How does regulatory uncertainty shape the innovation process? Evidence from the case of Nanomedicine

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Abstract

This study investigates the effect of regulatory uncertainty on the translation of scientific discovery on emerging research topics to technical applications in science-driven industry. Our empirical analysis using the case of the US Federal Drug and Food Administration's release of the report on the regulatory approach to nanomedicine in 2007 shows that; (1) the regulatory uncertainty decelerated the translation of nanomedicine research to technical applications, (2) this effect was particular for the nanomedicine research on emerging topics in the field. Our further analysis suggested that the effect of the regulatory uncertainty originated from the suppressed business activities in the field where the regulatory uncertainty presents. Contributions to the literature on the relationship between governmental regulation and innovation and the implication for science policymakers are discussed.

Keywords: regulatory uncertainty; nanomedicine; emerging technology; patent-paper citation

1. Introduction

Although regulatory governance over science and technology (S&T) is one of the crucial factors shaping the innovation process (Blind, 2012; Kesidou & Demirel, 2012; Konishi & Managi, 2020; Lee, Veloso, & Hounshell, 2011; Paraskevopoulou, 2012; Porter & Van der Linde, 1995; Taminiau, 2006), authorities do not always clearly establish the necessary regulatory frameworks nor practice them consistently, which results in the creation of so-called "regulatory uncertainty" (Birnbaum, 1984; Engau & Hoffmann, 2009). Anticipating the consequence of new scientific discovery and subsequent technology development in public safety or their environmental effects is challenging (Greer & Trump, 2019; Hamburg, 2012) as the developments of S&T are deeply integrated into a wide range of social systems that dynamically evolve (Dosi, 1982). The development of S&T could create new markets while reconfiguring existing ones where the introduction of a new regulation results in reconstruction of the pre-existing relationship among the market players (Breitzman & Thomas, 2015), exhibiting more difficulties in drawing on social consensus for defining and establishing the proper regulatory governance over S&T.

The regulatory uncertainty may be more prominent when it comes to emerging S&T (OECD, 2020). The ambiguity in its definition, the uncertainty of its impact on public welfare, and its fast-changing nature (Kuhlmann, Stegmaier, & Konrad, 2019; Roca, Vaishnav, Morgan, Mendonça, & Fuchs, 2017; Rotolo, Hicks, & Martin, 2015) make the existing regulatory framework quickly obsolete (Guston, 2008). Due to the inherent uncertainty but potentially prominent socio-economic impact (Martin, 1995), how to establish a proper regulatory framework for emerging S&T while promoting its diffusion has been a salient issue to the S&T policymakers and scholars (Conley, 2020; Guston, 2008, 2014; Hansson, 2020; Kuhlmann et al., 2019; Marchant, 2020). To this question, there has been broad discussion about the necessity of taking the "Responsive Regulatory

Framework" which emphasizes iterative, adaptive, and flexible regulative governance over emerging S&T (Greer & Trump, 2019; Guston, 2008, 2014; Hoffmann, Trautmann, & Hamprecht, 2009; Holdren, Sunstein, & Siddiqui, 2011; Stilgoe, Owen, & Macnaghten, 2013) along with arguments for properly incorporating top-down and bottom-up approach (Bosso, 2016; Rafols, van Zwanenberg, Morgan, Nightingale, & Smith, 2011). Yet, it has been also concerned that the emphasis on the flexibility/adaptability of the regulatory regime cause governance uncertainty (Fisher, 2019; Teeter & Sandberg, 2017), which may undermine the industrial exploitation of emerging S&T (e.g., Savolainen, 2013).

Then, how does regulatory uncertainty affect the innovation process for an emerging S&T? Although the answer can be informative for designing and implementing a governance framework over emerging S&T with a potential contribution to elaborating on the role of regulatory authority in shaping the innovation process, studies provide somewhat mixed viewpoints.

On the one hand, the classical management studies and the real-option theory (e.g., Engau & Hoffmann, 2009; Marcus, 1981) expect that the regulatory uncertainty may slow down firms' business activities including R&D investments. Under an external uncertainty, firms may prefer a "wait-and-see" strategy when irreversible investments are required (e.g., Bittlingmayer, 2000; Dixit, 1992; Dixit & Pindyck, 1994; Marcus, 1981). Because the R&D demands a series of irreversible investments (Czarnitzki & Toole, 2011), while regulatory uncertainty being the environmental uncertainty factor (Hoffmann et al., 2009), firms may postpone their R&D investment until the regulatory uncertainty is addressed.

On the other hand, strategic management scholars repeatedly find evidence showing that firms may build strategies to mitigate the uncertainty (e.g., lobbying, participating in the law-making process) (Carrera, Mesquita, Perkins, & Vassolo, 2003; Pinkse, 2007), or even take advantage of

the uncertainty to create the new business opportunity. When it comes to the emerging S&T under regulatory uncertainty, firms may even increase R&D efforts as a part of coping strategies to the uncertainty (Aragón-Correa & Sharma, 2003; Ettlie, 1983; Ettlie & Bridges, 1982; Goel & Nelson, 2021; Stern, 2017). This view expects that the regulatory uncertainty does not necessarily deter firms' innovation with emerging S&T.

The present research aspires to contribute to empirically solving this puzzling question by investigating how the regulatory uncertainty affects the innovation process for emerging S&T. Our focus is to examine the way the regulatory uncertainty shapes the translation of the new scientific discovery on emerging S&T into technical application development, which is a crucial part of the innovation process in the science-driven industry.

Our empirical setting is based on the case of the U.S. Food and Drug Administration (FDA)'s release of a report on the regulatory status of nanomaterials. In June 2007, FDA's task force released a report responding to the rising concern as to whether the FDA's current regulatory framework is adequate to assess the drug products containing nanomaterials (i.e., nanomedicine) (Bawa, 2011; Miller, 2002; Nature, 2007; Paradise, 2019). This report concludes that FDA's current regulatory approach is comprehensive enough to assess nanomedicine and, thus, a new regulatory approach is unnecessary. However, the report also implicated changes in the regulatory pathway for nanomedicine, as well as its regulatory status later in time. With the release of this report, the FDA also noticed that more specific guidance for manufacturers and sponsors of nanomedicine will be provided later. Yet, the first draft guidance became available after five years, leaving the period between 2007 and 2012 uncertain in terms of the regulatory framework for nanomedicine products (Bawa, 2011). Because regulatory authority's public disclosure of its ambiguous position with the absence of the specific guidance could result in the creation of the

regulatory uncertainty (Hoffmann et al., 2009), our empirical setting utilizes this event as the quasi-experimental case to identify the impact of regulatory uncertainty.

By using patent citation to research paper as the paper trail of the translation of scientific discovery into technical applications, we attempt to estimate the impact of the resulting regulatory uncertainty on the change in the rate of patent citations to the nanomedicine-related research papers on emerging research topics within the field. For the empirical setting, we choose Nano-Enabled Drug Delivery (NEDD) papers as the research publications on nanomedicine because NEDD is one of the prominent subdomains of the nanomedicine research fields (De Jong & Borm, 2008). As a comparison group, we use synthetic biology (SynBio) papers because, like NEDD, SynBio is one of the new biotechnology fields having a broad range of industrial applications including pharmaceutical products (Medema, Breitling, Bovenberg, & Takano, 2011; Weber & Fussenegger, 2009). We measure the degree to which the scientific discovery in a research paper relates to emerging technological topics within the field by using the emergence score algorithm (Carley, Newman, Porter, & Garner, 2018; Porter, Garner, Carley, & Newman, 2019).

Our Difference-in-Differences (DiD) and triple DiD (DDD) analyses of the NEDD and SynBio papers published from 2003 to 2012 shows that there was a substantial drop in the number of patent citations accrued to a NEDD paper that was published after the release of the FDA's report compared to a SynBio paper. We find that the observed drop was stronger as the NEDD papers are more related to emerging research topics. Our additional investigation of the daily rate of Premarket authorization submissions on nanomedicine to the FDA, beginning from one year before to one year after the release of the draft guidance in 2011, reveals that the observed drop might have originated from the suppressed business activities for nanomedicine development by the regulatory uncertainty.

The present study extends the scholarly efforts toward elucidating how firms' business decisions and innovation activities are influenced by governmental regulation by shedding new empirical light on the way the regulatory uncertainty shapes the innovation process for emerging S&T. Our study also provides implications for science policymakers and scholars. The findings that the translation of the scientific discovery on emerging research topics to technical applications is decelerated by the regulatory uncertainty suggests that there may be a tradeoff between making the regulatory governance over S&T flexibly/adaptable and promoting its diffusion.

