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PATENTS, DATA EXCLUSIVITY, AND THE DEVELOPMENT OF NEW DRUGS

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ABSTRACT

Pharmaceutical firms typically enjoy market exclusivity for new drugs from concurrent protection of the underlying invention (through patents) and the clinical trials data submitted for market approval (through data exclusivity). Patent invalidation during drug development renders data exclusivity the sole source of protection and shifts the period of market exclusivity at the project level. 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 first 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

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1 Introduction

The negotiations of the Trans-Pacific Partnership (TPP) – a trade agreement among initially twelve Pacific Rim states accounting for about 40% of the global economy – took more than five years and were closely followed by the public. TPP put the discussion on the design of intellectual property rights that protect new drugs against imitation and generic competition back on center stage (Luo and Kesselheim, 2015). In particular, the period of data exclusivity for novel pharmaceutical products and biological medicines 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. In a broader context, 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. On the one hand, strengthening the legal protection of novel drugs might increase the incentives to invest in risky R&D projects and yield more desirable new drugs. On the other hand, extending exclusivity rights might lead to welfare losses created by higher prices due to limited competition by generics. In fact, countries with either no or short data exclusivity periods[1] opposed demands for a uniform extension of data exclusivity to up to twelve years, referring to the risk of rising health care costs and restricted access to pharmaceuticals. The United States of America, in contrast, emphasized the role of longer data exclusivity periods in the provision of incentives to invest in the development of new drugs.[2]

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 intellectual property rights and the balance between dynamic social gains by greater innovation efforts and static losses due to granting monopoly power to innovators (see Scotchmer (2004) for a comprehensive discussion). The more recent empirical literature increasingly focuses on the causal relationship between intellectual property 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 (see Williams (2017) for an overview). Most of the existing theoretical and empirical work on innovation in the pharmaceutical industry, however, focuses on incentives provided by the patent system without taking into account its complex interplay with data exclusivity.[3] In this paper, we contribute to this literature by relating the overall duration of market exclusivity resulting from both patent protection *and* data exclusivity

[1] There exists no data exclusivity in Brunei. Australia, Chile, Malaysia, Mexico, New Zealand, Peru, Singapore, and Vietnam all provide relatively short periods of data exclusivity to originators.

[2] The talks on the Trans-Pacific Partnership were successfully concluded on October 4, 2015, and officials from the twelve participating countries signed the agreement on February 4, 2016. Whereas the United States of America's withdrew from the trade agreement in January 2017, the remaining eleven countries signed the deal on March 8, 2018 – with all provisions related to data exclusivity suspended.

[3] Budish et al. (2015) is a notable exception as they discuss the effect of data exclusivity in the theoretical section of their paper.

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 (in our context: molecules) 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 and mark the beginning of a lengthy development project in which pre-clincal and clinical tests have to be conducted. 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 at market approval is shorter than the period of data exclusivity, the latter provides additional protection. During the TPP negotiations it was argued that, in the light of 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.

Despite the intense policy debate surrounding the optimal design of intellectual property 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 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. In particular, 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 drug approval exceeds the period of data exclusivity, patent 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 in opposition (and market exclusivity remains unaffected). Linking the project-specific exogenous variation in the duration of market exclusivity to drug 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 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 of patent invalidation in our empirical analysis, we employ a novel instrument first proposed by Gaessler et al. (2017). 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 patent invalidation but uncorrelated with other factors that might determine originators' commercialization efforts. Instrumenting patent invalida-

tion hence creates exogenous variation that allows us to causally identify how innovation outcomes depend on the duration of protection against generic competition.

For our study, we construct a novel data set that links the development histories of pharmaceutical compounds from pre-clinical trials up to market approval (or the highest development stage reached) with information on the underlying patents. 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 920 unique drug candidates and their respective development histories with patents subject to invalidation proceedings. Drug candidates are often tested against more than one specific indication, so that one drug may be linked to multiple development projects. Ultimately, we identify 2,788 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. This sample includes drug candidates from the full spectrum of therapeutic areas, yet still differs from the overall population of (observable) drug projects. We focus on drug candidates that have entered at least pre-clinical trials and where the validity of at least one underlying patent has been challenged. As a consequence of this, these drug candidates are more valuable and promising compared to the overall population. This renders our estimates conservative as firm decisions should be less responsive to changes in the duration of market exclusivity for drug candidates with a high expected value.

