenditures for the PhRMA Member Companies (all major Pharmaceutical companies have been included). The share of clinical trials plus approval correspond to the component $(c+\omega)\lambda E_t \cdot M_t$ in our decomposition of the expected R&D cost (50).

The share of clinical trials cost in total pharmaceutical R&D expenditure has increased significantly for the last several decades. Figure (12) displays such a trend. From 1970s to 2000s, the share of clinical trials has increased from below 40% to more than 70%.

4.4 The Declining Qualified Innovation Ratio

Since 1938, although annual patent issuance for new drugs has grown quickly, the FDA kept approving only a stagnant number of new drugs for each year: varying around 30

[11] For example, PhRMA 2016 Biopharmaceutical Research Industry Profile.

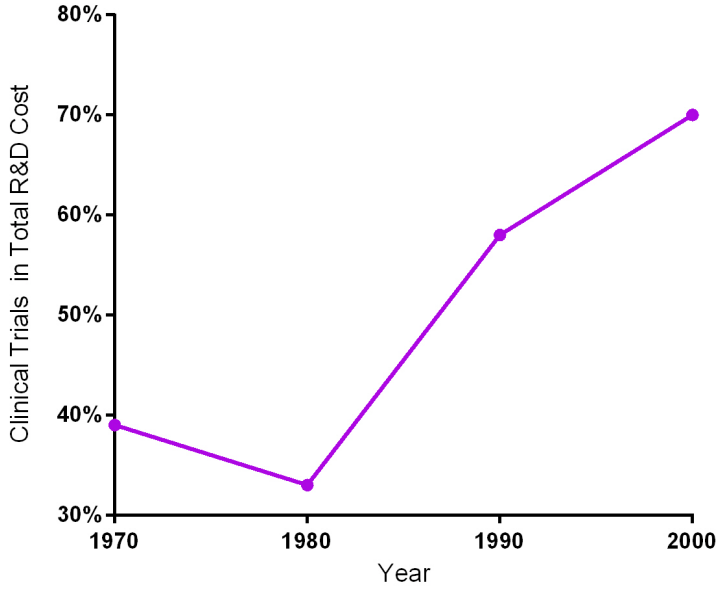


Figure 12: The Share of Clinical Trials Cost in Total R&D

New Molecular Entities (NMEs). Our first puzzling fact is the sharply declining Qualified Innovation Ratio ($= \frac{new\ products\ approved}{new\ patents\ issued}$), from around 10% in the 1950s down to 0.2% in the 2010s (see Figure 13). Existing growth theories focus on patents, and did not make a distinction between innovations and qualified innovations. In this section I will try to match our model with some empirical evidence, and explain the declining Qualified Innovation Ratio.

4.4.1 Dynamics of Qualified Innovation Ratio Q_t

The CDF function $F(b; M_t, q)$ is a decreasing functon of M_t : with the number of existing drugs M_t increasing, the probability of meeting the standards of approval is decreasing. A smaller and smaller share of new products can be qualified to meet the standards.

If the benefit is fixed, which means the threshold of a adopted drugs' adverse effects is fixed, the *Qualified Innovation Ratio* Q_t will decrease with an increasing M_t. Admittedly, there will always be a positive share of new product candidates that can satisfy the decision rule (9). Q_t is always a positive number, though Q_t is decreasing in M_t.

