Review of Economics and Statistics Just Accepted MS.
https://doi.org/10.1162/rest_a_00987

Patents, Data Exclusivity, and the Development of New Drugs

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ABSTRACT

Pharmaceutical firms enjoy market exclusivity for new drugs from concurrent patent protection and exclusivity of the clinical trials data submitted for market approval. Patent invalidation during drug development renders data exclusivity the sole source of protection and shifts the period of market exclusivity. In instrumental variables regressions we quantify the effect of a one-year reduction in expected market exclusivity on the likelihood of drug commercialization. The effect is largely driven by patent invalidations early in the drug development process and by the responses of large originators. We hereby provide estimates of the responsiveness of R&D investments to market exclusivity expectations.

KEYWORDS: patents, drugs, data exclusivity, clinical trials.

JEL Classification: K41, L24, L65, O31, O32, O34

We thank Senem Aydin, Christian Fons-Rosen, Georg von Graevenitz, Dietmar Harhoff, Matt Higgins, Josh Krieger, Malwina Mejer, Tim Simcoe, and Martin Watzinger for their valuable comments. Moreover, we are thankful to the editor and the anonymous reviewers. Fabian Gaessler gratefully acknowledges financial support by Deutsche Forschungsgemeinschaft (DFG) through CRC TRR 190 "Rationality and Competition". Stefan Wagner gratefully acknowledges financial support from the DFG through the Collaborative Research Center SFB 649 "Economic Risk".

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1 Introduction

The negotiations of the Trans-Pacific Partnership (TPP) put the discussion on the design of intellectual property rights (IP rights) that protect new drugs against imitation back on center stage (Luo and Kesselheim, 2015). The period of data exclusivity for novel pharmaceutical products was one of the most controversial issues. Data exclusivity refers to the period during which clinical trial results, detailing the approved drug's toxicology and efficacy, cannot be used by generic entrants for subsequent marketing approval. As clinical trials are costly, data exclusivity creates entry barriers and hence is a source of market exclusivity independent of patent protection. The debates around an extension of data exclusivity periods evolved around the trade-off between welfare gains arising from stronger incentives to innovate and additional cost to society due to (near) monopoly pricing. Strengthening the legal protection of novel drugs might increase the incentives to invest in risky R&D projects while extending exclusivity rights might lead to welfare losses created by higher prices due to limited competition by generics.

The trade-off between stronger incentives for innovation (stronger protection against imitation) and resulting costs to society (higher prices) has been well established in the innovation literature (Arrow, 1962). Starting with Nordhaus (1969), a broad stream of theoretical literature provides analyses of the optimal design of IP rights and the balance between dynamic social gains by greater innovation efforts and static losses due to market power of innovators (see Scotchmer (2004) for a discussion). The more recent empirical literature increasingly focuses on the causal relationship between IP rights and inventive activity, analyzing both the rate and the direction of innovation in the pharmaceutical industry (Budish et al., 2015; Kyle and McGahan, 2012; Qian, 2007) and beyond (Williams, 2017). However, it focuses on incentives provided by the patent system without taking into account its complex interplay with data exclusivity. In this paper, we contribute to this literature by relating the overall duration of

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market exclusivity resulting from both patent protection *and* data exclusivity to the likelihood of successful product commercialization in the pharmaceutical industry. Ultimately, we hereby provide estimates for the responsiveness of R&D investments to a change in the duration of market exclusivity.

The overall duration of market exclusivity for a new drug is derived from patents as well as data exclusivity, and determined by the time between initial patent filing and market approval: patents grant exclusive rights to inventions for a fixed period of time starting from the date of the patent application. In most cases, patent applications are filed upon the discovery of the molecule underlying a potential drug. Data exclusivity, in contrast, is granted for a fixed period upon the approval of a new drug for marketing. At market approval, a new drug enjoys concurrent protection from the remaining patent term and from the fixed period of data exclusivity. If the remaining patent term is shorter than the period of data exclusivity, the latter provides additional protection. During the TPP negotiations it was argued that, amid increasing durations of clinical trials and the implied reduction of effective patent terms, extended data exclusivity periods could remedy weakened R&D incentives. In their theoretical analysis of potential policy responses to skewed R&D incentives resulting from fixed patent terms, Budish et al. (2015) come to the same conclusion. For similar reasons, US regulations contain different expedited approval processes exploiting this mechanism.[1] Amongst them, the priority

[1]There are four different FDA programs to expedite drug development and review: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation (see https://www.fda.gov/.../Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf [last access: June 15, 2020]. In Europe, the Priority Medicines (PRIME) scheme of the European Medicines Agency (EMA) was enacted in 2016. It resembles the FDA's Breakthrough Therapy designation and intends to speed up drug development by offering early and proactive support to medicine developers to optimise the generation of clinical data and enable accelerated assessment for market approval.

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review designation, shortens the duration of FDA approval proceedings from ten months to six months, and thus increasing incentives to develop eligible drugs. In order to further increase these incentives, the Food and Drug Administration Amendments Act (FDAAA) of 2007 in the US introduced the priority review voucher program. It authorizes the FDA to award vouchers to reward manufacturers of newly approved drugs for neglected tropical or pediatric diseases (Ridley et al., 2006). The voucher can be used to assign any drug that addresses serious conditions to the FDA's priority review designation and thus increases profits for a drug with a potentially larger market than the rewarded drug. The voucher is therefore seen to create incentives to conduct research in neglected diseases.

Despite the intense policy debate surrounding the optimal design of IP rights in the pharmaceutical industry, there is little empirical evidence on how the overall duration of market exclusivity relates to originators' innovation efforts. An ideal experiment to study this question would be to randomly allocate varying durations of market exclusivity to firms *ex ante* and link them to observed innovation outcomes. Such an experiment is infeasible. As an alternative, we exploit a natural experiment that provides exogenous variation in the patent protection surrounding a drug development project. We analyze development histories of drugs for which underlying patents have been at risk of invalidation in opposition proceedings at the European Patent Office (EPO): when a patent is invalidated, data exclusivity becomes the sole source of market exclusivity. If the remaining patent term after approval exceeds the period of data exclusivity, invalidation will lead to a reduction in the overall duration of market exclusivity. We compare the outcomes of these treated development projects with outcomes of projects where patents have been upheld (and market exclusivity remains unaffected). Linking the project-specific exogenous variation in the duration of market exclusivity to development projects' outcomes enables us to causally identify how the duration of market exclusivity determines innovation efforts.

We account for the fact that our treatment (invalidation) might not be random as firm

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efforts put into defending a patent are likely to be determined by unobservable characteristics (such as early signs of a drug's efficacy or potential market size) that may also affect innovation efforts. To address the resulting endogeneity, we employ a novel instrument first proposed by Gaessler et al. (2019). This instrument uses random variation in the participation of the primary examiner, who initially granted the patent, in the opposition proceeding. Examiner participation is negatively correlated with invalidation but uncorrelated with other factors that might determine commercialization efforts. Instrumenting patent invalidation hence creates exogenous variation that allows us to causally identify how innovation outcomes depend on the duration of protection against generic competition.

A novel data set that links the development histories of pharmaceutical compounds from preclinical trials up to market approval (or the highest development stage reached) with information on the underlying patents is used for this study. Clarivate's Cortellis database and the EPO's PATSTAT statistical database are the major sources of our data. In total, we are able to link 935 unique drug candidates and their respective development histories with patents subject to invalidation proceedings. Drug candidates are often tested against more than one indication, so that one drug may be linked to multiple development projects. We identify 2,819 unique observations at drug-indication level where the decision on opposition takes place before drug approval or the termination of clinical trials – a prerequisite for our empirical strategy. We focus on drug candidates that have entered at least preclinical trials and where the validity of at least one underlying patent has been challenged.

We present estimates from linear probability models in which we relate commercialization outcomes to the duration of market exclusivity for development projects with and without patent invalidation. Our instrumental variables (IV) regression results indicate that a reduction in the duration of market exclusivity significantly affects project outcomes. We find that the loss of one year of market exclusivity lowers the likelihood of drug approval by about 4.9 percentage points relative to an unconditional approval rate of 30.8%. This response to a loss in expected

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market exclusivity is quite immediate: firms overwhelmingly abandon treated drug projects right after the patent is invalidated and do not pursue the next development phase. We further find that the effect is driven by (i) timing, as patent invalidation in early development phases has a statistically more significant effect and (ii) firm size, as originators with large pipelines react more strongly than originators with small ones. We argue that the more elastic responses in these two subsamples approximate the policy-relevant effect at the *extensive margin*, because in this context firms face lower sunk costs (i.e., most of the R&D costs occur at later stages) but higher opportunity costs (i.e., alternative drug projects are readily available).