We present estimates from linear probability models in which we relate commercialization outcomes to the overall duration of market exclusivity for development projects with and without patent invalidation. Our IV regression results indicate that a reduction in the overall duration of market exclusivity significantly affects project outcomes. In fact, we find that the loss of one year of market exclusivity lowers the likelihood of drug approval by about 3.5% relative to an unconditional approval rate of 30.5%. This response to a loss in expected 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 to reductions of market exclusivity periods 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 several 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, we find results that are comparable to our main findings. Second, drug candidates are often tested against multiple indications and results from pre-clinical 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 (US, Europe, 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 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 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 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

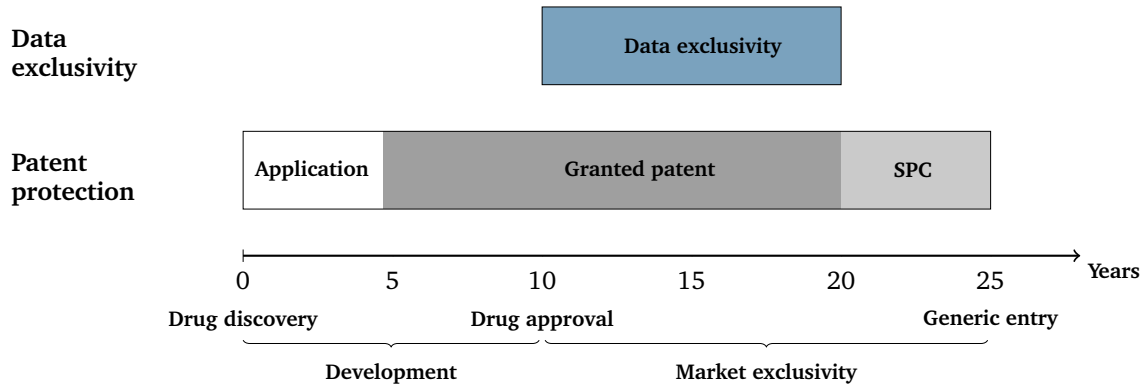
2.1 Institutional background

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 company markets the drug under exclusivity as imitation is prevented by patents and/or data exclusivity; and (iii) the post-exclusivity period, in which competition by generic products copying the initial drug is possible. The development period is highly regulated and typically consists of the discovery stage, pre-clinical 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 respective national regulatory authorities and request marketing authorization for specific markets.[4] Developing new drugs is a costly endeavor 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

[4]While generally following the system of stage I, II and III trials, national regulatory bodies migh have different requirements regarding the exact specification of clinical tests required for approval. In consequence, clinical trials are sometimes conducted in different jurisdictions. Since 1990, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), consisting of regulatory bodies from the US, Europe and Japan and other countries, has provided a forum to increase international harmonization of test requirements.

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.

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, tests, and market approval.

Pharmaceutical companies' decisions to make risky high upfront investments in developing new drugs largely depend on their expected pay-offs during the subsequent period of market exclusivity. Only if companies can expect to recoup R&D investments during the exclusivity period through high mark-ups on prices before generic entry takes place, will initial investments in development be made. 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 intellectual property rights in a schematic way. 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[5] and the period of data exclusivity. Longer periods of market exclusivity are related to higher pay-offs 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.