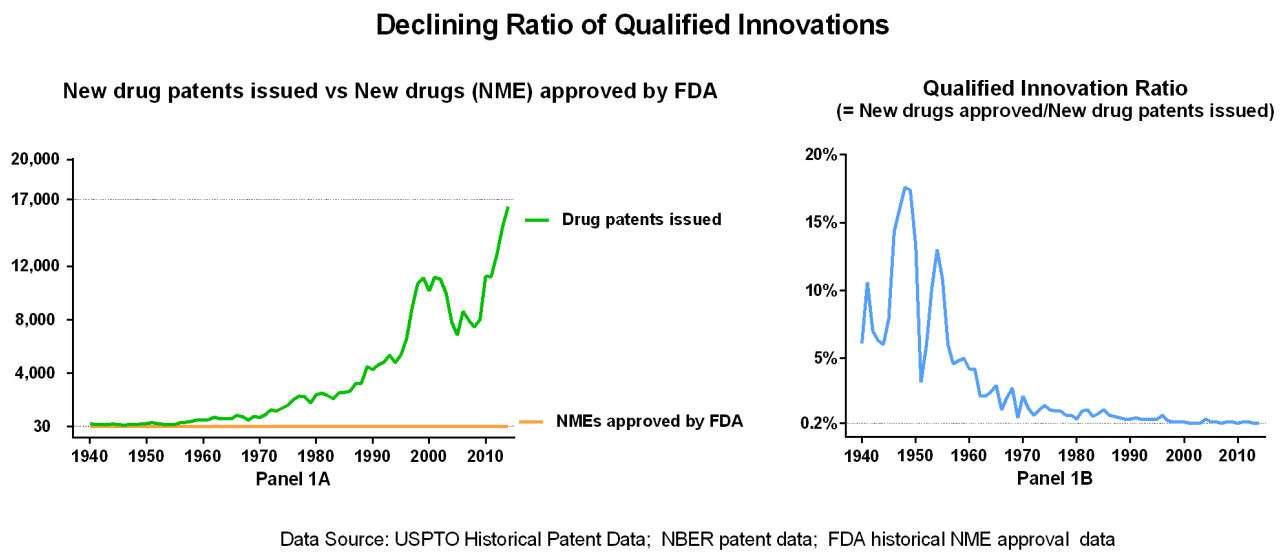
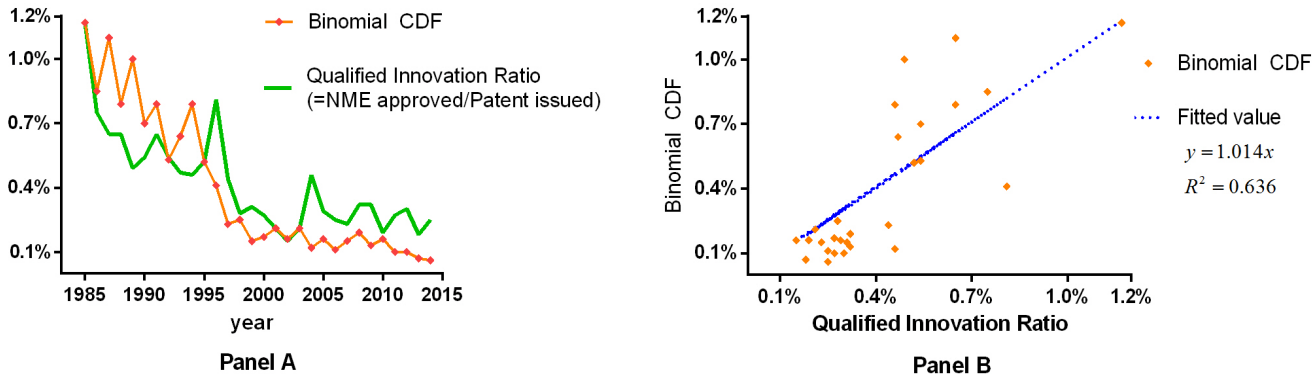


Figure 13: Patents Issued vs. New Products Approved by Regulator

4.4.2 Explaining Declining Qualified Innovation Ratio

The declining Qualified Innovation Ratio is our first puzzling fact as displayed by Figure 1. In the previous subsection, I have argued that based on our model, the Qualified Innovation Ratio Q_t is equal to a Binomial CDF $F(b; M_t, q)$.

Figure 14: Empirical match of the Binomial CDF and Qualified Innovation Ratio



The Qualified Innovation Ratio Q_t is directly calculated by (11), with the NBER patent data (category 31: pharmacy patents issued) and FDA's NME approval data.

I calibrate a Binomial CDF curve $F(b; M_t, q)$, using the estimated q in (54) and the total number of approved NME drugs as M_t. To fit the Qualified Innovation Ratio better, I also allow a slight upward slope in the threshold of aggregate risks.

Figure 14 shows the result. The left panel demonstrates the trend of the two curves. The right panel plots the Binomial CDF as a function of Q_t, and the fitted value has a reasonable R^2 value. We can claim that the model proposed before has some explanatory power for the declining Qualified Innovation Ratio.

4.5 Regulatory Regimes Classified by Data Generating Process

As described in Appendix A, the FDA's regulatory activities indeed cover the full lifespan of a new product: in the research lab, clinical trials, and adverse events reports from the market. Other regulators' activities usually resemble some stages of a full-range regulatory process.

Traditionally, the main regulatory mode of the EPA is close to the Postmarketing Surveillance stage of the FDA. The EPA only responds to a product after it is found to be the cause of a risk. For example, CO_2 emission is identified to be the major cause of global warming two hundred years later than the first introduction of steam engines. DDT (dichlorodiphenyltrichloroethane) was banned for environmental protection purpose after being globally used for half of a century. However, there has just been a major overhaul of the Chemical regulation in 2016: the Lautenberg Chemical Safety for the 21st Century Act starts to require safety testing for new chemicals before they are permitted to enter the market. The EPA is granted the new power to approve any new chemical. Chemical manufactures are required to submit a PMNs (Premanufacture Notices) for any of their new chemical products to the EPA for reviewal and approval according to the Lautenberg Act.

The CFPB (Consumer Financial Protection Bureau) largely adopts a regulatory regime of Postmarketing Surveillance. The CFPB records and traces consumers' numerous complaint reports about financial products on the market, and try to analyze and discover potential risks behind the heavily complained products.

4.6 A Proposal for Future Regulatory Reform

As discussed before, current regulatory regimes mainly use ex ante lab experiments and ex post market data generating to monitor and control risks. The FDA covers both methods, the CFPB only uses market data, and the EPA is making a transition from using sole market data to a mixed regime. Nevertheless, current regulatory regimes are not effective in detecting and regulating interactive risks and systemic risks.