The remainder of this paper is structured as follows. Section 2 reviews two contrasting views on how external environmental uncertainty influences firms' business activities and the literature describing the characteristics of the emerging S&T. Section 3 describes the data and methods for empirical analysis. Section 4 presents the findings, and Section 5 reports additional analyses results. Finally, section 6 discusses the contributions and implications of the present research.

2. Literature review

2.1. Uncertainty, Firm Investment, and Innovation

When uncertainty arises (e.g., political turmoil), firms seek ways to strategically respond to the uncertainty through various measures including adjustment of investment plan (Carter, 1990; Parnell, Lester, & Menefee, 2000; Teeter & Sandberg, 2017). In this section, we review two strains of literature that expect contrasting consequences of regulatory uncertainty (environmental uncertainty, more broadly) in firms' investment decisions.

On the one hand, the classical management literature anticipates that external uncertainty will deter firms from making long-term or irreversible investments. Because the external uncertainty creates difficulties in anticipating the consequence of a firm's action at the moment (Hoffmann, Trautmann, & Schneider, 2008; Milliken, 1987), the firm may prefer postponing its action until

the uncertainty is addressed (Bittlingmayer, 2000; Yang, Burns, & Backhouse, 2004). This logic is formally described by the real-option theory that predicts firms will prefer a "wait-and-see" strategy when deciding for irreversible investment in the light of an external uncertainty (Dixit, 1992; Dixit & Pindyck, 1994). A firm anticipates revenue and cost streams factoring the business risk into a discount factor. The discount factor increases by the emergence of environmental uncertainty, which consequently reduces the net present value of business projects in question and makes the firm defer their further actions but wait for the uncertainty to be addressed (Engau & Hoffmann, 2009; Marcus, 1981).

A series of empirical studies in various contexts provides supportive evidence. For example, by analyzing the relationship between the time trend of the antitrust case filing and the real investment and GDP, Bittlingmayer (2000) argued that the uncertainty in the stringency of antitrust law enforcement in the US is associated with the decreased-level of business investment activities. The analysis of the impact of the policy shocks on firms' investment decisions by Kang, Lee, and Ratti (2014) shows that the policy uncertainty suppressed firms' investment because the uncertainty leads firms to be conservative in the investment decision. Czarnitzki and Toole (2011) analyzed the survey data on product-innovating firms in Germany. From the analysis of the firm-level panel data, they showed that the volatility of the market revenue (market uncertainty) that a firm experienced was negatively associated with its R&D investment. Rivera and Oh (2013) demonstrated that the change in the level of regulatory uncertainty affect firms' market entry decision by showing that multinational corporation market entry increases as the environmental regulatory uncertainty decreases. By analyzing 300 organizations of which operations were liable under Australia's clean energy act, Teeter and Sandberg (2017) showed that regulatory uncertainty

created by the flexible (environmental) regulation by this act drove firms to focus on short-term investment rather than long-term investment.

Considering that R&D is a risky endeavor requiring decisions for and irreversible R&D investments (Czarnitzki & Toole, 2011), the regulatory uncertainty may deter firms from investing in the innovation process (Fleming, 2015; Gerard & Lave, 2005; Henisz & Zelner, 2001; Jones, 2015; Marcus, 1981). Several studies explain the various mechanisms. For example, Marcus (1981) explained that the regulatory uncertainty may deter firms' adoption of innovation due to the difficulty in assessing the associated risk or opportunities. Jones (2015) illustrated how the ambiguity in the regulatory pathway for technology may affect firms' investment into the development of the relevant technology by using the case of genome-edited crops. The authors argued that the absence of a clear conclusion on the regulatory status of the gene-edited crops may result in stifling firms' investment in gene-editing innovation. Fleming (2015) and Hoerr (2011) argued another pathway the way that regulatory uncertainty affects technology development and the innovation process. These studies suggest that the regulatory instability (i.e., uncertainty) may result in undersupply of early-stage venture capital investment that is crucial for innovation. Through the analysis of the panel data of 23 OECD countries over 20 years, Kalamova, Johnstone, and Haščič (2012) showed that the volatility in public expenditure on environmental R&D was negatively associated with the patenting activities in the environmental technology domain, supporting the argument that the policy uncertainty negatively impacts on the innovation activities.

On the other hand, a growing number of studies found that uncertainty does not necessarily negatively impact firms' innovation. As shown in many studies, firms respond to the external uncertainty strategically by adjusting their organizational structures to minimize the influence of the uncertainty, reorganizing their business portfolio (Carrera et al., 2003), or participating in the

relevant policymaking process (Engau & Hoffmann, 2009). Similarly, under regulatory uncertainty, firms may try to deploy their strategic assets to mitigate or even capitalize on the uncertainty. Thus, the impact of the regulatory uncertainty on innovation may be more complicated than one may expect. Several studies provided supportive evidence.

For instance, by analyzing the data on 54 equipment and packaging suppliers to food processing, Ettlie and Bridges (1982) and Ettlie (1983) found that firms under a greater level of environmental uncertainty deploy more aggressive technology policy that is believed to increase both product and process innovation. The authors interpreted this finding as firms' strategic response to cope with the external uncertainty. By analyzing the case of the German power generation industry under regulatory uncertainty imposed by the European CO2 emission trading scheme, Hoffmann et al. (2009) showed that firms facing regulatory uncertainty do not necessarily postpone their investment decisions due to the firms' strategic motivations.

Aragón-Correa and Sharma (2003) further suggested that managers of firms facing environmental uncertainty are more willing to use innovative strategies than those in environments with less uncertainty to take preventive action with anticipation of the probable environmental uncertainty. Recently, some scholars attempted to empirically examine whether and to what degree firms capitalize on the regulatory uncertainty for their business.

Stern (2017) investigated if a pioneering entrant of the medical device market enjoys the first-mover advantage over the latecomers, under regulatory uncertainty. The analysis using the case of the FDA's creation of the new category of a new drug product and the resulting regulatory uncertainty found that the pioneer entrant in this new market had disadvantages compared to the latecomers in market entry. The analysis found that for the pioneer entrant, the approval of the FDA was delayed much longer than the duration until FDA's approval for the latecomer's products.

Goel and Nelson (2021) found evidence showing that firms may invest more in innovation to mitigate economic or political uncertainty. Their analysis of the survey data on firms in 135 countries showed that the greater the level of uncertainty (either economic or political uncertainty) in the country where a firm operates, the greater the likelihood the firm introduces process innovations. From these findings, the authors argued that firms may attempt to "hedge" the regulatory uncertainty through innovation.

2.2. Emerging Science and Technology for Innovation

Emerging S&T changes the ways of doing while competing with the existing technology (and science), which expectedly impose a prominent socio-economic impact (Martin, 1995). However, the definition of an emerging S&T is often ambiguous (Rotolo et al., 2015), and the consequence of its applications in public health and environmental effect is as uncertain (or even risky). Due to these characteristics, identifying emerging S&T and building the proper governance have been challenging quests for policymakers.

To firms, the emerging S&T can be both an opportunity and a threat. On the one hand, a firm may capitalize on the emerging S&T as a new window of technological opportunities to compete over the market rivals through innovation (Hung & Chu, 2006). From the Schumpeterian perspective, this aspect implies that the emerging S&T could be a driver of the creative destruction that induces dynamic market competition and innovation by inducing active market entry and exit with the creation of the new market (Nelson, 2012).

On the other hand, because of the inherent uncertainty of the emerging S&T, it often becomes the subject of the various regulation by authorities, which consequently makes firms perceive the investment into innovation for emerging S&T as a risky business. The perceived risk by firms under the regulatory uncertainty is added by the inherent uncertainty of emerging S&T, and as

described in section 2.1, this could deter further firms from investing in innovation using the emerging S&T. When it comes to emerging S&T where scientific discovery is a crucial knowledge source for technical application development, this deterrence effect can result in decelerating the pace of translation of the scientific discovery into technical applications.

Utilization of the emerging S&T in downstream players and the consequential new application of emerging S&T add further difficulties to predicting the impact of the development of an emerging S&T on human health and the environment. The unpredictable evolution of emerging S&T applications leads scholars to discuss the importance of engaging stakeholders of the emerging S&T at various layers into defining proper governance. For instance, given the nature of nanotechnology that can be utilized in various ways by the downstream players (i.e. end-users), Rafols et al. (2011) argued for the necessity of expanding current discussion for governance over nanotechnology in the U.K. toward accounting for downstream uses of the nanotechnology. Based on an extensive review of the literature on nanotechnology and governance, Bosso (2016) reached a similar conclusion, showing that the scholarly discussion has advanced to the necessity of accommodating the use of nanotechnology by stakeholders in various layers of the value chain.