Pharmaceutical companies often seek to increase their R&D productivity either by broadening the market for a molecule through additional medical 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). Repositioning is characterized by a lower risk profile as these drugs have already been tested in previous clinical trials for at least one alternative indication and therefore have known toxicological and efficacy profiles. Additionally, existing clinical data often allows pharmaceutical companies to bypass early steps in the development

[5]Several jurisdictions grant patent term extensions for pharmaceutical inventions. In Europe, patent protection may be extended by filing a Supplementary Protection Certificate (SPCs); see below for details.

funnel such as pre-clinical trials (Ashburn and Thor, 2004). The investments to reposition an existing drug are therefore significantly lower than those needed to develop a new drug. Second, R&D productivity can be increased by extending the period of market exclusivity with the introduction of follow-on products. These second-generation products typically are incremental improvements of existing authorized drugs. The strategy of releasing second-generation products is called "evergreening" (Hemphill and Sampat, 2012). Originator companies often launch follow-on products shortly before they lose exclusivity for the first-generation product. In order to guarantee market exclusivity for the second-generation products, they typically continue to work on incremental improvements and obtain additional patents on these improvements 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.[6]

Patent rights

Patents rights are exclusive 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 original filing date (priority date of the patent). 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", i.e., 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). While originators generally target global markets, patents are national rights. For this reason, patents on novel pharmaceutical substances are typically filed internationally at several patent offices simultaneously.[7] Patentability rules are largely harmonized among the members of the World Trade Organization and international variation regarding their duration and protective scope is negligible in the context of our study.

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 so-called supplementary protection certificates (SPCs) for medicinal products according to Council Regulation (EEC) No 1768/92 of 18 June 1992 (see European Commission (2018) for details on the regulation of SPCs). 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.[8] In the United States of America, the 1984 Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Act")

[6] For a detailed discussion of evergreening strategies, see European Commission (2009).

[7] The set of international patent applications covering a given substance is called a patent family.

[8] Even if marketing authorization is granted only 15 years after the priority date of a patent the originator company can apply for an SPC of the maximum duration of five years, yielding a total period of exclusivity of ten years. Further note that 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.

allows qualifying companies to apply for a partial extension of patent life based on the time that the drug spent in clinical trials. Specifically, the act awards an additional half-year of patent life for every year spent in clinical trials, up to a maximum of 5 years not exceeding 14 years of patent protection in total (Saha et al., 2006). Note that in the following discussion, 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, etc. Secondary 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, i.e., the filing of a multitude of patents surrounding one product (see Abud et al. (2015) and European Commission (2009) for more detailed discussions). 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 in the process of obtaining market approval for a new drug. Before 1984 in the United States, and before 1987 in the European Union, pharmaceutical test data was protected as a trade secret. The introduction of new harmonized procedures for abridged applications for market approval of equivalent or essentially similar pharmaceutical products ("generic applications") with the 1984 Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Act") in the U.S. and the 1987 87/21/EEC Directive in the European Union further clarified the rules of clinical test data protection.[9] Data exclusivity (or test data protection) prevents marketing authorization bodies from processing so-called abridged applications for marketing a generic drug before a certain number of years after the first marketing authorization for the originator product have elapsed. Only after a drug's protection via patents (and SPCs) has 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 pre-clinical 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 barrier to entry for generic companies (Grabowski, 2004; Branstetter et al., 2017).

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 Com-

[9] A more complete discussion on the legal regulations and their development over time in different jurisdictions can be found in Sanjuan (2006).

mission harmonized data exclusivity regulations in Europe with legal effect from November 2005 (European Commission, 2009).[10] 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.[11] After a total period of ten years from the grant of the innovator company's marketing authorization, generic companies can also market their product.[12]

2.2 Market exclusivity and the incentives for drug development

As profits in the pharmaceutical industry can be realized only after regulatory approval of a new drug and its subsequent market launch, firms' investment decisions in pharmaceutical R&D projects can be characterized as forward-looking decisions weighing development costs against future profits conditional on market approval (Lakdawalla, 2018; Scherer, 2010). Starting a broad theoretical literature, Nordhaus (1969) argues that investments in the discovery of 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 Appendix C, we present an 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) duration of market exclusivity. In this model, investments in R&D need to be made before the innovator can earn profits conditional on having been successful in innovating. Further, investments in R&D increase the likelihood of successful innovations. For the pay-offs from being successful, assume that an originator company's profits during a new drug's period of market exclusivity π^m are greater than its profits after generic entry π^c since competition is absent (Cohen et al., 2000; Mansfield, 1986; Levin et al., 1987). Second, π^m is increasing in the duration of market exclusivity as generic entry is delayed further. Under these assumptions, a company's incentive to invest in risky R&D is strictly increasing in the duration of the 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).