Many financial products can pose unexpected risks due to their interlinkages with other financial products and economic sectors. Lab experiment is insufficient to detect this type of

complex and systemic risks, and sole postmarketing surveillance might be too late to prevent disasters.

A potential new regulatory regime to conduct field experiment[12] regarding new products can be adopted by regulators for discovering interactive, complex, and environment-contingent risks. Conducting field experiment for financial innovations might be appropriate: designing experiments and collecting data for new financial products in some typical senarios and economic environments. For Drug-drug Interactions, it becomes more and more costly to test increasing number of interactions due to the accumulation of innovations. Therefore choosing the most likely senarios to test will be more cost-effective.

[12] Pioneered by John List

5 Conclusions

This research makes three main contributions to the literature. This is the first research to empirically measure the "dark side" of innovations, in particular, negative externality caused by existing innovations. I document a new empirical fact about the relationship between innovations and innovation-induced risks.

Then I develop a new endogenous growth model with innovation risks and with a regulator. I explicitly model the qualification process of regulator who aims to control the risks induced by innovations. This new theoretical model can help us to understand better how we can regulate innovations, thus providing a link between the innovations literature and the regulation literature.

Our new theory can explain the rise of R&D cost for new drugs as well as greater expenditures on regulation and compliance. Fast-growing new innovation risks are the key driving force behind all these. The risk structure induced by previous innovations make the qualification of later innovations more and more difficult.

The rise of regulation over courts can be a result of the growing negative externality due to continuous innovative activities and economic growth. I classify current regulatory regimes in terms of different types of data generating processes, and propose to use field experiment method for some complex interactive risks and specific senarios.

Above model can be extended and applied the in various ways. As direct applications, it can be used to study environmental risks under the new Lautenberg Act that requires testing for all existing and new chemicals. Financial innovations oftentimes cause complex risks due to their linkages among themselves as well as other sectors of the economy. Therefore, this framework is ready for study the regulation of Consumer Financial Protection Bureau (CFPB) and financial innovations.

In Appendix E, I also characterize a generalized $Higher-Order$ Risk Space beyond the $2-dimensional$ case discussed in this paper. In a companion paper Xie (2016b), I generalize the risk space as well as the functions of the regulatory sector. This framework can also be extended to study endogenous disaster, as in Xie (2016c).

Our model and fact might be helpful to understand the link between innovations and innovation-induced macro risk structure, potentially useful to bridge two separate literatures of Macroeconomics: growth and business cycle. The new stylized fact enriches our understanding of the structure of shocks which are endogenously generated, in contrast to the assumption of the Real Business Cycle (RBC) models that TFP shocks are exogenous like a black box. This research might shed some light on a new analytical framework for growth and business cycles.

References

Arora, Sanjeev, Boaz Barak, Markus Brunnermeier, and Rong Ge. 2009. “Computational Complexity And Information Asymmetry In Financial Products”.

Atkeson, Andrew and Ariel Burstein. 2014. "Aggregate Implications of Innovation Policy", UCLA memo

Barro, Robert J. (2006). Rare disasters and asset markets in the twentieth century. The Quarterly Journal of Economics, 823-866.

Baker, Scott R., Nicholas Bloom, and Steven J. Davis. (2013). "Measuring economic policy uncertainty." Chicago Booth research paper 13-02.

Becker, Gary, and Kevin Murphy (1992). "The Division of Labor, Coordination Costs, and Knowledge." The Quarterly Journal of Economics 107, no. 4 1137-60.

Bloom, Nicholas. (2009). "The impact of uncertainty shocks." Econometrica 77, no. 3 pp 623-685.

Broecker, Wallace S. 1975. "Climatic Change: Are We on the Brink of a Pronounced Global Warming?", Science, New Series, Vol. 189, No. 4201, pp. 460-463

Brunnermeier, Marcus, and Martin Oehmke. “Complexity In Financial Markets”. 2009.

Ernst FR, Grizzle AJ., 2001. Drug-related morbidity and mortality: updating the cost-of-illness model. J Am Pharm Assoc (Wash) 41:192-9.

Gilboa, Itzhak, and David Schmeidler. (1989). "Maxmin expected utility with non-unique prior." Journal of mathematical economics 18, no. 2 141-153.

Grossman, Gene., and Alan Krueger. (1995). "Economic environment and the economic growth." Quarterly Journal of Economics 110, no. 2 : 353-377.

Hansen, Lars Peter, and Thomas J. Sargent. (2008). Robustness. Princeton university press.

Harpaz, Rave, Herbert S. Chase, and Carol Friedman. (2010). "Mining multi-item drug adverse effect associations in spontaneous reporting systems." BMC bioinformatics 11, no. 9 : 1.

Huang, Shiew-Mei, and Lawrence J. Lesko. 2004. "Drug-Drug, Drug—Dietary Supplement, and Drug—Citrus Fruit and Other Food Interactions: What Have We Learned?." The Journal of Clinical Pharmacology 44.6 pp.559-569.