The complexity and difficulties of effective governance of emerging S&T also lead scholars and policymakers to emphasize the "flexible" approach so that the governance can adaptably work according to the development of the various applications of emerging S&T (Holdren et al., 2011). Yet, because excessive flexibility could result in the creation of "uncertainty" in that governance, which could undermine the utilization of emerging S&T (Fisher, 2019; Savolainen, 2013; Teeter & Sandberg, 2017), it has been also argued that flexibility and adaptability of that governance could slow its diffusion.

In sum, because emerging S&T exhibits a high level of uncertainty in its definition and predicting the trajectory of development, there have been significant difficulties in establishing the proper (regulatory) governance. In the next section, we illustrate our research design to empirically identify the causal impact of regulatory uncertainty on the innovation process for emerging S&T.

3. Empirical setting

3.1. Release of the FDA's report on nanomaterials in 2007

Our empirical analysis is based on the release of the FDA taskforce's report on the view of drugs containing nanomaterials in 2007 (July 23, 2007)[1]. Nanotechnology has been expected to bring transformative impact to drug product development. However, because the biological and environmental effects of the nanomaterials have not been fully assessed (De Jong & Borm, 2008), FDA has increasingly encountered concerns if its current regulatory framework is appropriate to assess drug products containing nanomaterials (hereafter, nanomedicine) (Miller, 2002; Nature, 2007; Paradise, 2019). To this challenge, in October 2006, FDA's (acting) commissioner assembled a task force to assess the adequacy of the FDA's current regulatory framework for nanomedicine and recommend appropriate regulatory approaches if necessary. On July 23, 2007, the task force published the report addressing the following three parts: (1) review of the scientific information on the biological effect of nanomaterials, (2) analysis of the science issues on nanomaterials, and (3) analysis and recommendation for regulatory policy issues.

The report stated, "*FDA's authority over products subject to premarket authorization is comprehensive and provides FDA with the ability to obtain detailed scientific information needed to assess the safety and, as applicable, the effectiveness of products, including relevant effects of*

[1] Available at https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-task-force-report-2007 (accessed on June 10, 2021)

nanoscale materials (p.32)", indicating the current regulatory approach is capable of assessing nanomedicine without demanding a novel regulatory approach.

Interestingly, in the same paragraph, the report also implicated a probable change of the regulatory status of nanomedicine later in time by stating, "*the presence of nanoscale materials may change the regulatory status/regulatory pathway of products […]. It is important that manufacturers and sponsors be aware of the issues raised by nanoscale materials and the possible change in the regulatory status/pathway when products contain nanoscale materials* (p.32)". Along with the release of this report, FDA noticed that they would provide more detailed guidance for the sponsors and manufacturers of nanomedicine later. Yet, there have been no more updates on the FDA's view on the regulatory status of nanomedicine, nor the guidance, until the release of the "*Draft Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology*" in June 2011. Figure 1 summarizes the timings of these events.

[Insert Figure 1 about here]

The release of the FDA report on nanomedicine is useful to address our research question. First, this event created regulatory uncertainty to the range of stakeholders of nanomedicine development and manufacturing. Implicating the probable change in the regulatory approach and status of nanomedicine could create uncertainty in *Measures and Rules* (Hoffman et al., 2008) that the FDA may apply to nanomedicine in the future. Given that the nanomedicine field is the domain where academic research becomes the source for developing new products (Eaton, 2007), the release of this report with the absence of guidance until Mid-2011 created a regulatory uncertainty.

Second, the first version of the draft guidance became available five years after the publication of the report. As a result, what regulatory pathways that the manufacturers and sponsors need to account for when developing the nanomedicine has remained uncertain for at least five years. More

importantly, due to the announcement of the FDA on the future release of the guidance, the manufacturers and sponsors were forced to expose to the uncertain regulatory status of nanomedicine until the guidance is provided.

Third, utilizing this event allows us to conveniently conduct causal analysis because of the exogeneity of the timing of the event. Although there has been active discussion on whether the FDA's current regulatory framework is suitable for nanomaterial-containing drug products, when and in what way FDA responds to this concern was far from predictable. Furthermore, due to the first version of the draft guidance, prepared after five years by the FDA in consultation with national research institutes or FDA's research centers[2] without the participation of the sponsors or manufacturers of nanomedicine, the timing of the release of the draft guidelines was also quite exogeneous to most of the stakeholders of the nanomedicine.[3]

3.2. Overview of research design

We consider a research paper (journal articles or conference proceedings) as a container of scientific discovery. Considering that a research paper receives citations from patents when the patented inventions were built upon the discovery presented in the research paper, while a patent is granted to the invention when it is novel, not obvious, and industrially useful, we analyze the individual research paper as the unit of analysis, measuring the extent of scientific discovery as translated into technical applications with the total number of patent citations accrued to the research paper of interest.

Our econometric approach aims to estimate the relative change of the patent citation counts accrued to the research papers on nanomedicine (i.e., treatment group) compared to papers in a

[2] See, the footnote in the final version of guidance available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considering-whether-fda-regulated-product-involves-application-nanotechnology

[3] After the first draft guidance was released, the FDA called for comments and suggestions from the public for the final version of the guidance.

similar research domain but not of nanomedicine (i.e., comparison group). The estimated difference presents the causal impact of the regulatory uncertainty. Next, we investigate if the estimated difference is associated with the degree to which the scientific discovery in a research paper is relevant to emerging research topics within the field.

As the treatment group, we choose the research papers on Nano-Enabled Drug Delivery (NEDD). NEDD is one of the prominent subdomains of the nanomedicine research field. The bibliometric definition of NEDD has been established (Zhou, Porter, Robinson, Shim, & Guo, 2014). We consider research papers of synthetic biology (SynBio) as the comparison group for the following four reasons. First, like NEDD, SynBio is one of the prominent new biotechnology domains that are expected to bring transformative impact to a broad range of research fields and industries including enhancing biodiesel production or drug development process (Medema et al., 2011; Weber & Fussenegger, 2009). By integrating the engineering principle into bioscience, SynBio research aims to design biological blocks that have naturally non-existing novel functions or enhance the existing ones. Second, the bibliometric definition of SynBio has been built and refined by a series of prior studies (Oldham, Hall, & Burton, 2012; Shapira, Kwon, & Youtie, 2017; Van Doren, Koenigstein, & Reiss, 2013) while the SynBio domain is bibliometrically demarcated from the research on NEDD as no overlaps in their bibliometric definitions show.[4] Third, as both NEDD and SynBio either belong to or are relevant to, the biotechnology research domain, choosing SynBio as the comparison group helps to minimize the probable field-level heterogeneity. Fourth, although there were discussions and concerns regarding the adequacy of the current regulatory framework for synthetic biology, there were no notable events that could change

[4] To ensure that the SynBio and NEDD papers have no overlap, we have dropped overlapping records among the searched papers in the empirical analysis.

the existing regulatory frameworks for synthetic biology in the U.S during the period between 2003 and 2012.

Our analysis begins with estimating the average impact of the FDA's release of the report in 2007 on the patent citation accrued to a NEDD paper compared to a SynBio paper by using the Difference-in-Differences (DiD) approach. To examine if the sign and size of the impact differ by the degree to which the discovery in a research paper associates with emerging technological topics, we measure the degree to which a research paper contains emerging technological terms within the field of the paper (i.e., NEDD or SynBio), by using the recently developed emerging score algorithm (Carley et al., 2018; Porter et al., 2019). By using the text data in the title and abstract of a corpus of research papers in each research domain, this algorithm allows one to extract emerging terms and quantify the extent to which each of the extracted terms represents technological emergence within the field (i.e., emergence score). We calculate the paper-level emergence score by aggregating the emergence scores of all the appeared emerging terms in the abstract and title of each research paper (Kwon, Liu, Porter, & Youtie, 2019; Kwon, Youtie, & Porter, 2020). We use the paper-level emergence score as the measurement of the extent to which the scientific discovery addressed in the research paper is associated with the emerging technological topics within the field where the paper belongs. We test if the impact of the regulatory uncertainty differs by the paper-level emergence score by fitting our data to the triple DiD regression model (DDD). Section 3.4 provides analytical details of this research design.