We conduct robustness tests taking into account the complex institutional setting of this study. First, as drugs are often protected by more than one patent, one potential concern is that invalidation might not affect the primary patent associated to a drug's active ingredient but rather a secondary patent related to dosage or delivery channels. Considering primary patents exclusively does not alter our main findings. Second, drug candidates are often tested against multiple indications and results from preclinical and Phase I clinical trials can – under certain circumstances – be used across diseases. Restricting our sample to development histories of first indication drugs does not change our results. Finally, our main results consider drug approvals in any of the three largest pharmaceutical markets (USA, Europe, and Japan), even though we consider shifts of market exclusivity in European markets only. For this reason, our estimates should be interpreted as lower bounds of the effect of changes in exclusivity across all markets. Robustness tests using a subsample of biologic drugs, for which the data exclusivity regimes in Europe and the US are comparable, indeed yield somewhat larger effect sizes.

The findings from this study bear relevance not only for scholars interested in the economics of innovation but also for policy makers responsible for the design of law governing intellectual property (IP) protection. A further strengthening of the protection of new drugs by extending data exclusivity periods has been discussed contentiously but largely in the absence of empirical evidence (Diependaele et al., 2017; Grabowski et al., 2015; Higgins and

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https://doi.org/10.1162/rest_a_00987

Graham, 2009; Lietzan, 2016). Our work identifies how the duration of market exclusivity affects originators' commercialization efforts and quantifies how variations in the durations of exclusivity determine private incentives to complete drug development. Our findings have important implications: data exclusivity emerges as an effective policy instrument to provide market exclusivity in cases where the remaining patent term is short relative to the lengths of needed clinical trials, or where patent protection is uncertain.

2 Market exclusivity in the pharmaceutical industry

2.1 Institutional background

Context

The commercial life cycle of a drug consists of three periods (Scherer, 2000): (i) the development period, during which R&D takes place and clinical trials are conducted; (ii) the market exclusivity period, when the originator markets the drug under exclusivity; and (iii) the post-exclusivity period, in which competition by generic products is possible. The development period is highly regulated and typically consists of the discovery stage, preclinical trials, and Phase I, II, and III clinical trials, which ascertain the toxicity and efficacy of a molecule. On average, it takes between 8.6 and 11.5 years from discovery to marketing authorization, and only a small fraction of all drug candidates (molecules) entering development eventually reach regulatory approval (European Commission, 2009). In order to obtain marketing authorization in a given jurisdiction, originator companies have to submit data gathered during clinical trials to the respective national regulatory authorities and request marketing authorization.Developing new drugs is costly as evidenced by cost estimates in the range of USD 500 million to USD 2.6 billion (Adams and Van Brantner, 2006; DiMasi et al., 2016). Tests and clinical trials are responsible for the majority of the total R&D costs – the European Commission (2009) estimates that research-active pharmaceutical companies spend only 1.5% of their overall revenues on basic R&D (which includes the discovery of novel compounds) but 15.5% on clinical trials,

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tests, and market approval.

Pharmaceutical companies' decisions to make risky up-front investments in developing new drugs depend on their expected payoffs during the subsequent period of market exclusivity. Market exclusivity is derived through two legal mechanisms: patent rights and data exclusivity. Figure 1 presents a stylized life cycle of a drug and the associated IP rights. Upon discovery, companies typically file applications for patents covering the active substance of a drug and subsequently obtain a grant decision. Once clinical trials are completed and the collected data shows the non-toxicity and the effectiveness of a drug, it can be approved for marketing by regulatory authorities. This marks the starting point of a drug's period of market exclusivity, whose length is determined by the effective patent term and the period of data exclusivity. Longer periods of market exclusivity are related to higher payoffs for the originator company. After expiration of market exclusivity, generic manufacturers are likely to enter the market, which reduces prices and consequently the originator company's margins.

Originators often seek to increase their R&D productivity either by broadening the market for a molecule through additional indications or by extending the period of market exclusivity through improved versions of the original drug. First, they might try to "reposition" existing drugs for new indications (Ashburn and Thor, 2004). Second, R&D productivity can be increased by extending the period of market exclusivity with the introduction of follow-on products (so called "evergreening", Hemphill and Sampat (2012)). In order to guarantee market exclusivity for the second-generation products, they typically continue to work on incremental improvements and obtain additional patents throughout the life cycle of the first product. These additional patents expire later than the primary patents on the original product, extending the period of market exclusivity (European Commission, 2009).

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Patent rights

Patents rights are exclusion rights that allow the patent holder to exclude third parties from using the protected invention for a fixed term of 20 years starting from the priority date. Patents on a drug's active ingredients are easy to enforce and allow patent holders to prevent imitation and the entry of generic competition; they are considered the primary mechanism to appropriate value from innovation in the pharmaceutical industry (Cohen et al., 2000). The patents covering a potential drug are typically filed at "drug discovery", that is, during the basic R&D stage. For this reason, the duration of the resulting market exclusivity of the novel drug is directly determined by how much time lapses between the filing of the patents and the drug's market approval (see the detailed discussion below).

A number of jurisdictions provide mechanisms to extend the duration of patent protection for pharmaceutical products under certain conditions. In Europe, if the period of market exclusivity derived from patents is shorter than 15 years, companies can apply for supplementary protection certificates (SPCs) for medicinal products according to Council Regulation (EEC) No 1768/92 of June 18, 1992 (European Commission, 2018). SPCs effectively amount to an extension of the patent right for a maximum of five years as the total term of market exclusivity derived from the patent plus SPC is limited to 15 years.[2] In the United States of America, the 1984 Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Act") allows qualifying companies to apply for a partial extension of patent life based on the duration of clinical trials (Saha et al., 2006). In the following, we focus on European regulation.

Patents relating to a pharmaceutical product are typically divided into *primary patents*, protecting the active ingredient, and *secondary patents*, protecting all other aspects of a drug such as different dosage forms, components, production methods, and so forth. Secondary

[2]SPCs extend only to the specific medicinal product and use which was originally authorized – they do not cover subsequent authorizations of the same compound for different indications.

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patents often result from originators' efforts to extend the time of market exclusivity and to maintain or even expand the market that the product covers during market exclusivity. These objectives can be supported by specific patenting strategies, in particular the creation of so-called patent fences, that is, the filing of a multitude of patents surrounding one product (Abud et al., 2015; European Commission, 2009). Typically, the filing date (priority date) of the primary patent(s) surrounding a pharmaceutical product determines the duration of market exclusivity of a first-generation drug that can be derived from patents (and SPCs).

Data exclusivity

A second source of market exclusivity is data exclusivity, which protects the data collected in clinical trials and submitted to regulatory authorities. Before 1984 in the US, and before 1987 in the EU, test data was protected as a trade secret. The introduction of new procedures for abridged applications for market approval of equivalent or essentially similar pharmaceutical products ("generic applications") with the 1984 "Hatch-Waxman Act" in the US and the 1987 87/21/EEC Directive in the EU further clarified the rules of clinical test data protection (Sanjuan, 2006). Data exclusivity prevents abridged applications for marketing a generic drug before a certain number of years after the first marketing authorization for the originator product has elapsed. Only after a drug's protection via patents (and SPCs) have lapsed *and* in absence of data exclusivity, can generic companies file abridged applications. Abridged applications have the advantage that they do not require the applicant to provide results of preclinical tests or clinical trials, but only to demonstrate that a product is similar to the original drug. If a drug still enjoys data exclusivity, however, generic entrants need to submit data from complete clinical trials. In light of the costs of conducting clinical trials, data exclusivity creates a significant

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barrier to entry for generic companies (Grabowski, 2004; Branstetter et al., 2017).[3]

The duration of data exclusivity has not been harmonized internationally and is a subject of ongoing policy debates around the globe. In Europe, it varied considerably across countries ranging from six to ten years before the Directives 2001/83/EC and 2004/27/EC of the European Commission harmonized data exclusivity regulations in Europe with legal effect from November 2005 (European Commission, 2009). For marketing authorization applications made from November 2005 onward, the period of data exclusivity in Europe was harmonized as eight years from the date of first authorization in Europe with an additional period of two years.After a total period of ten years from the granting of the originator's marketing authorization, generic companies can also market their product.[4]

2.2 Market exclusivity and the incentives for drug development

Starting a broad theoretical literature, Nordhaus (1969) argues that investments in innovation rise with profits expected from it. Based on this argument, it is straightforward to show that the duration of market exclusivity is directly linked to investments into R&D in the pharmaceutical industry. In Online Appendix C, we present a simple model of how a firm's incentive to invest in risky R&D projects depends on expected future profits which in turn depend on the (expected)

[3]Apart from ethical considerations, the cost of conducting clinical trials seems to be large enough to prevent their duplication in order to circumvent data exclusivity periods. Additional interviews with executives from pharmaceutical companies did not reveal any cases where firms duplicated clinical trials.

[4]The originator's product may qualify for one further year of exclusivity. This additional year can be obtained in a number of circumstances, such as where the innovator company is granted a marketing authorization for a significant new indication for the relevant medicinal product. The regulation taking effect in 2005 is often labeled as "8+2+1" and provides market exclusivity of up to eleven years (see European Commission, 2009, p. 127).