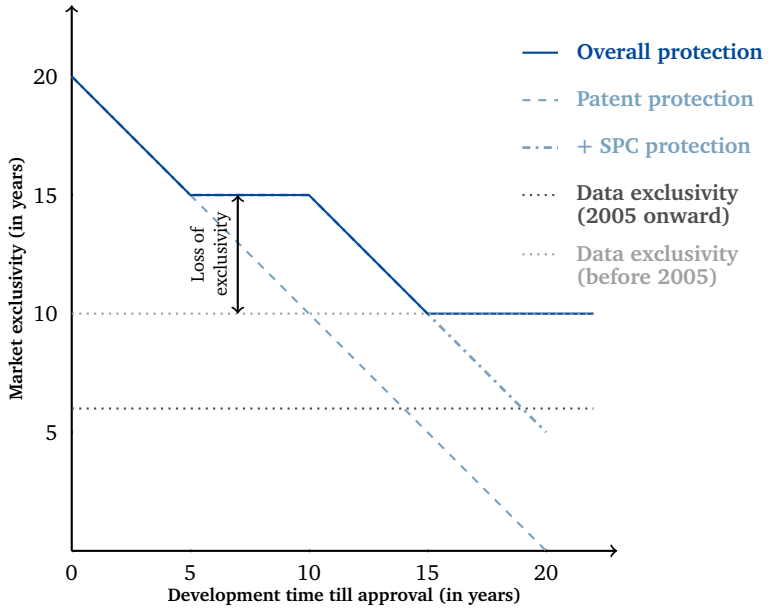
The actual duration of market exclusivity of successful development projects is determined by patent protection, development time and the length of the data exclusivity period and varies across

[10] The following countries granted six years of data exclusivity: AT, BG, CY, CZ, DK, EE, ES, EL, FI, HU, IE, IS, LI, LT, LV, MT, NO, PL, PT, RO, SE, SK. The following countries granted ten years of data exclusivity: BE, DE, FR, IT, LU, NL, SE, UK.

[11] This additional period of two years is officially termed "market exclusivity". Market exclusivity refers to the period of time during which a generic company may not market an equivalent generic version of the originator's pharmaceutical product (although their application for authorization may be processed during this period, such that they are in a position to market their product on the expiry of this additional two-year period). To avoid confusion, we stick to "data exclusivity" as an umbrella term.

[12] 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. For these reasons, 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).

Figure 2: Market exclusivity as a function of drug development time



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

development projects (see also Section 2.1, Figure 1). First, the effective patent term, i.e., 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 (and as in our example in Figure 1), 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: The dark blue (solid) line represent the total period of market exclusivity as a function of development time.

2.3 Firm responses to changes in market exclusivity

To date, there is little empirical evidence to what extent firms' innovation activities respond to changes in the expected duration of market exclusivity. The universal existence of harmonized IP systems renders empirical studies of the effect of different market exclusivity periods on the development of new drugs challenging. As a result, only limited empirical evidence exists on how firms' R&D investment decisions relate to the duration of market exclusivity. Moreover, since R&D

expenditures on the project level are hard to observe, scholars typically take observable product development projects as indicators of innovation activity. Most relevant to our study, 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 that have a long time 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. Wagner and Wakeman (2016) provide additional evidence on the link between patent protection and drug commercialization. Looking at variation in patent grant lag, 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 in a time-consuming process (Popp et al., 2004; Harhoff and Wagner, 2009), granted patents are generally at risk of invalidation after they have been granted. 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 simply 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 the responsiveness of firms' R&D activities to changes in the overall duration of market exclusivity.[13]