Jacubeit T, Drisch D, Weber E. 1990. "Risk factors as reflected by an intensive drug monitoring system," Agents Actions 29:117–125.

Johnell Kristina, and Klarin Inga, 2007. "The relationship between number of drugs and potential drug–drug interactions in the elderly. A survey of over 600,000 elderly patients from the Swedish Prescribed Drug Register", Drug Safety, 30, 911–918.

Jones, Chad. 2016. "Life and Growth," Journal of Political Economy.

List, John A., and Charles F. Mason. (1999). "Spatial aspects of pollution control when pollutants have synergistic effects: Evidence from a differential game with asymmetric information." The Annals of Regional Science 33, no. 4 : 439-452.

Mackowiak, Bartosz, and Mirko Wiederholt. 2011. "Inattention to Rare Events." Centre for Economic Policy Research Discussion Paper 8626.

McCarty, L. S., and C. J. Borgert. (2006). "Review of the toxicity of chemical mixtures containing at least one organochlorine." Regulatory Toxicology and Pharmacology 45, no. 2 pp104-118.

Mulligan, Casey B., and Andrei Shleifer.(2005). "The Extent of the Market and the Supply of Regulation." The Quarterly Journal of Economics, pp1445-1473.

Munos, Bernard. (2009). "Lessons from 60 years of pharmaceutical innovation." Nature Reviews Drug Discovery 8, no. 12, 959-968.

Molina, Mario J., and F. Sherwood Rowland. (1974). "Stratospheric sink for chlorofluoromethanes: chlorine atom-catalysed destruction of ozone." Nature 249.5460, pp810-12.

Nelson, Richard R., 2004: The Market Economy, and the Scientific Commons. In: Research Policy 33, 455–471.

National Science Foundation, 2007. "Changing U.S. Output of Scientific Articles: 1988–2003". May.

Percha B, Garten Y, Altman RB. 2012. "Discovery and explanation of drug-drug interactions via text mining, " Pac Symp Biocomput

Percha B, Garten Y, Altman RB. 2013. "Informatics confronts drug–drug interactions," Trends in pharmacological sciences.

Perrow, Charles, 1999. "Normal Accidents: Living with High-Risk Technologies," Princeton University Press, Updated edition.

Pigou, Arthur Cecil. (1924). The economics of welfare. Transaction Publishers.

Pirmohamed, M. , 1998. Ml O: Drug Interactions of Clinical Importance. London: Chapman & Hall.

Romer, Paul M. (1986). "Increasing returns and long-run growth." The journal of political economy : 1002-1037.

Romer, Paul M. (1990). "Endogenous Technological Change." Journal of Political Economy : S71-S102.

Scannell, Jack W., Alex Blanckley, Helen Boldon, and Brian Warrington. (2012). "Diagnosing the decline in pharmaceutical R&D efficiency." Nature reviews Drug discovery 11, no. 3, 191-200.

Shleifer, Andrei. 2012. "The Failure of Judges and the Rise of Regulators," The MIT Press.

Stigler, George J. 1971. "The theory of economic regulation." The Bell journal of economics and management science pp 3-21.

Teuschler, LK and Hertzberg, RC. (1995). "Current and future risk assessment guidelines, policy, and methods development for chemical mixtures," Toxicology 105:137-144.

UNEP (United Nations Environment Programme) 2010. "Environmental Effects of ozone depletion and its interactions with climate change: 2010 assessment".

US EPA 2000. "Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures."

Wang, Gehui, Renyi Zhang, Mario E. Gomez, Lingxiao Yang, Misti Levy Zamora, Min Hu, Yun Lin et al. (2016) "Persistent sulfate formation from London Fog to Chinese haze." Proceedings of the National Academy of Sciences : 201616540.

Weitzman, Martin L. 1998. "Recombinant growth." Quarterly Journal of Economics, pp.331-360.

World Health Organization. The Importance of Pharmacovigilance—Safety Monitoring of Medicinal Products. Chapter 2—A Short History of Involvement in Drug Safety Monitoring by WHO. http://apps.who.int/ medicinedocs/en/d/Js4893e/3.html

Daniel Xie (2016b). "Growth, Endogenous Risk, and Regulation: A General Mode," University of Chicago.

Daniel Xie (2016c). "Endogenous Disaster and Rational Ignorance," University of Chicago.

A Description of FDA's Regulatory Regime

The modern FDA is responsible for ensuring the safety and efficacy of all drugs. The FDA will request and review the Clinical trials information for new drug candidates before they can enter the market. Moreover, the EPA is starting to adopt a very similar qualification process for new chemicals conforming with the Lautenberg Act passed in June 2016.

After successful drug discovery, pharmaceutical firms will get some new drug candidates and patent them. Then the firms will conduct pre-clinical investigations for these new drug candidates. If the preclinical results are good enough, the firm will submit an *Investigational New Drug* (IND) application to the FDA.