3.3. Data

We begin by retrieving metadata of NEDD and SynBio research papers that were published between 2003 and 2012 from Clarivate's Web of Science Core Collection (WoS CC). We choose this period because it allows us to observe at least five-year-long publication records before and

after the event of interest, respectively. We use the five-year observations pre- and post-FDA report release for multi-term DiD analysis. The selection of this period is also based on the way the emergence score is calculated. According to the method that will be described in detail in the next section, emerging terms are extracted from, and their emergence scores are calculated by using the text in the abstract and title of papers published for at least 10-year periods. The period between 2003 and 2012 is 10-years long. Finally, although the FDA released the first version of the draft guidance on the regulatory status of biological products containing nanomaterials in June 2011, we include the papers published in 2012 to account for the probable delay in the impact of the guidance release being presented. To retrieve the metadata of NEDD papers, we use the bibliometric definition of NEDD that was formulated by Zhou et al. (2014). For SynBio papers, we employed the search strategy compiled by Shapira et al. (2017).

In our research design, we use the number of patent citations accrued to each research paper as the dependent variable. To obtain the information on patent citations accrued to research papers, we use recently disclosed data by Marx and Fuegi (2020) (hereafter, M&F data). These data contain the information of patent-cited research papers that are indexed in Microsoft Academic Graph (MAG). By applying the natural language processing and machine learning algorithm to the non-patent literature that was cited in patents, Marx and Fuegi (2020) identified papers that were cited by patents and link them to the research paper indexed in MAG.[5] By combining those data with our dataset based on the Document Object Identifier (DOI)[6], we count the patent citations that each paper received until the end of 2019. We drop the papers that have invalid bibliometric information (e.g., records without author information) and the records that are categorized as

[5] This data is avilable at http://relianceonscience.org/
[6] Therefore, papers that have no DOI were excluded from the final dataset.

SynBio and NEDD paper together.[7] Our final sample contains 41,321 NEDD (94%) and 2,705 SynBio papers, respectively. Our data show that the likelihood of a paper to receive patent citations is seemingly indifferent between NEDD and SynBio. According to the sample, 32% of the NEDD papers had received at least one patent citation while 34% of the SynBio papers received one or more patent citations until the end of 2019.[8]

3.4. Variables and econometric model specifications

Dependent variables. We use the number of US patent citations accrued to each research paper until the end of 2019 (*nUSPatCite*) as the dependent variable. Despite the benefits of the use of the patent citation counts, it is worthwhile highlighting that the patent citation accrued to a paper is not a flawless measurement of the degree to which scientific discovery in the paper of interest serves knowledge input for developing technical applications. Not all patents contain commercially valuable inventions nor are all commercially valuable inventions patented. For instance, in the information and communication technology domain, firms may incline to patent their inventions for strategic purposes (Hall & Ziedonis, 2001; Noel & Schankerman, 2013). In the food industry, inventions are less patented but more protected through secrecy (Cohen, Nelson, & Walsh, 2000). Nevertheless, in the context of the present research, the patent citation count can be still useful because pharmaceutical and biotechnology domains are the sectors where patenting is a major instrument for protecting valuable inventions while, in this domain, a patent corresponds to a distinctive technology that has commercial value (Cohen et al., 2000).

In counting the patent citations, we choose to use the US patent citation to take into account not only the fact that FDA's jurisdiction is restricted to the US but also a feature of the patent citation practice of USPTO. In the U.S., inventors are obliged to cite all the known prior art when

[7] In the original data, we found that 96 articles were included both in NEDD and SynBio.
[8] About 23% and 25% of the NEDD and SynBio papers received one or more US patent citations, respectively.

filing patent applications (by the Inequitable Conduct Doctrine). If it is found that inventors did not cite any of the "known" prior art in the patent application, the patent can be invalidated, even after it is granted. In contrast, in EPO, the patent examiners are mostly responsible for searching prior art / adding citations and, hence, examining the patentability of the inventions. Studies have emphasized that such difference needs to be properly considered in patent citation analysis (Alcacer & Gittelman, 2006; Criscuolo & Verspagen, 2008). Our use of the citation counts originated from US patents is to mitigate the probable systematic difference arising from the different citation practices by patent authorities.[9]

Use of the accumulated patent citation count until the end of 2019 becomes subject to a truncation problem. To account for this right-truncation problem, we additionally employ the fixed-window (seven-year-long since publication) patent citation count as an alternative dependent variable (*7YrPatCite*)[10].

Independent variables. Our econometric analysis employs the standard multi-term DiD design. We generate the following three sets of variables as the independent variables. First, we create ten binary variables that respectively take the value of 1s for each of the publication years between 2003 and 2012 (PY_k, $k \in [2003,..,2012]$). For example, if a research paper was published in 2003, the binary variable PY_{2003} takes the value 1. Second, we create a dummy variable that takes the value of 1 for NEDD papers (*NEDD*) and 0 for SynBio papers. Finally, we generate ten interaction terms between *PY*s and *NEDD* (*PY X NEDD*). The coefficients of these interaction terms are the DiD estimators. If the regulatory uncertainty decelerated (accelerated) the

[9] For the robustness check, we conducted additional analyses by using the total patent citation count without restriction to the US patent citation. Our analyses showed the consistent findings with our main regression results. The robustness check result is available upon request.

[10] This is because, in our data, the last year of patent citation to the papers published in 2012 is 2019. To account for the 2019 patent citation is unlikely to be complete due to the delay between patent filing and its publication, we count patent citation made until 2018 (7-year window).

translation of scientific discovery in NEDD to technical application, negative (positive) and statistically significant coefficients of *PY X NEDD* after 2007 are expected.

To test if the impact was prominent for scientific discovery on emerging research topics within each field, we employ a paper-level emergence score algorithm that quantifies the degree to which a research paper of interest contains emerging technological terms within each field where the focal paper belongs. The paper-level emergence score proxies for the degree to which the discovery addressed in a research paper relates to emerging research topics. The higher the paper-level emergence score, the greater the extent to which the research paper contains new knowledge on emerging research topics within the research field (i.e., NEDD or SynBio in our analysis). For calculation of the paper-level emergence score, we follow the procedures described by Kwon et al. (2019) and Kwon et al. (2020). First, from each of the NEDD and SynBio datasets, we extract the emerging terms by using the algorithm as proposed by Carley et al. (2018). The emergence score algorithm generates a list of emerging terms with their "emergence score" that takes a non-negative value, by operationalizing the four characteristics– persistence, novelty, growth, community, and scope. The emergence score of each term is calculated by aggregating three types of trend of the term in question appear in the corpus of papers— active trend, recent trend, and slope (see section 2.3 of the paper by Kwon et al. (2019)). Second, for each paper, we aggregate the emergence scores of the emerging terms in the paper's abstract and title. To account for the right-skewed distribution of the paper-level emergence scores that have 0 as the minimum value, we take a natural log on the paper-level emergence score with an increment of 1 (*lES*). If a paper takes the value of 0 for its *lES*, this indicates that any of the extracted emerging terms has not appeared in abstract nor title of the paper in question. Then, we generate triple interaction terms between *lES*, *PYs*, and *NEDD* (*lES X PY X NEDD*). If the impact of the regulatory uncertainty was more (less)

prominent for translating scientific discovery on emerging research topics to technical application, post-2007 triple interaction terms are expected to take negative (positive) and statistically significant coefficients.

Control variables. To rule out probable spurious effects, we introduce several control variables that may simultaneously correlate with our dependent and independent variables.

First, we control for the research team size (*Team Size*). Studies have found that research team size is associated with research impact (including technology impact) with the growth of the size of the research team over time (Cohen & Bailey, 1997; Larivière, Gingras, Sugimoto, & Tsou, 2015; Vogel, Hall, Fiore, Klein, Bennett, Gadlin et al., 2013). Meanwhile, the average research team size differs by the field of research due to the different levels of required resources by research domain. Accordingly, the probable difference between NEDD and SynBio papers in terms of the post-2007 patent citation counts could be driven by the simultaneous correlations among the research team size growing at a different rate between NEDD and SynBio, research domain, and patent citation counts. Controlling for the number of authors of the paper of interest accounts for this confounding effect.

Second, we account for the number of cited references as the proxy for the number of prior studies to the focal research paper. Because the number of relevant prior research papers positively associates with the academic research activity around the relevant field, it is also likely to correlate with technology development activities. Meanwhile, the number of citable references for a paper increases over time by the accumulation of the published research papers. Introducing the natural log-transformed number of cited references added by 1 (*lnRef*) as a control variable helps to account for this confounding effect.