As an in-depth discussion of the institutional details surrounding patent invalidation is beyond the scope of this paper, we restrict ourselves to briefly highlighting key aspects in Europe and their counterparts in the United States. 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 a patent's validity within nine months after its grant. Opposition proceedings at the EPO are governed by Section V of the European Patent Convention (EPC). Opponents can challenge patents for grounds specified in Article 100 EPC, which relate to the subject-matter of the patent not being patentable, failure to disclose the invention clearly and the patent's subject-matter extending beyond the content of the application. The opposition division, which consists of three technically qualified EPO patent examiners, at least two of whom have not taken part in the grant of the opposed patent), decides on the opposition. Possible outcomes are a narrowing of the protective scope of a patent (amendment) or the patent's entire invalidation (revocation). A

[13]Note that our research design allows us to identify the intensive margin only. In order to identify the extensive margin, one would need to observe projects that are not put into trials by pharmaceutical firms expecting a weak IP position and short periods of market exclusivity. We discuss how our results relate to the extensive margin at a later point in the paper.

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.[14] While invalidation of a patent via opposition has the potential to reduce the market exclusivity period of a drug, opposition has be filed years ahead of a potential generic entry at a point in time where it is not even clear whether a drug candidate will eventually be approved at all. Preliminary evidence points to "legal spillovers", where patent invalidation through opposition at the EPO calls into question the validity of the patent's counterparts in other jurisdictions.[15] Gaessler et al. (2017) finds similar spillover effects for follow-on innovation. Hence, opposition outcomes at the EPO can be expected to be correlated with the strength of the IP protection of a drug candidate in other jurisdictions.

Models of firm investments into the discovery and development of innovation predict that investments rise with the profits expected from it. As the profits from successful drug development increase in the duration of market exclusivity, we expect a loss of exclusivity due to patent invalidation to have a negative effect on firms' innovative activities. As we are not able to measure project-specific R&D investments directly, we 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. In our context, patent invalidation that reduces the expected duration of market exclusivity is expected to lower the likelihood of project continuation and thus commercialization. Given that we have considerable variation in the loss of exclusivity across our sample, our research design allows us to provide a first quantification of firms' responsiveness to market exclusivity durations in the pharmaceutical industry.

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 or to abandon a project. In this setting, a negative shock to the expected profits from successful commercializa-

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

[15] With uniform requirements for patentability, the US counterpart of an EP patent is prone to the same novelty-destroying prior art (independent of origin and language) (Merges, 2012).

tion due to a loss of exclusivity will affect firm responses stronger 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 pay-off 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. As prior investments in a drug candidate are generally considered to be sunk, a reduction of the final pay-off at a later stage of drug development should have a smaller effect on investment incentives when compared to a loss of exclusivity that materializes early in the process.

Second, the magnitude of our main effect should also depend on firm size. Firms likely 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). Most relevant, Girotra et al. (2007) point out that the marginal value of a project is smaller for pharmaceutical firms with large project portfolios for at least two reasons. The chances to successfully release a drug for a given market (indication) increase in the number of alternative drug 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. 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. Contrary, firms with a thin project pipeline might be more likely to hold on to projects in order to avoid fixed assets being underutilized. Thus, we expect the negative effect of a loss of exclusivity on the likelihood of successful drug commercialization and continuation to be more pronounced for firms with large development pipelines.

3 Research design, data and variables

3.1 Research design

We study how the duration of market exclusivity is related to innovation incentives in the pharmaceutical industry. Linking development histories of drug projects with associated IP rights allows us to identify how variation in the duration of market exclusivity periods affect companies' innovation efforts. We use a project's successful completion of different stages in the development funnel (pre-clinical, phase I, II, and III trials) and the eventual marketing authorization as key indicators of innovation outcome. Simply linking the outcomes of drug development processes to expected periods of market exclusivity, however, will be plagued by selection biases. To overcome this challenge, we exploit a natural experiment created by post-grant validity challenges: Conditional on one of the

patents associated to a drug candidate being opposed at the EPO, we observe development projects being at risk of patent invalidation and hence a reduction of the duration of the market exclusivity period. Patent invalidation thus 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, on the other hand, do not endure a loss of exclusivity and hence 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, however. First, our treatment (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 proceedings 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. We have argued in Section 2.3 that patent invalidation at the EPO is likely to be correlated with a weakening of the IP position in other jurisdictions. These cross-jurisdictional spillovers will reduce the extent to which we underestimate the full effect.