After review, the FDA will give the firm a permission (IND approval) for the high-quality drug candidates to conduct human clinical trials. After three stages of clinical trials (I, II, III) with satisfying testing results, firms may choose to submit a *New Drug Application* (NDA) to the FDA. The FDA will review the NDA information carefully and reach final decision of approval or rejection. Even after approval by the FDA and entering the market, some drugs can still be withdrawn from the market if the FDA finds they can cause intolerable adverse effects during the postmarketing surveillance stage.

A.1 Guidances

Guidances for IND and NDA applications inform the industry of detailed requirements about what items to test, what protocols, procedures and standards to follow. The FDA has also issued specific guidances for testing and controlling the risks of DDIs.

A.2 Submission, Reviewal and Approval

Innovative firms firstly conduct their drug discovery and then do preclinical-trial investigations. Firms clearly know the requirement and standards of the FDA. So rational firms will only submit final applications with fair testing results which can almost surely get approval. The FDA reviews the preclinical-trial information (for IND) and clinical trials information (for NDA). Then the FDA evaluates the total benefit and cost of a drug candidate and decide its qualification for marketing.

A.3 Labeling

Drug labels provide important information to consumers about all the possible side effects and DDIs. The FDA has very detailed requirements for the format of the labels. All drugs are required to have a specific section on the label to list all important DDIs.

The Blackbox Warnings The most severe warnings about side effects and DDIs are emphasized with black box in the product label.

A.4 Postmarketing Surveillance

The FDA still has the responsibility of monitoring drugs after they enter the market. This includes the FAERS system, the Medwatch, and the REMS conforming to the FDA

Amendments Act (FDAAA) of 2007. Pharmaceutical companies' Phase IV clinical trial is also an essential part of the Postmarketing surveillance.

A.5 Withdrawal from the Market

If there are severe adverse effects being found for some drugs, they will be recalled and required to withdraw from the market.

The U.S. FDA is actually the first regulator who conducts Risk regulation.

B Model Proofs

B.1 Proof for Proposition 1

Proof. From $u_t = \frac{1-\alpha}{\alpha} M_t \cdot l_t \frac{1}{\left(1+\frac{D_t}{M_t}\right)^{\frac{\alpha}{1-\alpha}}} = \frac{1-\alpha}{\alpha} \cdot \underbrace{\frac{M_t}{\left(1+\frac{D_t}{M_t}\right)^{\frac{\alpha}{1-\alpha}}}}_{Risk\ discounted\ TFP} \cdot l_t$

I assume $\frac{D_t}{M_t} \gg 1$, and omit the 1 in $1+\frac{D_t}{M_t}$.

Then the Risk discounted TFP $\frac{M_t}{\left(1+\frac{D_t}{M_t}\right)^{\frac{\alpha}{1-\alpha}}} \approx \frac{M_t}{\left(\frac{D_t}{M_t}\right)^{\frac{\alpha}{1-\alpha}}} = \frac{M_t^{\frac{\alpha}{1-\alpha}+1}}{D_t^{\frac{\alpha}{1-\alpha}}} = \frac{M_t^{\frac{1}{1-\alpha}}}{D_t^{\frac{\alpha}{1-\alpha}}} = \left(\frac{M_t^{\frac{1}{\alpha}}}{D_t}\right)^{\frac{\alpha}{1-\alpha}}$.

Iff $D_t = O(M_t^{\sigma}), \sigma \geq \frac{1}{\alpha}$,the Risk discounted TFP is decreasing in M_t. ■

B.2 ODEs for the Optimal Allocation Problem

For the optimization problem (38) , I derive the following first order conditions:

$[l_t]$:

$\beta^t \cdot M_t \left(1+\frac{D_t}{M_t}\right)^{\frac{\alpha}{\alpha-1}} \cdot \left[M_t \cdot l_t \left(1+\frac{D_t}{M_t}\right)^{\frac{\alpha}{\alpha-1}}\right]^{-\gamma}$

$+\mu_t \cdot \frac{\lambda E_t}{1+c\lambda M_t E_t}$

$+\xi_t \cdot F(b, M_t, q) \cdot \frac{\lambda E_t}{1+c\lambda M_t E_t}$

$+\varphi_t \cdot \left[\int_0^b \nu \cdot f(\nu, M_t, q) d\nu\right] \cdot F(b, M_t, q) \cdot \frac{\lambda E_t}{1+c\lambda M_t E_t} = 0$

$[E_{t+1}]$:

$\mu_t - \mu_{t+1} \cdot \left(1+\lambda\left(L-l_{t+1}\right) \cdot \frac{d}{dE_{t+1}}\left(\frac{E_{t+1}}{1+c\lambda M_{t+1} E_{t+1}}\right)\right)$

$-\xi_{t+1} \cdot F(b, M_{t+1}, q) \cdot \lambda\left(L-l_{t+1}\right) \cdot \frac{d}{dE_{t+1}}\left(\frac{E_{t+1}}{1+c\lambda M_{t+1} E_{t+1}}\right)$