Third, we control for whether the research paper of interest was originated from international collaboration. The greater the inclusion of international collaboration, the greater the visibility of the research works (Van Raan, 1998), which could positively associate with the patent citation counts (also U.S. citations for the same reason). Conversely, technologically impactful research may need the collaboration of researchers across countries. Either way, whether the research was conducted based on international collaboration may associate with the extent to which the research outcomes served as the knowledge inputs for technological application developments. Meanwhile, studies have found that the international collaboration for research has steadily grown with field-level heterogeneity in its prevalence (Gazni, Sugimoto, & Didegah, 2012; Wagner, Park, & Leydesdorff, 2015). To account for this international collaboration-induced confounding effect, we introduce a binary variable that takes the value of 1 if the authors' countries are two or more, and 0 otherwise (*IntCollabo*) as a control variable in the regression analysis.

Finally, we control for whether the lead author of the research paper was located in the US by introducing a binary variable that takes the value of 1 if the first author of the paper in question was located in the US (*1stAuthorInUS*). This variable is to take into account the fact that the knowledge diffusion is localized (e.g., Jaffe, Trajtenberg, & Henderson, 1993), and the FDA's jurisdiction is limited in the U.S.

Econometric model specifications: Because the dependent variable is a count variable having right-skewed distribution (i.e., overdispersion problem), we fit our data to the generalized negative binomial (GNB) regression model that allows capturing the overdispersion parameter into the analysis.[11] To investigate the total impact of the regulatory uncertainty on the translation of

[11] As an alternative regression model, a zero-inflated negative binomial regression model can be considered. However, because the zero-inflation factor is unknown, fitting our data to the zero-inflated negative binomial regression model is infeasible. As another alternative model, Veugelers and Wang (2019) used the probit regression model by employing a binary variable that takes the value of 1 if the research paper in question received at least one patent citation, as the dependent variable. Our alternative regression analysis using the same approach yielded consistent findings with the generalized negative binomial regression analyses.

scientific discovery into technological applications, we fit our data to the following regression model specification using robust standard errors.

$$nPatCite_i^* = \beta_0 + \sum_{t=2003}^{2006} \beta_{1t} \times PY_{i,t} \times NEDD_i + \sum_{t=2008}^{2012} \beta_{2t} \times PY_{i,t} \times NEDD_i + \sum_{t=2003}^{2012} \beta_{3t} \times PY_{i,t} + \beta_4 \times NEDD_i + \sum_j \gamma_j \times C_{i,j} + \epsilon_i$$

where $nPatCite_i^*$ is either *nUsPatCite* or *7YrPatCite*, $C_{i,j}$is jth control variable of paper i and ϵ_i is the error term. To examine if the impact of the regulatory uncertainty was particular, we fit our data to the triple DiD model (DDD), as presented in the following formula.

$$nPatCite_i^* = \beta_0 + \sum_{t=2003}^{2006} \beta_{1t} \times PY_{i,t} \times NEDD_i \times lES_i + \sum_{t=2008}^{2012} \beta_{2t} \times PY_{i,t} \times NEDD_i \times lES_i + \sum_{t=2003}^{2012} \beta_{3t} \times PY_{i,t} \times lES_i + \sum_{t=2003}^{2012} \beta_{4t} \times PY_{i,t} \times NEDD_i + \beta_5 \times NEDD_i \times lES_i + \sum_j \gamma_j \times C_{i,j} + \epsilon_i$$

4. Results

4.1. Descriptive analyses

Table 1 presents the summary statistics of the key variables and their pairwise correlations for NEDD (upper table) and SynBio papers (lower table), respectively.[12]

[Insert Table 1 about here]

All the correlation coefficients are below 0.4, both for NEDD and SynBio papers, indicating no significant multi-collinearity issues found. The mean value of *lES* of NEDD papers (2.19) is

[12] Because *PY*s are mutually exclusive dummy variables, we present the publication year of the paper as is in the correlation analysis.

greater than that of SynBio (0.83). The average number of co-authors (i.e., Team Size) of a NEDD paper (5.91) is greater than that of a SynBio paper (4.87), suggesting that one more researcher collaborates for NEDD research than SynBio research. 29% of the NEDD papers in the sample had a US scientist as the lead author, whereas 40% of the SynBio papers had a US scientist as the first author. There are virtually no differences between NEDD and SynBio papers in the mean values of the rest of the variables.

4.2. Main regression results

[Insert Table *2* about here]

Table *2* reports the main regression results. In the first two columns, we present the regression results without introducing the triple interaction terms to estimate the aggregated effect of the regulatory uncertainty. In the first column, we use *nUSPatCite* as the dependent variable. The DiD estimators for pre-2007 (from *PY2003 X NEDD* to *PY2006 X NEDD*) are all statistically insignificant at the 0.1 significance level, indicating no evidence for a pre-2007 difference between NEDD and SynBio papers in the time trend of the patent citation counts. However, from *PY2011 X NEDD*, the coefficients turn negative and statistically significant at the 0.1 significance level with an increase in size. The second column presents regression results using the *7YrPatCite* as the dependent variable. From *PY2010 X NEDD*, the coefficients are all negative and statistically significant at the 0.05 significance level.

From the third to fourth columns, we report the regression results including the triple interaction terms. In the third column, we report the regression results using *nUSPatCite* as the dependent variable. The coefficients of *PY2010 X NEDD X lES* and *PY2011 X NEDD X lES* are negative and statistically significant at the 0.1 significance level. In the fourth column, only the coefficient of *PY2011 X NEDD X lES* is negative and statistically significant at the 0.01

significance level. In contrast, in both columns, the coefficients of *PY2008 X NEDD* through *PY2012 X NEDD* are all insignificant at the 0.1 significance level. These results indicate that the drop in the patent citation to a NEDD paper was particular to the papers containing emerging terms.

For a clearer illustration of our findings, we conduct an additional analysis by dividing our sample into the papers that have positive emergence score (*lES*>0, papers on emerging research topics) and those have 0 as the *lES*. Then, we fit these subsamples to DiD regression models separately. The fifth and sixth columns of Table 2 report the regression results using the papers with positive *lES*. The coefficients of *PY2010 X NEDD* and *PY2012 X NEDD* are negative and statistically significant at 0.1 significance level minimum in both columns. In contrast, the regression results reported in the seventh and eighth columns with the papers having *lES*=0 show that any of the coefficients of the DiD estimators are statistically significant at the 0.1 significance level. Our additional analysis confirms that the drop in the patent citation counts accrued to a NEDD paper was specific to the NEDD papers on emerging research topics within the field.

5. The origin of impact

In this section, we present two additional empirical analyses to explore the origin of the observed impact. First, we examine if our findings can be explained by the declined research impact of NEDD research after 2007. Second, we examine if the suppressed business activities for nanomedicine by the "uncertainty" was the main driver of our finding, as expected by real-option theory, by examining the change in the business activities for nanomedicine after the regulatory uncertainty is addressed by the release of the first draft guidance by FDA in June 2011.

5.1. Has NEDD paper's research impact declined?

An alternative explanation of our findings is that NEDD research became less impactful after 2007 for unknown reasons. We investigate the empirical validity of this explanation by examining

if the research impact of NEDD declined compared to that of SynBio after 2007. For this analysis, we analyze the change in the number of paper citations accrued to a research paper as the dependent variable (*Time Cited*). By considering the number of paper citations that a focal paper received as the proxy for the focal paper's research impact, we analyze if a NEDD paper received fewer paper citations than a comparable SynBio paper after 2007.

[Insert Table *3* about here]

Table *3* reports GNB regression results. In the first column, we present the DiD regression results without triple interaction terms. The coefficients of DiD estimators are all insignificant at the 0.1 significance level. In the second column, the regression results including the triple interaction terms are presented. The coefficient of *PY2010 X NEDD X lES* is positively significant at the 0.05 significance level. The third and fourth columns show the regression result with samples of lES>0 and lES=0, respectively. All the coefficients of the DiD estimators in both columns are statistically insignificant at the 0.1 significance level. Our analysis finds no evidence of declined research impact of NEDD papers compared to SynBio published after 2007.

5.2. Evidence from the Premarket authorization submission activities

If the regulatory uncertainty deters firms from investing in the R&D process and thus slowed the translation of scientific discovery into technical applications, wouldn't the mitigation of the regulatory uncertainty result in the recovery of the business activities on nanomedicine? Because empirical evidence of this expectation can be complementary to our main analysis, we conduct an analysis examining the response of organizations to the mitigated regulatory uncertainty in their business activities on nanomedicine development by FDA's release of the first draft guidance on nanomedicine development in June 2011.