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duration of market exclusivity. Under fairly broad assumptions, investment can be shown to increase in the duration of market exclusivity. Note, we abstract from additional determinants of future profits including market size, level of market saturation, and competitive dynamics in the targeted therapeutic area (Acemoglu and Linn, 2004; Dubois et al., 2015; Krieger, 2017; Rao, 2018).

The duration of market exclusivity is determined by patent protection, development time and the length of the data exclusivity period and varies across development projects (see also Section 2.1, Figure 1). First, the effective patent term, that is, the duration of patent protection while a new drug is on the market, is linearly decreasing in development time as patents are filed at the beginning of the development stage. If a drug is approved only after five years of development or later, a company can obtain an SPC which extends patent-based market exclusivity for another five years (limited to a maximum total duration of market exclusivity of 15 years). Second, if the remaining effective patent term at approval is lower than the period of data exclusivity, the overall duration of market exclusivity is determined by the duration of data exclusivity independently of the development time. In the majority of cases, the data exclusivity period expires before the lapse of relevant patents and SPCs. The data exclusivity period extends beyond the patent term only in cases of relatively long development times (European Commission, 2009). Figure 2 summarizes these relations between development time and the duration of market exclusivity.

2.3 Firm responses to changes in market exclusivity

Existing work often relates measures of market size to innovation activity in the pharmaceutical industry (Blume-Kohout and Sood, 2013; Dubois et al., 2015; Krieger et al., 2018). The universal existence of harmonized IP systems, however, renders empirical studies of the effect of different market exclusivity periods on the development of new drugs challenging. As a result, limited empirical evidence exists on how firms' R&D investment decisions relate to the

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duration of market exclusivity. Most relevant, Budish et al. (2015) argue that, in contrast to the fixed patent length, the *effective* duration of patent protection varies. Innovations that can be commercialized at the time of invention enjoy patent-based market exclusivity of the full patent term, whereas innovations with a long lag between invention and commercialization (such as drugs) receive only a substantially reduced period of patent-based market exclusivity. Budish et al. (2015) show that firms disproportionately invest in projects with longer effective patent protection and discuss negative welfare effects due to this distortion. Looking at variation in patent grant lags, Wagner and Wakeman (2016) they find that once the uncertainty about patentability is resolved, the likelihood and speed of successful drug development increase significantly.

Adding to this sparse literature, we study how firms' innovation activities respond to variation in project-specific market exclusivity durations and exploit a natural experiment that provides exogenous variation in the patent protection surrounding a drug development project. While patent applications are thoroughly examined (Popp et al., 2004; Harhoff and Wagner, 2009), granted patents are at risk of invalidation after their grant. In case of invalidation, data exclusivity becomes the sole source of market exclusivity. If the remaining patent term from the invalidated patent exceeds the period of data exclusivity, patent invalidation will reduce the duration of market exclusivity; we refer to this reduction as *loss of exclusivity* (see also Figure 2). We focus exclusively on development projects where the underlying patent has been at risk of invalidation before project completion. Comparing outcomes of development projects with and without an actual loss of exclusivity allows us to measure how firms' R&D activities respond to changes in the duration of market exclusivity.

As an in-depth discussion of the institutional details surrounding patent invalidation is beyond the scope of this paper, we restrict ourselves to key aspects in Europe and in the US. In Europe, the validity of a patent can be challenged by any third party in court any time after its grant. In addition, the European Patent Office (EPO) offers the possibility to challenge

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a patent's validity within nine months after its grant. Opponents can challenge patents on grounds specified in Article 100 of the European Patent Convention (EPC). Possible opposition outcomes are a narrowing of the protective scope of a patent (amendment) or the invalidation of the entire patent (revocation). A structurally equivalent mechanism of post-grant validity challenges at the United States Patent and Trademark Office (USPTO) ("Post Grant Review") was introduced with the Leahy-Smith America Invents Act (AIA), which went into effect on September 16, 2012. Since opposition proceedings are significantly less costly than validity challenges in national courts, they represent the main channel of patent invalidation in Europe (Harhoff and Reitzig, 2004). Between 1980 and 2007, about 7.4% of all granted pharmaceutical patents at the EPO have been opposed at the patent office (Harhoff et al., 2016).

Third parties typically challenge patents of higher value (Harhoff and Reitzig, 2004), but there is little evidence about the underlying motives of the opponents. Unlike the US, there are no formalized incentives for third parties to challenge the validity of patents protecting novel drugs in Europe.[5] While invalidation of a patent via opposition has the potential to reduce the market exclusivity period of a drug, opposition has to be filed years ahead of a potential generic entry at a point in time where it is not clear whether a drug candidate will eventually be approved at all. Note that "legal spillovers", where patent invalidation through opposition at the EPO calls into question the validity of the patent's counterparts in other jurisdictions, seem plausible (De Corte et al., 2012, p. 140).

Models of firm investments into innovation predict that investments rise with the profits expected from it. As the profits from successful drug development increase in the duration of

[5]In the US, the Hatch-Waxman Act provides incentives for generics companies to challenge patents. Generics companies that file an Abbreviated New Drug Application (ANDA) under Paragraph IV are granted a 180-day exclusivity period for their generic drug without any further generic entry allowed (Branstetter et al., 2016). The European regulations do not have an equivalent to these Paragraph IV challenges.

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market exclusivity, we expect a loss of exclusivity due to patent invalidation to have a negative effect on firms' innovative activities. We are not able to measure project-specific R&D investments directly, but relate a loss of exclusivity to observable project-specific likelihoods of successful product commercialization and project continuations, which can be expected to be strongly correlated to underlying investments.

There are at least two sources of heterogeneity that may affect the magnitude of our main effect. First, we expect its strength to depend on the timing of patent invalidation relative to a drug candidate's position in the development process. Having completed a given stage of the development process, originators must decide whether to further invest in the next phase of trials. A negative shock to the expected profits from successful commercialization will affect firm responses more strongly if it materializes in early stages. This prediction is in line with general models of staged investment decisions and optimal stopping problems (Dixit and Pindyck, 1994; Pindyck, 1991): the probability of success (obtaining market authorization) and hence the expected payoff from investments in subsequent development stages increases with each completed trial stage. At the same time, both uncertainty and the total cumulative amount of further investments necessary to reach the market decrease.

Second, the magnitude of our main effect should depend on firm size. Firms differ in the availability of alternative investment projects (outside options) when assessing a given R&D project (Chan et al., 2007; Girotra et al., 2007; Kavadias and Loch, 2004). Girotra et al. (2007) point out that the marginal value of a project is smaller for pharmaceutical firms with large project portfolios. The chances to successfully release a drug for a given market (indication) increase in the number of alternative candidates for this market in a firm's development pipeline. The value of a given project hence decreases in the number of alternative candidates. Consequently, the likelihood that a project is abandoned as consequence of a loss of exclusivity should be higher for large firms compared to small firms. Additionally, conducting clinical trials requires firms to hold available relevant resources, such as clinical trial sites and bio-statisticians.

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It is costly to scale the capacity of these resources up or down as they resemble fixed assets (Girotra et al., 2007). Firms with a larger pipeline of projects can be expected to be more willing to abandon a project in case it frees up the constrained resources for another pipeline development project.

3 Research design, data, and variables

3.1 Research design

Linking development histories of drug projects with associated IP rights allows us to identify how variation in market exclusivity periods affects companies' innovation efforts. We use a project's successful completion of different stages in the development funnel (preclinical, Phase I, II, and III trials) and the eventual marketing authorization as key indicators of innovation outcome. We exploit a natural experiment created by post-grant validity challenges: conditional on one of the patents associated with a drug candidate being opposed at the EPO, we observe development projects being at risk of patent invalidation and hence a reduction of the market exclusivity period. Patent invalidation constitutes our treatment – projects affected by the loss of patent protection and consequently a loss of exclusivity. Cases in which the opposed patents are upheld do not endure a loss of exclusivity and provide us with a control group. We focus on projects where the opposition outcome has been communicated before the termination of the development project (either abandonment by the company or approval of the drug). This makes comparison of development outcomes of projects in the treatment group with those of projects in the control group possible and identifies how variation in the duration of market exclusivity affects project outcomes.

This approach has two caveats. First, our patent invalidation might not be exogenous but determined by unobservables that affect the likelihood of being treated as well as the incentives to complete drug development. We address potential endogeneity in an instrumental variables approach, which is discussed in detail in Section 5.1. Second, focusing on opposition proceed-

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ings at the EPO implies that we observe a loss of exclusivity only for European markets, while a new drug might be marketed globally. As a consequence, our effect sizes need to be interpreted as a lower bound of the "real" effect of a reduction of the duration of market exclusivity. If the loss of exclusivity occurred in all markets uniformly, its effect would be more pronounced.

3.2 Data sources

We collect data on drug development histories at the drug-indication level and link it to the underlying IP protection. We draw on the commercial Clarivate's Cortellis database (March 2018), which provides curated information on patent-drug relationships such as associated patents' priority filings and their classification in primary and secondary patents. We augment this data with further patent indicators extracted from the EPO's PATSTAT database.