$-\varphi_{t+1} \cdot \left[\int_0^b \nu \cdot f(\nu, M_{t+1}, q) d\nu\right] \cdot F(b, M_{t+1}, q) \cdot \lambda\left(L-l_{t+1}\right) \cdot \frac{d}{dE_{t+1}}\left(\frac{E_{t+1}}{1+c\lambda M_{t+1} E_{t+1}}\right)$

$= 0$

$[M_{t+1}]$:

$\xi_t + \beta^{t+1} l_{t+1} \cdot \left[M_{t+1} \cdot l_{t+1}\left(1+\frac{D_{t+1}}{M_{t+1}}\right)^{\frac{\alpha}{\alpha-1}}\right]^{-\gamma} \cdot \frac{d}{dM_{t+1}}\left(M_{t+1} \cdot \left(1+\frac{D_{t+1}}{M_{t+1}}\right)^{\frac{\alpha}{\alpha-1}}\right)$

$-\mu_{t+1} \cdot \lambda E_{t+1}\left(L-l_{t+1}\right) \cdot \frac{d}{dM_{t+1}}\left(\frac{1}{1+c\lambda M_{t+1} E_{t+1}}\right)$

$-\xi_{t+1} \cdot \left(1+\lambda E_{t+1}\left(L-l_{t+1}\right) \cdot \frac{d}{dM_{t+1}}\left(\frac{F(b, M_{t+1}, q)}{1+c\lambda M_{t+1} E_{t+1}}\right)\right)$

$-\varphi_{t+1} \cdot \lambda E_{t+1}\left(L-l_{t+1}\right) \cdot \frac{d}{dM_{t+1}}\left(\frac{F(b, M_{t+1}, q)}{1+c\lambda M_{t+1} E_{t+1}}\left[\int_0^b \nu \cdot f(\nu, M_{t+1}, q) d\nu\right]\right)$

$= 0$

$[D_{t+1}]$:

$\varphi_t - \varphi_{t+1} + \beta^{t+1} \cdot M_{t+1} \cdot l_{t+1} \cdot \left[M_{t+1} \cdot l_{t+1}\left(1+\frac{D_{t+1}}{M_{t+1}}\right)^{\frac{\alpha}{\alpha-1}}\right]^{-\gamma} \cdot \frac{d}{dD_{t+1}}\left(\left(1+\frac{D_{t+1}}{M_{t+1}}\right)^{\frac{\alpha}{\alpha-1}}\right) = 0$

Together with three LOMs:

$$E_{t+1} - E_t = \lambda \frac{L - l_t}{1 + c\lambda M_t E_t} E_t \tag{55}$$

$$M_{t+1} - M_t = F(b, M_t, q) \cdot \lambda \frac{L - l_t}{1 + c\lambda M_t E_t} E_t \tag{56}$$

$$D_{t+1} - D_t = F(b, M_t, q) \cdot \lambda \frac{L - l_t}{1 + c\lambda M_t E_t} E_t \cdot \left(\int_0^b \nu \cdot f(\nu, M_t, q) d\nu \right) \tag{57}$$

At the steady state,
$l_t = L$; $L - l_{t+1} = 0$
$[E_{t+1}] : \mu_t - \mu_{t+1} = 0$
$[M_{t+1}] : \xi_t - \xi_{t+1} + \beta^{t+1} L \cdot \frac{d}{dM_{t+1}} \left(M_{t+1} \cdot \left(1 + \frac{D_{t+1}}{M_{t+1}} \right)^{\frac{\alpha}{\alpha-1}} \right) = 0$
$[D_{t+1}] : \varphi_t - \varphi_{t+1} + \beta^{t+1} \cdot M_{t+1} \cdot L \cdot \frac{d}{dD_{t+1}} \left(\left(1 + \frac{D_{t+1}}{M_{t+1}} \right)^{\frac{\alpha}{\alpha-1}} \right) = 0$

B.3 Proof for Propositon 2

Proof.
With and without one more intermediate, the sum of discounted utilities after T:
$\sum_{t=T+1}^{\infty} \beta^t \cdot \frac{1-\alpha}{\alpha} \bar{M} \left(1 + \frac{\bar{D}}{\bar{M}} \right)^{\frac{\alpha}{\alpha-1}} \cdot L$
$\sum_{t=T+1}^{\infty} \beta^t \cdot \frac{1-\alpha}{\alpha} \left(\bar{M} + 1 \right) \left(1 + \frac{\left(\bar{D} + \left[\int_0^b \nu \cdot f(\nu, \bar{M}, q) d\nu \right] \right)}{\left(\bar{M} + 1 \right)} \right)^{\frac{\alpha}{\alpha-1}} \cdot L$
With ETC spent at t, there will be one additional qualified innovation introduced.
Before this, a large portion of labor is devoted to R&D. After reaching the threshold or time T, no labor will be devoted to R&D.
From patents' law of motion equlation (39) , because $l_t > 0$ we can derive that $E_{t+1} - E_t < \frac{\lambda E_t L}{(1 + c\lambda M_t E_t)} = \frac{L}{\frac{1}{\lambda E_t} + cM_t} < \frac{L}{cM_t}$. That is, the choice set for E_{t+1} at t is bounded by:

$$E_{t+1} - E_t < \frac{L}{cM_t} \tag{58}$$

When M_t grows large enough, $\frac{L}{cM_t}$ can shrink to such a small level that the choice set for E_{t+1} is even smaller than 1. This implies that R&D will stop.
■

B.4 Proof for Propositon 3

Proof.