Our additional analysis is based on analyzing the rate of submissions for Premarket approval (PMA) of nanomedicine before and after June 2011. There are two FDA-controlled regulatory pathways for Drug products in the U.S. The first is premarket notification (510(k)). Under this pathway, the applicant is required to demonstrate that the products (or medical devices) of interest are as safe and effective as substantially equivalent (already marketed) products (devices) in the market. The second pathway is the PMA. Under this pathway, new drug products (or medical devices) with high-risk profiles (i.e., class III[13]) are reviewed and assessed regarding safety and effectiveness. The PMA requires the applicant to provide various types of scientific information and data demonstrating the safety and effectiveness of the product under examination (e.g., requiring both data on Non-clinical Laboratory Studies and clinical Laboratory Studies), which incurs substantial and irreversible costs of the applicant. If a product under the PMA process comes to undergo a new regulatory process due to the change of rules, the applicant's investments made until then turn to sunk costs. Meanwhile, according to the FDA's report released in 2007, it concludes that although the premarket authorization is comprehensive enough to cover the nanomedicine, the rules may change in the future. Accordingly, we argue that the response of firms and sponsors of the nanomedicine to the change in the level of regulatory uncertainty will be reflected in their submission of nanomedicine PMAs.

In this analysis, we consider the release of the first version of the draft guidance regarding the regulatory status of and approach for, nanomedicine on June 14, 2011,[14] as the event that partially mitigated the regulatory uncertainty. By the release of this draft guidance, more detailed

[13] The FDA defines class III devices as "*those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."* (see, https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma)

[14] "Draft Guidance for Industry; Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology "(available at https://www.federalregister.gov/documents/2011/06/14/2011-14643/draft-guidance-for-industry-considering-whether-an-fda-regulated-product-involves-the-application-of, accessed on June 10, 2021)

information that the manufacturers and sponsors need to take into account regarding the FDA's regulatory stance for the business of nanomedicine, has become available. For example, it clarified that the FDA will account for (1) whether products under consideration contain nanometer-scale materials, and (2) whether the size of the materials of the product attributes to its properties including biological effects. The draft guidance also recommended for manufacturers of nanomedicine to consult with the FDA early in the product development process.

We retrieve the information of all the PMA applications from the FDA PMA database[15] and profile the daily submission numbers of PMAs on nanomedicine (nano-PMAs) from June 14, 2010, to June 14, 2012 (1-year before to 1-year after the release of the guidance). We consider the PMAs submissions as nano-PMAs if the terms matched with "nano*" appeared in the description, tradename, or generic name of the products of the application in question. We expect a surge in the number of nano-PMA submissions after June 14, 2011, if the mitigated regulatory uncertainty by the release of the first guidance induced recovery of business activities regarding the nanomedicine. Figure 2 presents our analysis result.

[Insert Figure 2 about here]

The red and gray bars present the number of submitted nano-PMA submissions and the number of all the PMA submissions during the period, respectively. The daily number of all PMA submissions (gray) shows no notable difference between before and after June 14, 2011. Meanwhile, the number of nano-PMA submissions filed before June 14, 2011, was only three, while the number of nano-PMA submissions filed after that date was 15 (increase by 400%). The observed surge in the number of submissions of the nano-PMA applications suggests that the business activities related to nanomedicines recovered after the mitigation of the regulatory

[15] Bulk data is available at https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals (access July 20,2021)

uncertainty by the release of the draft guideline.[16] Our additional analysis of the nano-PMA further suggests that the decelerated translation of scientific discovery in NEDD research to patented technological applications might have originated from the suppressed business activities on nanomedicine development by the regulatory uncertainty.

6. Discussion and conclusions

In the present study, we examined how regulatory uncertainty influences the translation of scientific discovery into technical applications in a science-driven industry. For the empirical analysis, we utilized the case of the regulatory uncertainty created by the FDA's release of the report on nanomaterials in 2007.

Our analyses using the patent citations accrued to NEDD and SynBio research papers with the recently developed emergence score algorithm found that the regulatory uncertainty of interest has decelerated the translation of new scientific discovery in nanomedicine research to technical applications. This impact was particular to the scientific discovery on emerging research topics of NEDD. Our further analysis using the data on the daily rate of nano-PMAs submissions showed that the observed effect of the regulatory uncertainty might have originated from the suppressed business activities on nanomedicine development by the regulatory uncertainty. From the findings, we conclude that in this science-driven industry, the regulatory uncertainty could decelerate the diffusion of scientific discovery on emerging topics to technological applications development.

Does our finding imply that regulatory uncertainty "negatively" impacts innovation? Although our findings seemingly answer positively, because the diffusion of scientific discovery is a crucial part of the innovation process, it may be too early to conclude based on our findings alone. In addition to the translation of scientific discovery into technical applications, there are more

[16] Although comparing between nano-PMAs and SynBio-PMAs is ideal, identifying the SynBio-PMAs was bolometrically infeasible.

processes of innovation such as interfirm R&D collaboration, governmental R&D, venture capital investment in early-stage R&D, collaborations between universities and firms for innovation, etc. Evidence on how regulatory uncertainty affects other processes of innovations in various contexts is necessary for a comprehensive conclusion.

Our finding that the slowed translation of scientific discovery into technical applications was particular to the research outcomes on emerging research topics implies that there may be a tradeoff between seeking flexibility/adaptability of the regulatory governance over emerging S&T and promoting the diffusion of emerging S&T for innovation. Defining and formulating the adequate rule (or law) to govern emerging S&T is crucial for transforming emerging S&T into innovation. Because the way emerging S&T influences society is far from predictable, there has been growing emphasis on the necessity of engaging various stakeholders of emerging S&T into the discussion of defining the adequate governance over emerging S&T (e.g., Bosso, 2016; Rafols et al., 2011), and flexibility/adaptability of the regulatory approach has been emphasized accordingly (Greer & Trump, 2019; Guston, 2008, 2014; Hoffmann et al., 2009; Holdren et al., 2011; Stilgoe et al., 2013). Although this effort is necessary given the nature of the emerging S&T, the emphasis on the flexibility/adaptability and the importance of socio-technical integration may cause governance uncertainty as scholars discuss (Fisher, 2019; Teeter & Sandberg, 2017). To this discussion, our analysis indicates that the resulting regulatory uncertainty may decelerate the diffusion of the emerging S&T for innovation. Therefore, we argue that it is important to manage this tradeoff, and policymakers may need to carefully devise a way of finding the balance between bearing regulatory uncertainty and pursuing the diffusion of the emerging S&T.

The present research extends two strains of literature. First, our study contributes to studies on the relationship between governmental regulation and innovation. It has been one of the prominent

research topics for environmental scientists, economists, management scholars, and public policy researchers as to whether governmental regulation positively or negatively impacts innovation (among others, "Poter's hypotheses" by Porter & Van der Linde, 1995). Since the seminal work by Porter and Van der Linde (1995), there have been myriad empirical studies showing the "stringency" of governmental regulation is associated with firms' innovation activities (e.g., Cecere & Corrocher, 2016; Johnstone, Haščič, Poirier, Hemar, & Michel, 2012; Kesidou & Demirel, 2012). In addition to these studies, our research contributes to advancing the understanding of how other aspects of the regulatory action of governmental authority other than the "stringency" affects innovation, by shedding empirical light on the way the *regulatory uncertainty* shapes the innovation process.

Second, our study contributes to the studies on the factors involved in the translation of scientific discovery into technical applications. Promoting the diffusion of scientific discovery into industrial sectors has been one of the missions of science policymakers because knowledge transfer is one of the crucial sources of technological innovation. To this end, scholars have attempted to explore various factors including scientific, technological, and organizational factors (e.g., Bercovitz, Feldman, Feller, & Burton, 2001; Caldera & Debande, 2010; González-Pernía, Kuechle, & Peña-Legazkue, 2013; Landry, Amara, & Ouimet, 2007; Shane, 2002; Veugelers & Wang, 2019) that may facilitate or hinder the translation of scientific discovery to technology and what policy instruments are worthy of consideration to maneuver those factors. Our research extends these efforts by adding the "*regulatory uncertainty*" as an institutional factor that decelerates the translation of scientific discovery into technical applications.

The present study has several limitations that we wish future studies to address. First, as discussed, our empirical setting was based on a single event of the regulatory uncertainty in the

nanomedicine sector in the U.S. Because the way the mechanism we explained may differently work in other conditions, it is necessary to conduct more empirical analyses in various contexts for more generalizable conclusions.

Second, we measured the translation of scientific discovery into technical applications with the patent citation count accrued to research papers, which exhibits many flaws, as discussed in section 3.4. To this limitation, using the number of new nanomedicine products developed during the period of observation may be an alternative and more direct measurement, and yet, due to the lack of data, our study was limited to the patent citation analysis. We wish future studies to examine the impact of the regulatory uncertainty using alternative measurements.