Cortellis reports for each development project whether and when a particular development stage was reached. We rely on Cortellis's information on discontinuation of drug development to distinguish truncation from actual project termination at a given development stage and exclude pending development projects. Our research design requires drug development projects to be linked to at least one opposed EP patent. Moreover, the decision on the opposition case must fall between the start of drug development (discovery) and its completion (either drug approval or abandonment). Consequently, we construct our final sample as follows: first, we identify all non-pending drug development projects at the drug-indication level in the Cortellis universe that are associated with at least one EP patent that has been challenged in opposition proceedings. In a second step, we remove drug-indication observations where the decision on opposition succeeded the end of drug development.

In total, we are able to identify 1,769 unique drugs or drug candidates for which at least one of the associated EP patents has been challenged in opposition proceedings. Cortellis contains information regarding a drug's indication(s), we are able to construct development histories at the drug-indication level. The 1,769 drug candidates for which at least one underlying patent

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has been opposed at the EPO correspond to 6,442 unique development histories at the drug-indication level. For 2,819 of these observations (935 at drug level), the opposition outcome was published while the drug development was ongoing; our analysis focuses on these cases.

3.3 Variables

Dependent variable

We observe whether a drug has passed major milestones of the drug development process at the drug-indication level. These milestones are the successful completion of preclinical trials, Phase I, II, and III clinical trials, as well as final marketing authorization. We create two indicator variables. *Approval* equals one if a drug reaches market approval in Europe, US, or Japan, and zero otherwise. *Next stage* captures whether a development project enters the next development stage after the opposition case has been decided. For instance, if an opposition case is decided while a drug candidate is in clinical trials Phase I, *next stage* is equal to one if the drug candidate enters clinical trials Phase II and zero otherwise.

Independent variables

Opposition outcome: Opposition at the EPO leads to one of three outcomes: the opposed patent is declared valid with no changes requested (*valid*), the opposed patent is upheld but its scope is narrowed (*valid in amended form*), or the opposed patent is declared invalid (*invalid*). In line with prior literature (cf. Galasso and Schankerman, 2015; Gaessler et al., 2019), we interpret *valid in amended form* as a substantial weakening of a patent's strength and therefore pool it with the outcome *invalid*. The indicator variable *invalid* is equal to one if the patent has been invalidated or amended in opposition and zero otherwise.[6]

Loss of exclusivity: We compute the loss of exclusivity (*LoE*) due to patent invalidation as

[6]The decision of the opposition division can be subject to appeal. However, the reversal rate of the boards of appeal is low and we focus on opposition outcomes exclusively.

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the difference between the remaining patent term at drug approval and the duration of data exclusivity (see Section 2, Figure 2). *LoE* therefore is a function of development time, defined as the time lapsed between the date of patent application (date_{PatApp}) and the date of market approval of the drug ($\text{date}_{Approval}$), as well as the duration of data exclusivity ($\text{dur}_{DataExcl}$). Note that SPC protection (if granted) increases *LoE* by up to five years. We calculate SPC protection for all drug-indication cases and adjust our measure of *LoE* accordingly. Note further that *LoE* is fully determined only once the date of market approval of a drug is known. For this reason, we have to predict the expected date of approval ($\widehat{\text{date}_{Approval}}$) for drugs with truncated development histories. We derive these estimates from median development times in a given indication of the Cortellis clinical trials universe of all drugs.[7] In order to maintain as much project-level variation for our observations as possible, we employ a recursive procedure. First, we compute median durations of each phase of drug development in a given indication (preclinical, Phase I, II, and III). Second, actual development times for observations in our final sample are added to the population median of the duration of subsequent stages until approval. We approximate a firm's expectation regarding the loss of exclusivity as the difference between the expected remaining patent term at drug approval and the length of the exclusivity period, that is, $LoE = \max\left[\left(20 \text{ years} - \left(\widehat{\text{date}_{Approval}} - \text{date}_{PatApp}\right) - \text{dur}_{DataExcl}\right); 0\right]$. We compute this measure for all patents in our sample irrespective of subsequent invalidation.

Drug and drug development characteristics: We distinguish between drugs on a chemical and a biological basis. We account for potential differences in drug development by introducing a *biologics* indicator variable equaling one for biologics and zero otherwise based on Cortellis' classification.

About 30% of all drugs in Cortellis list development projects for multiple therapeutic indi-

[7] Figure A-1 in the Online Appendix illustrates the distribution of clinical trials lengths. We uniformly add 4 years for the preclinical phase and another 12 months for registration after completion of Phase III clinical trials.

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cations. To account for this heterogeneity, we map Cortellis indications to their International Statistical Classification of Diseases and Related Health Problems (ICD-9) condition codes and add a set of *Disease fixed effects* based on aggregate ICD-9 levels Krieger (2017). We construct a count variable of the *number of indications* per drug and include it in our analyses, and create a variable indicating whether at the time of opposition outcome the drug has been already *approved for another therapeutic indication* than the one of the focal observation.

A drug's *development stage at opposition outcome* is captured by a set of indicator variables reflecting whether the opposition was decided during preclinical trials, Phase I, II, or III clinical trials. We further include the *duration between drug discovery and opposition outcome* in order to control for heterogeneity in the speed of trial completion.

Originator characteristics: Originators differ across various dimensions with potential implications for their drug development activities (Arora et al., 2009; Dranove et al., 2014) and their behavior in opposition proceedings (Harhoff and Reitzig, 2004; Harhoff et al., 2016). We construct a size classification based on the number of parallel development projects a company is involved in at the time of the opposition outcome. Originators are categorized as small if they are involved in fewer than the median of development projects (i.e., 8) and large if involved in more. In addition, we distinguish originators as being corporate entities or not (e.g., universities) and by their *place of incorporation* (European vs. non-European) and include dummy variables in the regressions.

Opponent characteristics: We control for whether the opponent is a corporate entity or not and its *place of incorporation* (Europe or not). Oppositions can be filed by multiple independent parties. We include a variable capturing the *number of opponents*. In case of multiple opponents, we set the respective indicator to one if at least one party is a corporate entity or European.

Patent characteristics: Drugs typically are surrounded by more than one patent and we use

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total number of patents linked to a particular drug as stated in the Cortellis.[8] We are further able to distinguish *primary patents* linked to a drug from *secondary patents*.[9]

Moreover, we seek to characterize heterogeneity regarding patent protection of drugs by using correlates to a patent's value and its characteristics. Our regressions include a dummy variable for *international patent applications (PCT)*, a count variable for DOCDB patent *family size*, and the number of *forward citations* within the first three years after filing. A discussion of these indicators can be found in Wagner and Wakeman (2016). We also include a count of *different IPC4 subclasses*, the *number of claims*, the *number of inventors*, the *number of references to patent documents* and the *number of references to non-patent literature* and account for the *time between filing and examination*, the *duration of the examination* itself, as well as the *place and the language of the examination procedure*. Finally, we add *technology field fixed effects* based on the OST/ISI concordance table (Schmoch, 2008) and fixed effects for *patent age at opposition*, the *year of patent grant* and the *year of opposition decision*.

4 Descriptive statistics

4.1 Sample composition

Drug-level statistics

Cortellis contains information on 44,764 unique drug candidates with non-truncated development information (column 1, Table 1). About one third (14,149) of these observations is linked to at least one EP patent (column 2, Table 1), including 1,769 unique drug candidates with at least one of the underlying EP patents having been challenged in opposition proceedings at the EPO (column 3, Table 1). In order to identify the effect of patent invalidation on

[8]We avoid potential endogeneity and restrict the patent count to patents that were filed before the opposition outcome was communicated.

[9]Figure A-2 in the Online Appendix shows the distribution of patent-drug relationships by opposition outcome.

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drug development, we require the decision on the opposition case to be communicated before drug approval (or project termination), which reduces our sample further to 935 unique drug candidates (column 4, Table 1).

Table 1 presents summary statistics of selected drug and patent characteristics for the different subsamples of the Cortellis data and shows that the final sample is likely skewed towards high-value drugs. The number of different patent families associated with a drug is an indicator of a drug's value as it is related to a company's costly effort to create a strong IP position surrounding a drug ("patent fence"). Drugs associated with at least one opposed patent are surrounded by an average of 17.44 different patent families, and drugs in our final sample (opposition decision prior to project termination) by 22.49 different patent families; see columns 3 and 4 of Table 1. Compared to an average of only 4.10 patent families for all projects with known patent links, these numbers are significantly higher and indicate that opposition is associated with higher value drugs. Similarly, the share of drugs with approval for at least one indication is about 56% in the final sample but only 17% for all drugs with a patent link. Finally, drugs with opposed patents have been tested against 3.57 different indications on average compared to 2.04 indications for drugs with known patent links.[10] These differences are partly driven by cohort effects, as drugs associated with opposed patents are on average older in terms of discovery year. However, value may also constitute an important additional determinant of differences in observed patent characteristics and selection into opposition. The selection towards more valuable projects renders our results conservative.