For the Binomial CDF $F(b, M_t, q)$, if $b \leq M_t \cdot q$, which can be easily satisfied when M_t is large enough, there is the **Hoeffding's inequality** that gives an upper bound:

$$F(b, M_t, q) \leq \frac{1}{e^{\frac{2(q \cdot M_t - b)^2}{M_t}}} \tag{59}$$

Combine (59) and (49), we can derive a lower bound $\underline{ERC}$ for ERC:

$$ERC \geq \underline{ERC} = \frac{\frac{1-\alpha}{\alpha}\alpha^{\frac{\alpha}{1-\alpha}} M_t \left[1 + (c+\omega)\lambda E_t M_t\right]}{\lambda E_t} \cdot e^{\frac{2(q \cdot M_t - b)^2}{M_t}} \tag{60}$$

We can further derive the limiting property for $\underline{ERC}$:

$$\lim_{M_t \to \infty} \underline{ERC} = \frac{1-\alpha}{\alpha}\alpha^{\frac{\alpha}{1-\alpha}} (c+\omega) \cdot e^{-4qb} \cdot M_t^2 \cdot e^{2q^2 \cdot M_t} \tag{61}$$

therefore we have the following result[13] for $\underline{ERC}$:

$$O(\underline{ERC}) = M_t^2 \cdot e^{M_t} \tag{62}$$

■

B.5 Proof for Propositon 4

Proof.

By substituting (45) into (48), we can get

$$\sum_{\tau=t+1}^{\infty} \frac{l_\tau}{\prod_{s=t+1}^{\tau} [1 + r_s]} \leq \frac{M_t \left(1 + (c+\omega)\lambda E_t M_t\right)}{\alpha \lambda E_t \times F(b, M_t, q)} \tag{63}$$

We know $l_\tau \leq L$, and $r_s \geq \rho > 0$. So $\sum_{\tau=t+1}^{\infty} \frac{l_\tau}{\prod_{s=t+1}^{\tau} [1+r_s]} \leq \sum_{\tau=t+1}^{\infty} \frac{L}{\prod_{s=t+1}^{\tau} [1+\rho]} = \frac{L}{\rho}$.

Then we have the following constraint:

$$\frac{M_t \left(1 + (c+\omega)\lambda E_t M_t\right)}{\alpha \lambda E_t \times F(b, M_t, q)} \leq \frac{L}{\rho} \tag{64}$$

$\frac{M_t(1+(c+\omega)\lambda E_t M_t)}{\alpha \lambda E_t \times F(b, M_t, q)}$ is an increasing function of M_t. It is bounded above by $\frac{L}{\rho}$.

Therefore there must exists $\hat{M}$, so that $M_t < \hat{M}$, satisfying (64).

Eqn (63) will have strict "<" when $M_t > \hat{M}$, and R&D stops.

Moreover, a larger labor force L can relax the RHS of the constraint (64) and admits a higher $\hat{M}$.

■

[13] in terms of big O notation

C Data Description

C.1 FDA's FAERS Database

The FAERS data mainly include the following main files

1. Demographic information of patients;
2. Drug information ;
3. Patient outcome information;
4. Drug Therapy Start/End Dates

C.1.1 Demographic Information File

primaryid: Unique number for identifying a FAERS report
event_dt: Date the adverse event occurred or began
age: Numeric value of patient's age at event
sex: Code for patient's sex
wt: Numeric Value of Patient's Weight
occp_cod: Abbreviation for the reporter's type of occupation
occr_country: The country where the event occurred

C.1.2 Drug Information File

is what we are particularly interested in
Major Info
primaryid: is the Unique code for identifying a FAERS case report.
drug_seq: is the Unique number for identifying a drug in a FAERS case
each FAERS case report includes one or multiple drugs
drugname: Name of medicinal product
prod_ai: Product Active Ingredient
role_cod: Code for drug's reported role in a case.
Codes including following roles:
PS Primary Suspect Drug
SS Secondary Suspect Drug
C Concomitant
I Interacting
however, the role information is very rough