FIGURES

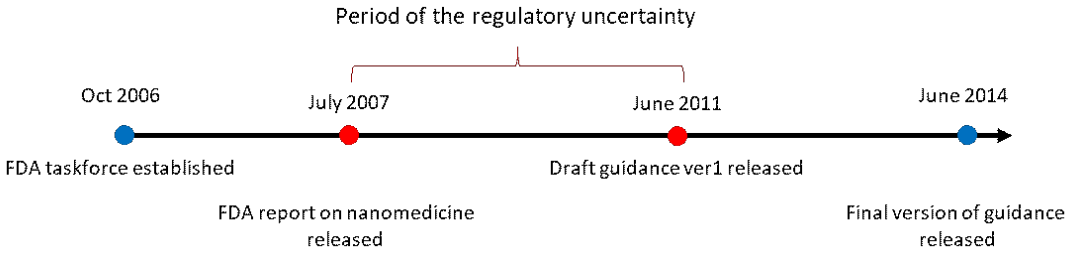

Figure 1. FDA nanomedicine-related documents release timing

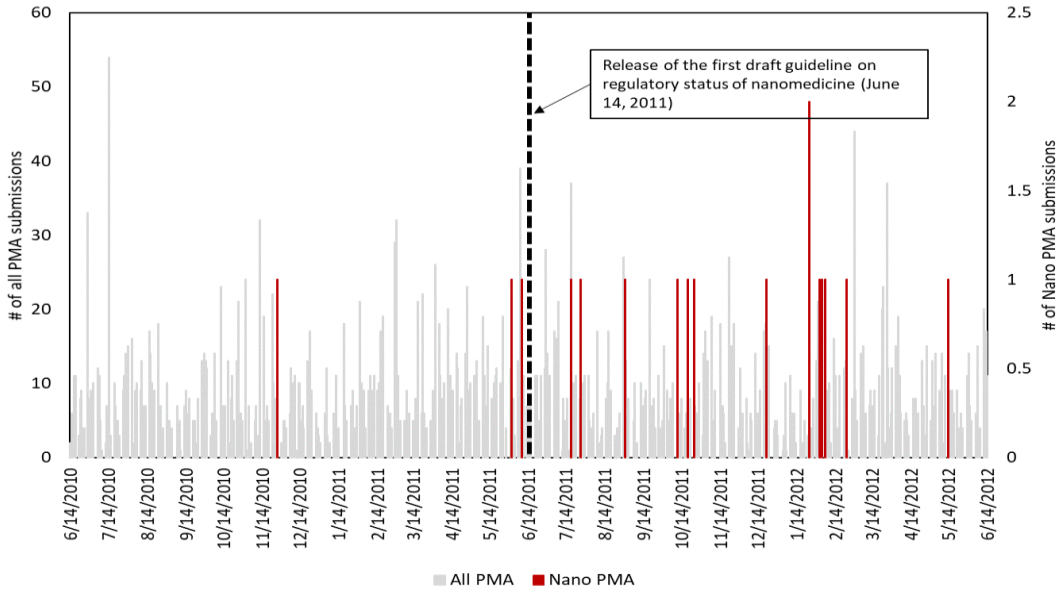

Figure 2. Premarket authorization submission (by submission date)

TABLES

Table 1. Pairwise correlations and summary statistics

NEDD	nUSPatCite	7YrPatCite	PY	lES	Team Size	ln(nRef+1)	Int Collabo	1st author in USA
nUSPatCite	1.00							
7YrPatCite	0.88	1.00						
PY	-0.15	-0.10	1.00					
lES	-0.04	-0.03	0.25	1.00				
Team Size	0.07	0.09	0.05	-0.10	1.00			
ln(nRef+1)	0.00	0.01	0.10	0.01	0.01	1.00		
Int Collabo	0.01	0.01	0.02	-0.03	0.22	0.06	1.00	
1st author in USA	0.11	0.12	-0.13	-0.17	-0.05	0.10	-0.05	1.00
Obs	41,321	41,321	41,321	41,321	41,321	41,321	41,321	41,321
Mean	1.36	0.89	2008.96	2.19	5.91	3.61	0.20	0.29
Std.Dev	7.10	4.30	2.60	1.63	3.14	0.48	0.40	0.45
Min	0	0	2003	0	1	0	0	0
Max	521	155	2012	5.500495	57	6.326149	1	1

SynBio	nUSPatCite	7YrPatCite	PY	lES	Team Size	ln(nRef+1)	Int Collabo	1st author in USA
nUSPatCite	1.00							
7YrPatCite	0.90	1.00						
PY	-0.13	-0.04	1.00					
lES	0.00	0.03	0.33	1.00				
Team Size	0.12	0.12	0.00	-0.07	1.00			
ln(nRef+1)	0.00	0.01	0.09	0.12	0.05	1.00		
Int Collabo	-0.04	-0.04	0.03	0.00	0.24	0.07	1.00	
1st author in USA	0.15	0.15	0.00	0.04	-0.05	0.06	-0.14	1.00
Obs	2,705	2,705	2,705	2,705	2,705	2,705	2,705	2,705
Mean	2	1	2,009	1	5	3.58	0.22	0.40
Std.Dev	6.83	4.69	2.76	1.06	3.23	0.56	0.41	0.49
Min	0	0	2003	0	1	0	0	0
Max	113	82	2012	3.84	53	5.82	1	1

Table 2. Main regression results

	DiD estimation		DDD estimation		lES>0		lES=0	
VARIABLES	nUSPatCite	7YrPatCite	nUSPatCite	7YrPatCite	nUSPatCite	7YrPatCite	nUSPatCite	7YrPatCite
PY2003XNEDDxlES			-0.281	-0.741*				
			(0.338)	(0.382)				
PY2004XNEDDxlES			-0.240	-0.477				
			(0.280)	(0.359)				
PY2005xNEDDxlES			0.0360	-0.00617				
			(0.266)	(0.260)				
PY2006xNEDDxlES			0.138	0.177				
			(0.247)	(0.266)				
PY2008xNEDDxlES			-0.0239	-0.00672				
			(0.344)	(0.351)				
PY2009xNEDDxlES			-0.0724	-0.0582				
			(0.280)	(0.286)				
PY2010xNEDDxlES			**-0.303***	-0.244				
			(0.155)	(0.154)				
PY2011xNEDDxlES			**-0.558*****	**-0.551*****				
			(0.156)	**(0.157)**				
PY2012xNEDDxlES			-0.160	-0.166				
			(0.132)	(0.131)				
PY2003xNEDD	0.519	0.437	0.569	0.696*	0.254	-0.263	0.558	0.585
	(0.371)	(0.334)	(0.414)	(0.356)	(0.530)	(0.601)	(0.554)	(0.439)
PY2004xNEDD	0.245	0.0846	0.297	0.264	0.0150	-0.399	0.267	0.150
	(0.359)	(0.303)	(0.398)	(0.338)	(0.490)	(0.606)	(0.538)	(0.420)
PY2005xNEDD	-0.133	-0.290	-0.105	-0.254	-0.189	-0.241	0.00286	-0.275
	(0.383)	(0.333)	(0.447)	(0.401)	(0.411)	(0.416)	(0.578)	(0.477)
PY2006xNEDD	-0.0370	-0.149	-0.0750	-0.267	0.168	0.140	0.00630	-0.280
	(0.369)	(0.318)	(0.434)	(0.395)	(0.375)	(0.411)	(0.563)	(0.464)
PY2008xNEDD	-0.214	-0.436	-0.144	-0.406	-0.0771	-0.167	-0.124	-0.522
	(0.469)	(0.422)	(0.611)	(0.570)	(0.477)	(0.488)	(0.719)	(0.630)
PY2009xNEDD	-0.281	-0.409	-0.0397	-0.197	-0.318	-0.317	-0.0382	-0.316
	(0.404)	(0.359)	(0.540)	(0.518)	(0.365)	(0.351)	(0.650)	(0.571)
PY2010xNEDD	-0.463	**-0.568****	0.0244	-0.139	**-0.623***	**-0.566***	-0.0373	-0.307
	(0.336)	**(0.270)**	(0.406)	(0.346)	**(0.335)**	**(0.333)**	(0.559)	(0.445)
PY2011xNEDD	**-0.684***	**-0.834*****	0.311	0.156	**-1.139*****	**-1.171*****	0.894	0.637
	(0.368)	**(0.308)**	(0.424)	(0.366)	**(0.369)**	**(0.367)**	(0.562)	(0.449)
PY2012xNEDD	**-0.737****	**-0.894*****	-0.249	-0.389	**-0.712****	**-0.758****	-0.391	-0.642
	(0.328)	**(0.258)**	(0.390)	(0.325)	**(0.321)**	**(0.317)**	(0.543)	(0.422)
PY2003xlES			0.312	0.752**				
			(0.336)	(0.380)				
PY2004xlES			0.232	0.416				
			(0.280)	(0.359)				
PY2005xlES			-0.0731	-0.0347				
			(0.265)	(0.261)				
PY2006xlES			-0.170	-0.179				
			(0.249)	(0.267)				
PY2008xlES			-0.0317	-0.0410				
			(0.346)	(0.352)				
PY2009xlES			-0.0749	-0.0870				
			(0.282)	(0.289)				
PY2010xlES			0.169	0.0918				
			(0.158)	(0.157)				
PY2011xlES			0.341**	0.319**				
			(0.158)	(0.159)				
PY2012xlES			-0.0750	-0.0869				
			(0.135)	(0.134)				
PY2003	0.403	0.0732	0.393	-0.103	0.753	0.833	0.530	0.102
	(0.353)	(0.310)	(0.390)	(0.311)	(0.510)	(0.581)	(0.526)	(0.390)
PY2004	0.435	0.200	0.460	0.192	0.719	0.681	0.532	0.324
	(0.342)	(0.281)	(0.375)	(0.297)	(0.470)	(0.591)	(0.511)	(0.373)