[10]Drugs in our final sample have been tested against 4.6 different indications. We exclude development histories with opposition outcomes before project start or after its termination. The final sample therefore contains only about 3.01 indications per drug.

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Drug-indication level statistics

A given drug's efficacy is typically tested against multiple indications independently. In total, Cortellis contains 75,396 different non-pending drug-indication level projects (each of the different 44,764 drug candidates is associated with an average of 1.54 different indications) out of which about 8% are approved. Attrition patterns differ by sample definition (see Figure A-3 in the Online Appendix). The majority of cases (62%) of all drug-indication level projects are terminated after the preclinical phase before major investments in clinical trials are due. Development projects with patent links are characterized by higher approval rates (17%) and terminated at later stages compared to the population of non-pending projects. The 2,819 different drug-indication projects in our final sample follow a similar pattern of comparably late termination and average approval rates of 31%.

4.2 Patent invalidation and development outcomes

We present descriptive evidence on how patent invalidation in opposition proceedings affects the expected duration of exclusivity and ultimately the development outcomes at the drug-indication level. First, Figure 3 shows the distribution of (potential) loss of exclusivity. Each stacked bar represents the fraction of observations that are subject to a given loss of exclusivity. Each bar is split into observations associated to drugs in the treatment group (invalidated in opposition, dark bar) or the control group (upheld in opposition, light bar). In about 62% of all cases, patent invalidation is not related to a loss in the duration of expected market exclusivity for the focal drug project; in these cases, the remaining patent term at expected market approval is less than or equal to the duration of data exclusivity. The ratio of potential loss of exclusivity to realized loss of exclusivity is fairly stable across the distribution, allowing us to use the loss of exclusivity as a linear treatment variable in our regressions.

To explore how the timing of the opposition outcome affects project success, we report the advancement through the development funnel for all projects in our final sample by a drug's

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development stage at time of opposition outcome in Figure 4a. Patent invalidation does not only lower the likelihood drug approval but also the likelihood of initiating the next stage of the development process. As expected, early patent invalidation has a stronger negative effect on a drug project's progress. Figure 4b breaks down approval and continuation by firm size (small vs. large originators). Drug invalidation lowers the likelihood of approval and continuation for small and large originators. We report aggregate outcomes in Figure A-4 in the Online Appendix.

5 Multivariate analysis

5.1 Identification

Estimation approach

In our multivariate analyses we relate measures of IP protection, most importantly the loss of exclusivity after patent invalidation, to measures of drug development success; *approval* indicates whether the drug candidate reached marketing authorization; *next stage* indicates whether a drug candidate entered the next development stage after the opposition case was decided. We estimate linear probability models at the drug-indication level to identify the effect of a loss of exclusivity due to patent invalidation on development success. Our main empirical specification is:

$$Approval \;=\; \gamma\,(Invalidation \times LoE) \;+\; \beta_0 \;+\; \beta_1\, Invalidation \;+\; \beta_2\, LoE + \beta_3\, X + \epsilon.$$

The interaction between *Invalidation* and *LoE* identifies cases in which a patent invalidation (*Invalidation* $= 1$) leads to an actual loss of exclusivity. The coefficient γ captures the effect of a realized loss of exclusivity *LoE* (treatment effect) on the likelihood that a drug candidate will be approved for marketing or advances to the next stage of clinical trials after the opposition case has been resolved. If $\gamma < 0$, a reduction of the period of market exclusivity lowers the chances of drug approval. To control for heterogeneity in the underlying drug development projects, originators, and patents, we include a set of additional independent variables X in

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our regressions.[11]

We include development projects multiple times in the estimations to account for cases with more than one opposed patent per drug-indication development project. Each observation per drug-indication project is weighted by the inverse of the number of associated patents. Since drug candidates can be involved in separate development histories for different indications, we report two-way clustered standard errors at the drug as well as at the indication level.

Instrumenting patent invalidation

The major empirical challenge is that patent invalidation is likely to be endogenous as the opposition outcome might be determined by unobservable characteristics (such as early signs of a drug's efficacy or potential market size) that affect (i) the effort put into defending the patent, as well as (ii) the incentives to commercialize a drug. This would generate a positive correlation between ϵ and *Invalidation* in our regression and therefore bias the ordinary least squares (OLS) estimate of γ. To address potential endogeneity of the opposition outcome, we employ an instrumental variable that affects the likelihood of patent invalidation but does not belong in the drug approval equation.

Following Gaessler et al. (2019), we use the granting patent examiner's participation in the opposition proceeding to construct an instrument by exploiting variation in the participation of the patent examiner who initially granted the patent in the opposition division. Gaessler et al. (2019) demonstrate that examiner participation in opposition proceedings lowers the likelihood of patent invalidation. This negative correlation allows us to rely on examiner participation as instrument for our treatment variable (*Invalidation*). Although the rules and regulations of the EPO allow personnel overlap in the examination and opposition procedure, they do not require the involvement of the initial patent examiner in the opposition division. In

[11] A comprehensive list of the control variables can be found in Table B-1 in the Online Appendix. Summary statistics can be found in Table B-2 in the Online Appendix.

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fact, the average examiner participation rate is about 68% across all opposition proceedings at the EPO and varies over time and technology fields. The variation in examiner participation is a result of the temporary non-availability of other examiners and can be considered random to the focal patent (Gaessler et al., 2019). Figure A-5 in the Online Appendix presents the annual number of opposition proceedings and the annual rate of examiner participation.

We instrument the opposition outcome (*Invalidation*), as well as its interaction with *LoE*, with the predicted probability of invalidation obtained from a probit model $\widehat{\text{Prob}(\textit{Invalidated})} = \Phi(\gamma_1 \textit{Examiner participation} + \gamma X)$. Furthermore, if $\widehat{\text{Prob}(\textit{Invalidated})}$ is a valid instrument for *Invalidation*, then $\widehat{\text{Prob}(\textit{Invalidated})} \times \textit{LoE}$ is a valid instrument for *Invalidation* × *LoE*. Based on this reasoning we estimate the two-stage model:

$$\textit{Invalidation} = \alpha\, \widehat{\text{Prob}(\textit{Invalidated})} + \theta\, X + u$$

$$\textit{Approval} = \gamma\, \widehat{(\textit{Invalidation} \times \textit{LoE})} + \beta_0 + \beta_1\, \widehat{\textit{Invalidation}} + \beta_2\, \textit{LoE} + \beta_3\, X + \epsilon.$$

Gaessler et al. (2019) discuss the instrument's randomness and relevant exclusion restrictions in detail. Most importantly, indicators of patent value, the length of the initial examination of the patent applications, and characteristics of the patent holder as well as the opponent do not significantly affect the likelihood of the initial examiner's participation in the opposition proceeding. The exclusion restriction of the instrument prevails given that the patent holder is unlikely to foresee the examiner's participation for two reasons. First, participation rates calculated at examiner level show little concentration at zero and one, but rather follow a normal distribution around the overall participation rate (Gaessler et al., 2019). Second, the opposition division members are disclosed only during the oral proceeding, which typically results in a final decision on the opposition case.

Table 2 presents patent-level results from probit regressions relating examiner participation to opposition outcomes controlling for other sources of heterogeneity. A patent might be associated with more than one development project if the associated drug is tested against multiple indications. For this reason, we include all patent-indication observations in the regressions

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and employ weighted estimators in which we use the inverse of the number of drug indications per patent as weights, and report standard errors clustered at the level of individual patents. In total, these regressions are based on 1,129 unique patents that are associated with 2,741 observations at drug-indication level, amounting to 5,974 observations at unweighted drug-indication-patent level.[12] Examiner participation is negatively and highly significantly related to patent invalidation in opposition proceedings even after controlling for a comprehensive set of other factors (see Table 2, column 2). Opposition divisions are less likely to invalidate a patent if the initial examiner participates.

Assumptions for identification

A key assumption of our identification strategy is that patent validity is independent of a drug project's probability of success. There are two potential concerns arguing against this assumption. First, patent validity may be directly affected by the virtue of a drug. However, patentability is hardly related to a drug's (social) value and its chance of market approval (Roin, 2008). Irrespective of this, our instrumental variable estimations would assure identification even if (unobservable) patent characteristics correlated with the drug's likelihood of market approval. Second, patent validity (or the existence of patent protection in general) might be taken into account by authorities that decide on a drug's market approval. However, legal regulations prevent any form of "patent linkage" of drug approval. In Europe, the marketing authorization decision needs to be exclusively based on scientific criteria related to public health considerations – most importantly toxicology and efficacy – while other criteria such as patent protection are not considered (European Commission, 2009). Patent validity hence can be seen as independent of a drug candidate's likelihood of success in terms of market approval.

[12]The difference to the overall sample (2,819) is due to perfect prediction when estimating the first stage with the full set of control variables.