Other Info
val_vbm: Code for source of DRUGNAME
route: The route of drug administration
dose_vbm: Verbatim text for dose, frequency, and route, exactly as entered on report

cum_dose_chr: Cumulative dose to first reaction
cum_dose_unit: Cumulative dose to first reaction unit
dechal: Dechallenge code, indicating if reaction abated when drug therapy was stopped
rechal: Rechallenge code, indicating if reaction recurred when drug therapy restarted
lot_num: Lot number of the drug
exp_dt: Expiration date of the drug
nda_num: NDA number
dose_amt: Amount of drug reported
dose_unit: Unit of drug dose
dose_form: Form of dose reported
dose_freq: Code for Frequency

C.1.3 Patient Outcomes File

primaryid: Unique number for identifying a FAERS case report
outc_cod: Code for a patient outcome CODE MEANING
- DE Death
- LT Life-Threatening
- HO Hospitalization - Initial or Prolonged
- DS Disability
- CA Congenital Anomaly
- RI Required Intervention to Prevent permanent Impairment/Damage
- OT Other Serious (Important Medical Event)

C.1.4 Drug Therapy Start/End Dates

primaryid: Unique number for identifying a FAERS report
caseid: Number for identifying a FAERS case (example. 3123456)
dsg_drug_seq: Drug sequence number for identifying a drug for a Case
start_dt: A date therapy was started (or re-started) for this drug
start_dt_num: A date therapy was started (or re-started) for this drug
end_dt long: A date therapy was stopped for this drug. (YYYYMMDD)
end_dt_num: A date therapy was stopped for this drug. (YYYYMMDD)
dur: Numeric value of the duration (length) of therapy
dur_cod: Unit abbreviation for duration of therapy

C.2 Drugbank Database Description

The DrugCard for each drug (molecule) has >200 data fields. Half of the information is drug/chemical data and the other half is drug target or protein data. I list the useful data categories as below:

DrugBank ID (Primary Accession Number) Unique DrugBank accession number consisting of a 2 letter prefix (DB) and a 5 number suffix.

Brand Names Brand names from different manufacturers

Synonyms Alternate names of the drug

Patents The first and last drug patent, including approval and expiry dates

Chemical Formula Chemical formula describing atomic or elemental composition

FDA Label Food and Drug Administration approval label (if it exists)

Indication Description or common names of diseases that the drug is used to treat

Toxicity Lethal dose (LD50) values from test animals, description of side effects and toxic effects seen in humans

Contraindications Cautions or conditions indicating why or when the drug should not be taken

Drug Interactions Drugs that are known to interact, interfere or cause adverse reactions when taken with this drug

Food Interactions Foods that are known to interact, interfere or cause adverse reactions when taken with this drug

C.3 Drug Name Mapping and Standardization

Drug names are messy in the FAERS database. Different proprietary names, brand names, and abbrievations can correspond to one NME (a common molecular entity).

Drugbank categorizes drugs based on the molecular entity, and has a set of disparate drug names correspond to each molecule. I use this set of drug names to identify and map the drug names in the FAERS to a standard molecule.

D Calibration Parameters

Table 2. Some Calibration parameters

		Value	Notes
γ	risk aversion	2	Standard
β	Discout factor	0.96	Standard
λ	R&D efficiency	0.001	
q	probability of interaction	3.5%	my estimation

E Generalization of the Higher-Order Risk Space and NP-Complete Problem

In the most general case, any combinational interaction between any number of intermediate inputs can possibly generate adverse effects. These complex interactions can be represented by an $M-dimensional$ random tensor. Each element is represented by $\tilde{d}_{i_1,i_2,,,i_M}$,a random variable indexed by $i_1, i_2, , , i_M$. Each subscript $i_k \in \{0,1\}$, where k is the k^{th} intermediate product. For example, $\tilde{d}_{1,0,1,1,0,0,,,0}$, where $i_1 = 1, i_2 = 0, i_3 = 1, i_4 = 1, i_5 = 0, , , i_M = 0$, stands for the adverse effect due to the interaction between intermediate products #1, #3 and #4.

I define this random tensor as **Macro Risk Tensor**.

Proposition 5 *The number of elements in the Macro Technology Tensor is* $O(2^M)$.

The total number of elements in the Macro Technology Matrix is equal to all possible interactions between M intermediate products. I can easily derive this by summing up all the possible combinations from 1 to M intermediate products: $\sum_{k=1}^{M} \binom{M}{k} = 2^M - 1$. I deduct one here from 2^M for the case of no hazards for any combination.

Proposition 6 *If allowing multiple copies of each technology up to number N, the number of elements in the Macro Risk Tensor is* $O(N^M)$.

When I allow replicas of each technology, there will be much more possible combinations.

This $M-dimensional$ random matrix can be very sparse. Nevertheless, as M increases, the total number of elements in this Macro Technology Tensor will explode exponentially. This captures the essential idea of **Complex Uncertainty**, which describes increasing externality due to technological progress. The curse of dimension might work against innovation and adoption of new intermediate products in the long run.

There has been some empirical evidence showing the existence of Higher-order risks, for example, $(Cyclophosphamide, Prednisone, Vincristine)$ and $(Cyclophosphamide, Doxorubicin, Prednisone, Rituximab)$, examplified by Harpaz et al (2010).