PY2005	0.424	0.243	0.506	0.333	0.453	0.186	0.506	0.408
	(0.366)	(0.315)	(0.419)	(0.369)	(0.392)	(0.399)	(0.546)	(0.438)
PY2006	0.0946	0.0964	0.216	0.243	-0.159	-0.203	0.235	0.312
	(0.355)	(0.300)	(0.410)	(0.354)	(0.358)	(0.395)	(0.533)	(0.415)
PY2008	-0.190	0.122	-0.149	0.185	-0.415	-0.206	-0.0620	0.342
	(0.459)	(0.411)	(0.598)	(0.552)	(0.464)	(0.476)	(0.699)	(0.603)
PY2009	-0.313	0.0326	-0.245	0.126	-0.392	-0.158	-0.284	0.150
	(0.392)	(0.345)	(0.524)	(0.499)	(0.346)	(0.331)	(0.626)	(0.545)
PY2010	-0.492	-0.0604	-0.697*	-0.165	-0.471	-0.209	-0.566	0.0419
	(0.322)	(0.251)	(0.381)	(0.310)	(0.317)	(0.316)	(0.527)	(0.401)
PY2011	-0.704**	-0.183	-1.219***	-0.660**	-0.510	-0.105	-1.575***	-0.962**
	(0.356)	(0.293)	(0.401)	(0.334)	(0.354)	(0.351)	(0.529)	(0.404)
PY2012	-1.018***	-0.481**	-0.970***	-0.410	-1.210***	-0.784***	-0.926*	-0.301
	(0.312)	(0.238)	(0.362)	(0.284)	(0.300)	(0.297)	(0.508)	(0.372)
NEDD	-0.0460	0.0942	-0.184	-0.0533	-0.119	-0.0955	-0.210	0.0335
	(0.286)	(0.202)	(0.305)	(0.217)	(0.245)	(0.240)	(0.475)	(0.331)
lES			0.115**	0.131***				
			(0.0486)	(0.0501)				
Constant	-0.986***	-1.497***	-1.047***	-1.583***	-1.213***	-1.640***	-0.430	-0.974*
	(0.348)	(0.288)	(0.384)	(0.324)	(0.303)	(0.299)	(0.617)	(0.521)
Lnalpha	2.076***	2.084***	2.068***	2.074***	2.013***	2.014***	2.160***	2.180***
	(0.0185)	(0.0206)	(0.0185)	(0.0208)	(0.0238)	(0.0261)	(0.0291)	(0.0337)
Observations	44,026	44,026	44,026	44,026	30,606	30,606	13,420	13,420
Model	GNBREG	GNBREG	GNBREG	GNBREG	GNBREG	GNBREG	GNBREG	GNBREG
Sample	All	All	All	All	lES>0	ES>0	lES=0	ES=0
Pseudo R2	0.0424	0.0316	0.0434	0.0329	0.0502	0.0390	0.0292	0.0211

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
Note. Control variables were removed for the space constraint. The full regression table is available upon request.

Table 3. Testing Research Impact Change

VARIABLES	(1) TimesCited	(2) TimesCited	(3) TimesCited	(4) TimesCited
PY2003XNEDDxlES		0.197		
		(0.187)		
PY2004XNEDDxlES		0.155		
		(0.212)		
PY2005xNEDDxlES		-0.157		
		(0.104)		
PY2006xNEDDxlES		0.00813		
		(0.119)		
PY2008xNEDDxlES		0.0469		
		(0.0948)		
PY2009xNEDDxlES		-0.131		
		(0.0978)		
PY2010xNEDDxlES		**0.156****		
		(0.0655)		
PY2011xNEDDxlES		0.0107		
		(0.0534)		
PY2012xNEDDxlES		0.0256		
		(0.0558)		
PY2003xNEDD	0.147	0.115	0.494	0.0277
	(0.162)	(0.174)	(0.331)	(0.187)
PY2004xNEDD	0.252	0.153	0.510	0.0934
	(0.171)	(0.179)	(0.354)	(0.193)
PY2005xNEDD	0.121	0.178	-0.0656	0.0903
	(0.141)	(0.145)	(0.248)	(0.161)
PY2006xNEDD	0.0668	0.00732	0.231	-0.114
	(0.148)	(0.154)	(0.259)	(0.169)
PY2008xNEDD	0.0428	0.00780	0.179	-0.0991

	(0.136)	(0.141)	(0.231)	(0.158)
PY2009xNEDD	-0.201	-0.0840	-0.294	-0.133
	(0.143)	(0.154)	(0.221)	(0.171)
PY2010xNEDD	-0.0346	-0.209	0.151	-0.246
	(0.132)	(0.150)	(0.199)	(0.169)
PY2011xNEDD	-0.0823	-0.0557	0.0399	-0.184
	(0.120)	(0.138)	(0.178)	(0.158)
PY2012xNEDD	-0.0243	0.0110	0.0814	-0.0680
	(0.122)	(0.156)	(0.176)	(0.181)
PY2003xlES		-0.184		
		(0.185)		
PY2004xlES		-0.124		
		(0.211)		
PY2005xlES		0.166		
		(0.103)		
PY2006xlES		0.0128		
		(0.119)		
PY2008xlES		-0.0722		
		(0.0948)		
PY2009xlES		0.0944		
		(0.0983)		
PY2010xlES		-0.168**		
		(0.0658)		
PY2011xlES		-0.0528		
		(0.0543)		
PY2012xlES		-0.0863		
		(0.0567)		
PY2003	0.215	0.350**	-0.0170	0.432**
	(0.152)	(0.158)	(0.322)	(0.171)
PY2004	0.0735	0.205	-0.0986	0.290
	(0.164)	(0.170)	(0.348)	(0.182)
PY2005	0.0945	0.0825	0.344	0.155
	(0.134)	(0.134)	(0.243)	(0.148)
PY2006	0.0623	0.102	-0.0526	0.192
	(0.142)	(0.147)	(0.254)	(0.160)
PY2008	-0.125	-0.0569	-0.289	0.0377
	(0.131)	(0.132)	(0.227)	(0.146)
PY2009	-0.0107	-0.0839	0.0357	-0.0454
	(0.140)	(0.148)	(0.218)	(0.162)
PY2010	-0.261**	-0.129	-0.495**	-0.0871
	(0.128)	(0.142)	(0.195)	(0.157)
PY2011	-0.387***	-0.389***	-0.583***	-0.266*
	(0.116)	(0.130)	(0.175)	(0.149)
PY2012	-0.668***	-0.638***	-0.865***	-0.552***
	(0.118)	(0.149)	(0.173)	(0.170)
NEDD	0.147	-0.0694	0.0231	0.0217
	(0.102)	(0.101)	(0.158)	(0.123)
lES		0.168***		
		(0.0149)		
Constant	1.595***	1.418***	1.702***	1.626***
	(0.119)	(0.117)	(0.173)	(0.169)
Lnalpha	0.0456***	0.00399	0.000654	0.0445***
	(0.00897)	(0.00915)	(0.0109)	(0.0157)
Observations	44,026	44,026	30,606	13,420
Model	GNBREG	GNBREG	GNBREG	GNBREG
Sample	All	All	lES>0	lES=0
Pseudo R2	0.0177	0.0227	0.0200	0.0236

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Note. Control variables were removed for the space constraint. The full regression table is available upon request.

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