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5.2 Results

Main specification

In Table 3, we report results from regressions relating loss of exclusivity to market approval and project continuation using linear probability and IV models, in which we instrument patent invalidation and its interaction term. In columns 1 and 2 (*approval*), as well as in columns 5 and 6 (*next stage*) of Table 3, we do not account for the loss of exclusivity but focus merely on the effect of patent invalidation. The estimates of the effect of patent invalidation on drug approval is statistically indistinguishable from zero for approval as well as next stage. The coefficients of invalidation, however, do not reflect the resulting loss of exclusivity and that – in case of patent invalidation – the realized loss of exclusivity varies considerably across projects, which likely explains the high standard errors of the coefficient estimates. This finding is a first indication that patent invalidation does not affect innovative activity *per se*.

To quantify how a loss of exclusivity affects drug commercialization, we include the potential loss of exclusivity measured in years (*LoE*) and its interaction with patent invalidation in the regressions (Table 3; columns 3 and 4, as well as columns 7 and 8). Across all specifications, the IV estimates point to a stronger and more precisely estimated effect negative effect of the interaction term. This difference is likely driven by unobserved variables (such as early signs of efficacy or commercial attractiveness of an indication) that affect patent invalidation (as a function of opponent effort) and drug approval, resulting in an upward biased OLS estimate. The results from the IV regression suggest that a one-year reduction of expected market exclusivity reduces the likelihood of drug approval by 4.9 percentage points (Table 4, column 4). This a meaningful effect given that the average likelihood of drug commercialization in our sample is 30.8% and the average market exclusivity length is about 10 years. The main effect of patent invalidation is again insignificant in these specifications. In line with theoretical models, innovative activity is affected by reduction of market exclusivity but not by patent

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invalidation *per se*. At the mean, a one-year reduction of expected market exclusivity thus reduces the likelihood of drug approval by 15.9% ($0.049/0.308 = 0.159$) in relative terms. This point estimate is within the range of the semi-elasticities of R&D investment with respect to a one-year change in commercialization lags (which determine market exclusivity periods) of 7% to 23% reported by Budish et al. (2015, p. 2074).

The results regarding the likelihood of project continuation are comparable. Loss of exclusivity induced by patent invalidation significantly lowers the likelihood of project continuation with more pronounced and more precisely estimated effects in the IV specifications. The results in column 8 of Table 3 imply that a one-year reduction in the expected market exclusivity leads to an average decrease in the likelihood of project continuation of 4.6 percentage points. Compared to an average continuation rate of 50.8% across all development stages, this again is a meaningful effect and suggests that firms immediately respond to a change in market exclusivity. Taken together, we consider this strong evidence for the originator's reduction of commercialization efforts in response to *ceteris paribus* lower expected profits due to a shorter duration of the market exclusivity period.[13]

All regression specifications include a comprehensive set of control variables capturing characteristics of the drug, the development project, the originator, the opponent, and the underlying patent, as well as time and disease fixed effects. We do not report coefficients for these variables but briefly comment on the most important findings here. While drug characteristics are jointly significant in our regressions, individual variables have little explanatory power. In particular, our findings suggest that biologics are not characterized by different approval rates. Regarding patent indicators, we find that development projects associated with patents

[13]Figure A-6 in the Online Appendix shows binned scatter plots of the residuals for two of our regressions (column 4 and column 8 in Table 3, respectively). These figures do not only underline the linearity of the effect of the realized market exclusivity loss on drug development outcomes but also highlight once again that patent invalidation *per se* has little effect.

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of higher value (as indicated by patent family size) have a higher likelihood of approval. This finding is in line with Wagner and Wakeman (2016), who attribute these differences to applicants creating stronger protection around more promising drugs. With respect to originator characteristics, we find development projects of small originators associated with lower approval rates compared to medium and large originators.

Timing of invalidation

We have argued above that early losses of exclusivity should have a more pronounced effect on firm decision making (Dixit and Pindyck, 1994; Pindyck, 1991). In order to test this prediction, we split the sample in development projects with opposition decisions at an early stage (preclinical/Phase I trials) and at a late stage (Phase II/Phase III trials). About 65% of the projects in our final sample had the opposition outcome of the underlying patent(s) during preclinical/Phase I trials and 35% at later stages. In columns 1 to 4 in Table 4, we report the effect of a loss of exclusivity due to invalidation on drug approval and next stage based on this sample split. While the coefficient on the interaction carries a negative sign across all specifications, only the effect of early invalidation is significantly different from zero. A one-year loss of exclusivity due to patent invalidation at an early stage of development reduces the likelihood of drug approval by 6.3 percentage points (DV mean: 31.5%) and the likelihood of starting the next stage of clinical trials by about 6.3 percentage points (DV mean: 60.3%), where the former is a considerably greater effect compared to our baseline effect reported in Table 3. A reduction in the exclusivity period affects firm behavior more significantly when received early, that is, at a stage of the development funnel where the majority of investments still have to be committed. The fairly large standard errors for the estimates in the late stage subsample hint at considerable heterogeneity in firm responses. This is probably due to the fact that some drug projects in this subsample require little to no further investments to reach approval.

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Originator size

Finally, we split our sample into small and large originators depending on the number of pending development projects at the time of opposition outcome. About 40% of the projects are associated with small orginators and 60% with large originators. In columns 5 to 8 of Table 4, we report the effect of a loss of exclusivity due to invalidation on drug approval and next stage based on this sample split. While overall the direction of the effect of the loss of exclusivity due to invalidation is comparable to the baseline results in Table 3, we do find some differences in significance by originator size. A realized loss of exclusivity has no significant effect on approval or continuation for small originators (see columns 5 and 7 of Table 4), while projects of large originators are significantly affected. A one-year reduction in exclusivity lowers the likelihood of drug approval by 4.6 percentage points and the likelihood of starting the next stage by 5.7 percentage points (see columns 6 and 8 of Table 4). Portfolio considerations are a likely explanation of the observed size differences.[14] Large companies are more likely to drop a project as they can reallocate their resources to alternative drug projects. In contrast, the marginal value for a given project is higher for firms with smaller portfolios (and hence with fewer outside options) (Girotra et al., 2007).

5.3 Robustness tests and extensions

In order to assess the robustness of our findings, we estimate a number of alternative regression specifications. To start, our results are not sensitive towards the choice of the regression model applied. Employing biprobit models in order to account for the binary nature of the outcome variable does not change our findings; in fact, the coefficients are estimated with higher precision. Moreover, we find highly consistent results when replacing the variable *Potential LoE (in yrs)* with the dummy *Potential LoE* > 0 (Table B-4 in the Online Appendix), or when con-

[14] In Table B-3 in the Online Appendix, we split up our sample by timing *as well as* the originator's portfolio size.

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sidering amended patents as *Invalidated* only if they lost an above average number of claims (Table B-5 in the Online Appendix). In the following, we investigate to what extent aspects of the drug development process and the institutional setting affect our results.

First, we restrict our analysis to the first indication a drug candidate is tested against and define the sample accordingly. In these specifications, we rule out the possibility that our findings are driven by originators' decisions whether to reposition a drug in additional indications depending on patent invalidation. Furthermore, the determination of expected market exclusivity is less ambiguous for first indication drug projects compared to subsequent indications (see Section 2). Focusing on first indications exclusively, we observe highly similar estimates relative to the sample's higher average approval rate (see Table B-6 in the Online Appendix). Restricting the analyses to the primary patent underlying each drug project leads to results that also compare well to the main findings reported above (see Table B-7 in the Online Appendix).

Our main findings have been obtained by relating drug approval in Europe, US, or Japan to the loss of exclusivity incurred in Europe. Table B-8 in the Online Appendix reports the results where we focus exclusively on drug approvals in Europe. Again, the results are quite similar, but less precisely estimated. Furthermore, some jurisdictions have different regulations for biological drugs when compared to traditional pharmaceuticals. For instance, in the US, biologics are subject to longer data exclusivity periods (12 years) than small molecule drugs (five years). As a result, market exclusivity lengths in Europe and the US are more comparable for biologics. We exploit this fact to address concerns that our effect sizes are potentially downward biased as we calculate European market exclusivity periods. Table B-9 in the Online Appendix reports the findings for biological drugs exclusively, which indeed indicates somewhat stronger effects. It is important to note, that abridged applications for marketing generic biological drugs (biosimilars) only became possible with legislation passed in 2004 in the EU and even later in the US (Morton et al., 2018). For this reason, we focus on post-2003 invalidations in Online Appendix Table B-10 and observe a considerably stronger effect of loss of exclusivity

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on continuations for biologic drug candidates, albeit a weaker and insignificant effect on drug approval.

Finally, our key explanatory variable measures the reduction of the period of market exclusivity in absolute terms (years). We replicate the main regressions in Table B-11 in the Online Appendix, but measure the loss of exclusivity this time in relative terms, that is, as one minus the fraction of the reduced duration of market exclusivity after patent invalidation relative to the full duration. The estimates correspond to our baseline findings and further gain in statistical significance.

6 Concluding remarks

This paper investigates the causal effect of the duration of market exclusivity on the likelihood of successful product commercialization in the pharmaceutical industry. Patent invalidation due to post-grant opposition at the EPO provides a natural experiment in which some drug development projects are exposed to a shift in the expected duration of market exclusivity while others are not. Instrumenting potentially endogenous opposition outcomes allows for causal identification. Our regression results highlight that a reduction in the expected duration of market exclusivity upon drug approval by one year reduces the likelihood of drug approval in our sample by 4.9 percentage points relative to a mean approval rate of 30.8%. Early exclusivity loss has a more significant impact than an exclusivity loss at later stages. Moreover, the negative effect of a loss of exclusivity on the likelihood of successful drug commercialization is driven by large originators whereas small originators seem less responsive.

While the natural experiment underlying the analysis allows for the clean identification of causal effects, our study is subject to some limitations. First, we observe outcomes for projects that have already been initiated at the time when the duration of market exclusivity is unexpectedly reduced. We therefore study firm responses at the *intensive margin*. Policy makers, in particular, might be interested in understanding firm responses to market-wide regulatory

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changes at the *extensive margin*. This needs to be considered in the interpretation of our results. On the one hand, firms might respond more strongly at the extensive margin as both uncertainty as well as the necessary investments for successful commercialization are higher. In this case, our baseline effect is a lower bound for the effect of a market-wide shock to the incentives for drug development. Moreover, our estimates for the responses of large firms with exclusivity loss in early stages of drug development provide a closer approximation of the effect at the extensive margin. Large companies have broad pipelines of alternative drug candidates, reducing the marginal value of any given project, in particular those in early stages. On the other hand, market-wide reductions of exclusivity periods might render alternative projects equally less profitable. In this case, firms would be less responsive at the extensive margin and our baseline effect no longer a lower bound. In fact, small firms with fewer alternative projects to switch to are less responsive to reduction of exclusivity durations in our sample. Overall, the magnitude of the baseline effect in our estimations is comparable to the elasticities to a market-wide change in the duration of data exclusivity reported in Budish et al. (2015). Second, our evidence from the pharmaceutical industry may not be generalizable to industries that are less reliant on patents. Nonetheless, our study stands out from other studies on the pharmaceutical industry, as our estimates have been derived across a wide range of therapeutic areas. Finally, we leave aside questions pertaining to strategic interactions between originators and do not examine the incentives to challenge a granted patent. Future research may complement our results by explicitly modeling competition.

The effect of the duration of market exclusivity periods on the likelihood of drug approval has implications for scholars as well as policy makers concerned with the pharmaceutical industry. It provides evidence that, as posited by the theoretical literature on the incentives for innovation, R&D efforts of firms are muted in case of reduced periods of market exclusivity. Recent research provides evidence that pharmaceutical companies target their R&D efforts to drugs with shorter development times to enjoy longer periods of market exclusivity derived

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from longer effective patent terms. This effect might induce socially inefficient allocation of private R&D expenditures. Our findings suggest that data exclusivity can indeed be an effective policy lever to restore incentives in case of long drug development periods, as it determines the duration of market exclusivity periods in these cases. They also suggest that granting priority in drug approval processes is an effective means to generate targeted incentives for drug development as they can also extend market exclusivity periods. Introducing expedited paths to drug approval including voucher programs such as the priority voucher might be a cost effective way to provide targeted incentives in jurisdictions beyond the US. Extending data exclusivity periods as a policy instrument, however, is not uncontested. It restricts access to drugs as companies enjoy longer periods in which they can charge high prices. Additionally, extending data exclusivity periods might cause redundant clinical trials that are inevitably linked to ethical questions. These aspects deserve further consideration in future work on the interplay of distinct intellectual property rights and the private, as well as the social costs of developing new drugs.

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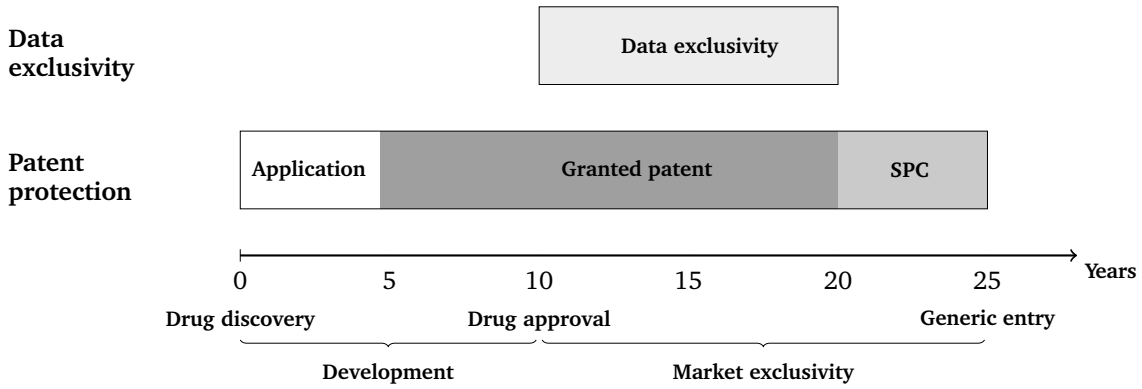
Figure 1: Life cycle of pharmaceutical products



Notes: This figure is a schematic presentation of the typical drug life cycle. SPC protection is optional and generic entry may occur earlier due to authorized entry. Data exclusivity corresponds to the EU regulations of 2005 onward.

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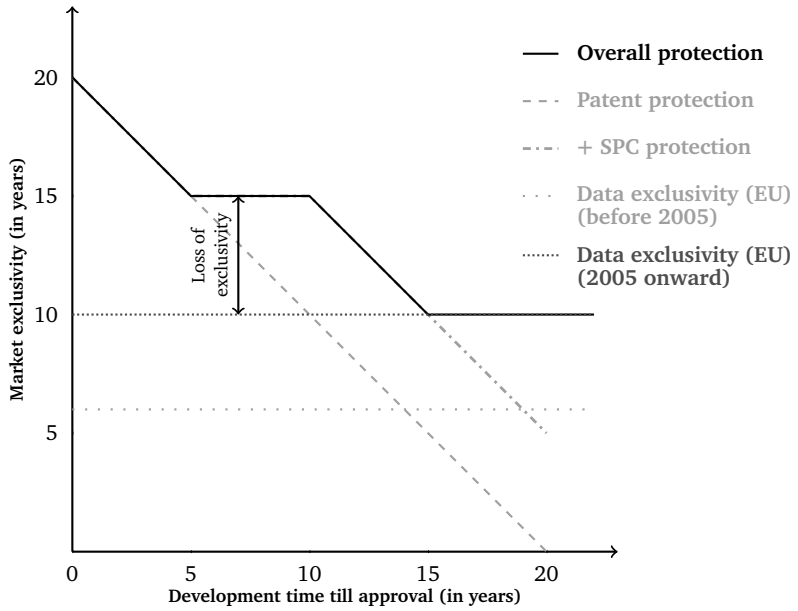
Figure 2: Market exclusivity as a function of drug development time (EU regime)



Notes: This figure illustrates the relationship between development time and market exclusivity in Europe. SPC protection is optional. "Loss of exclusivity" refers to the loss of market exclusivity due to patent invalidation.

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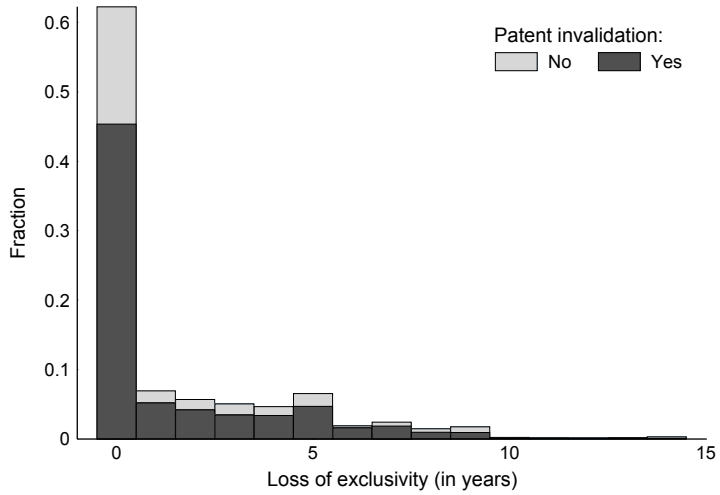
Figure 3: Distribution of loss of exclusivity (drug-indication level)



Notes: This figure shows the distribution of the (potential) loss of exclusivity in our final sample of analysis. The bars are stacked and their total height represents their fraction in the sample. The figure is based on the final regression sample ($N = 2,819$).

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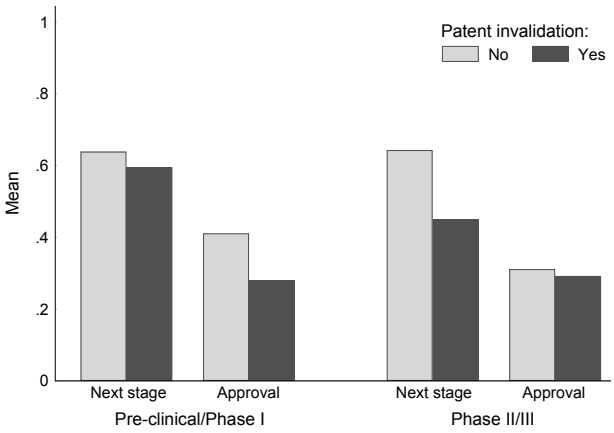
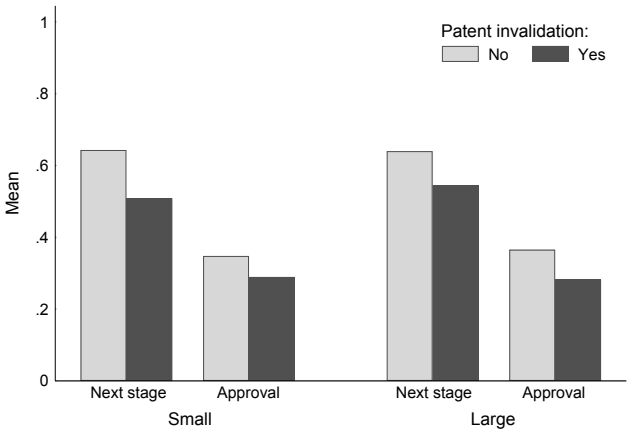
Figure 4: Project advancement at the drug-indication level

(a) By development stage



(b) By size of orginator



Notes: This figure presents progression of drug projects (drug-indication level) conditional on their development stage at time of opposition outcome for the regression sample.

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Table 1: Drug characteristics

	(1) All drugs	(2) All drugs w/ patent link	(3) All drugs w/ opposition	(4) All drugs in in final sample
Drug level	N= 44,764	N= 14,149	N= 1,769	N= 935
	Mean	Mean	Mean	Mean
Drug characteristics				
Biologic (d)	0.31	0.33	0.40	0.44
Drug discovery (yr)	2002.73	1999.53	1993.68	1994.89
Latest development (yr)	2008.43	2009.33	2008.37	2011.20
Approval one or more indications (d)	0.06	0.17	0.56	0.56
# Indications	1.54	2.04	3.57	4.60
# Indications (in opposition sample)				3.01
Patent protection				
# Patent families		4.10	17.44	22.49
# Opposed patents			2.51	3.06
# Invalidated patents			1.85	2.31

Notes: Observations are at the drug level. "All drugs" refers to all non-pending drug projects with development information in Cortellis. "All drugs with patent link" refers to the subset of drug projects with a link to a patent family containing at least one EP patent. "All drugs with at least one opposition" refers to the subset of drug projects with at least one EP patent challenged in opposition proceedings. "All drugs in opposition sample" refers to all drug projects that are part of our final sample of analysis. Patent families follow the INPADOC patent family definition.

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Table 2: 1st-stage regression: examiner participation and opposition outcome

	(1)	(2)	(3)
Estimation method	Probit	Probit	Probit
Dep var	Invalidated	Invalidated	Examin. partic.
Exam. participation (d)	−0.056***	−0.059***	
	(0.021)	(0.018)	
Potential LoE (in yrs)			−0.002
			(0.005)
Set of control variables included (see Section 3.3)	No	Yes	Yes
Model degrees of freedom	1	110	109
χ^2-statistic	6.9	936.8	329.5
Pseudo-R^2	0.005	0.190	0.129
Observations	5,974	5,974	5,968
Observations (weighted)	1,129	1,129	1,129

Notes: The probit regressions in columns (1) and (2) highlight the relevance of the *Examiner participation* dummy for the outcome of the opposition proceeding. The invalidation predictions of the probit regression in column (2) are used as instrument in the 2SLS instrumental variables regressions throughout the remainder of the paper. Column (3) shows the probit regressions of the *Examiner participation* dummy on our main independent variables of interest while controlling for other variables. A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the Online Appendix. 23 observations dropped due to perfect prediction in column (3). Marginal effects are reported in all columns. Standard errors are clustered by patent. Observations are weighted by the inverse of the number of different drug projects per patent. Significance levels: * p<0.1, ** p<0.05, *** p<0.01.

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https://doi.org/10.1162/rest_a_00987

Table 3: Impact of patent invalidation on drug development (baseline)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Estimation method	OLS	IV	OLS	IV	OLS	IV	OLS	IV
Dep var	Approval				Next Stage			
Dep var mean	0.308	0.308	0.308	0.308	0.508	0.508	0.508	0.508
Invalidated	−0.029	−0.133	0.008	−0.024	0.008	−0.142	0.035	−0.020
	(0.030)	(0.121)	(0.030)	(0.123)	(0.031)	(0.116)	(0.033)	(0.127)
Invalidated × Potential LoE (in yrs)			−0.020**	−0.049***			−0.016*	−0.054***
			(0.009)	(0.019)			(0.008)	(0.016)
Potential LoE (in yrs)			0.034***	0.055***			0.003	0.030**
			(0.008)	(0.015)			(0.007)	(0.013)
Set of controls variables included (see Section 3.3)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Underidentification test		36.5		33.9		36.5		33.9
Weak identification test		53.2		24.2		53.2		24.2
Observations	5,974	5,974	5,974	5,974	5,974	5,974	5,974	5,974
Observations (weighted)	2,741	2,741	2,741	2,741	2,741	2,741	2,741	2,741

Notes: Columns (1) and (2) as well as (5) and (6) provide a comparison between the OLS and the 2SLS regressions for the impact of invalidation on drug development (approval or continuation to next stage) when accounting for the actual loss of exclusivity. Columns (3) and (4) as well (7) and (8) include an interaction term capturing the loss of exclusivity in linear form. In each 2SLS regression the *Invalidated* dummy is instrumented with the corresponding probability predicted by a probit regression on the *Examiner participation* dummy and all other exogenous variables. The underidentification and weak identification tests are the heteroskedasticity-robust Kleibergen and Paap (2006) rk LM and Wald F statistics, respectively. A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the Online Appendix. Standard errors are two-way clustered by drug and indication. Observations are weighted by the inverse frequency at drug-indication-patent level. Significance levels: * p<0.1, ** p<0.05, *** p<0.01.

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Table 4: Impact of patent invalidation on drug development by timing and portfolio size

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Dep var	Approval		Next Stage		Approval		Next Stage	
Sample	Pre-clinic & Phase I	Phase II & Phase III	Pre-clinic & Phase I	Phase II & Phase III	Small	Large	Small	Large
Dep var mean	0.315	0.295	0.603	0.332	0.303	0.313	0.506	0.510
Invalidated	−0.049	0.018	−0.048	0.042	−0.248	0.065	−0.202	0.154
	(0.148)	(0.176)	(0.150)	(0.196)	(0.180)	(0.180)	(0.186)	(0.179)
Invalidated × Potential LoE (in yrs)	−0.063***	−0.039	−0.063***	−0.040	−0.041	−0.046**	−0.057	−0.057***
	(0.021)	(0.031)	(0.018)	(0.031)	(0.028)	(0.023)	(0.036)	(0.019)
Potential LoE (in yrs)	0.082***	0.017	0.039***	0.006	0.043**	0.053***	0.032	0.031**
	(0.017)	(0.025)	(0.014)	(0.025)	(0.022)	(0.019)	(0.030)	(0.015)
Set of controls variables included (see Section 3.3)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Underidentification test	30.1	20.8	30.1	20.8	20.7	18.5	20.7	18.7
Weak identification test	21.0	13.5	21.0	13.5	18.1	12.6	18.1	12.8
Observations	4,334	1,640	4,334	1,640	2,464	3,510	2,464	3,510
Observations (weighted)	1,786	955	1,786	955	1,157	1,584	1,157	1,584

Notes: Columns (1) to (4) show 2SLS regressions for the impact of invalidation on drug development on subsamples defined by the development stage of the drug project at the time of opposition outcome. The samples used in columns (1) and (3) include drug projects only if the patent opposition outcome occurred during the preclinical phase or in Phase I clinical trials. Likewise, the samples used in columns (2) and (4) include drug projects only if the patent opposition outcome occurred during Phase II or III clinical trials. Columns (5) to (8) show 2SLS regressions for the impact of invalidation on drug development on subsamples defined by the size of the drug originator. The samples used in columns (5) and (6) include drug projects only if the drug originates from small entities.

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Notes (continued from Table 4): Likewise, the samples used in columns (7) and (8) include drug projects only if the drug originates from large entities. In each 2SLS regression the *Invalidated* dummy is instrumented with the corresponding probability predicted by a probit regression on the *Examiner participation* dummy and all other exogenous variables. The underidentification and weak identification tests are the heteroskedasticity-robust Kleibergen and Paap (2006) rk LM and Wald F statistics, respectively. A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the Online Appendix. Standard errors are two-way clustered by drug and indication. Observations are weighted by the inverse frequency at drug-indication-patent level. Significance levels: * $p<0.1$, ** $p<0.05$, *** $p<0.01$.