3.2 Data sources

We collect data on drug development histories at the drug-indication level and link it to the underlying IP protection. Linking drug development projects to patents represents a non-trivial endeavor (WIPO, 2014). Some jurisdictions have introduced regulations enforcing publication of patents linked to marketed pharmaceutical products (Bouchard et al., 2010). These publicly available patent-drug databases, such as the Orange Book or the DrugBank database, however, are restricted to approved drugs. Yet, our study requires additional information on patents related to drug candidates which have not gained approval and on patents that have been invalidated prior to a drug's market approval. We therefore draw on a commercial database, i.e., Clarivate's Cortellis database (March 2018), that provides curated information on patent-drug relationships such as associated patents' priority filings and their classification in primary and secondary patents.[16] We augment this data with further patent indicators extracted from EPO's PATSTAT database.

Cortellis reports for each development project whether and when a particular development stage (and ultimately marketing authorization) was reached. We rely on Cortellis' information on discontinuation of drug development to distinguish truncation from actual project termination at a given

[16] Cortellis has been used before in a similar fashion in Krieger (2017) and Krieger et al. (2018).

development stage.[17] Based on this information, we exclude pending development projects from our analyses. Our research design requires that we restrict the analysis to drug development projects that are 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 the 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. As Cortellis contains information whether a drug is commercialized for one indication exclusively or whether it is addressing multiple indications we are able to construct development histories at the drug-indication level. The 1,769 drug candidates for which at least one underlying patent has been opposed at the EPO correspond to 6,442 unique development histories at drug-indication level. For 2,788 of these observations (920 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 pre-clinical trials, phase I, II, and III clinical trials as well as final marketing authorization. Based on this information we create two indicator variables. The first indicator (*approval*) equals one if a drug reaches market approval in Europe, US or Japan and zero otherwise.[18] The second indicator (*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*

[17] A small number of projects are never officially discontinued and remain with the label "no development reported". We consider projects labeled as "no development reported" abandoned only if the last status update occurred in 2013 or earlier. Our results are robust to earlier cut-offs.

[18] Market approval can be granted at national level or across the European Union by the European Medicines Agency (EMA). Market approval by the EMA has become the predominant route since the harmonization of data exclusivity terms in 2005.

in amended form), or the opposed patent is declared invalid (*invalid*). In line with prior literature (cf. Galasso and Schankerman, 2015; Gaessler et al., 2017), 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.[19]

Loss of exclusivity

We compute the loss of exclusivity (*LoE*) due to patent invalidation as 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 ($\text{dur}_{DataExcl}$) with:

$$\begin{aligned} LoE &= \max\left[(\text{Remaining patent term} - \text{dur}_{DataExcl}); 0\right] \\ &= \max\left[\left(20 \text{ years} - \left(\text{date}_{Approval} - \text{date}_{PatApp}\right) - \text{dur}_{DataExcl}\right); 0\right]. \end{aligned}$$

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.[20] Note further that *LoE* is fully determined only once the date of market approval of a drug is known. Our sample is restricted to cases, however, where opposition (and potential patent invalidation) takes place before a drug's approval, which renders the exact date of drug approval unknown. For this reason, we predict a drug's expected date of approval ($\widehat{\text{date}}_{Approval}$) at the time of patent invalidation. We derive these estimates from median development times in a given indication of the Cortellis clinical trials universe of all drugs.[21] 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 (pre-clinical, 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 till approval (their actual duration is unknown at the time of the communication of the opposition outcome).

Based on this estimate of the time of drug approval, we approximate a firm's expectation regarding the loss of exclusivity simply as the difference between the expected remaining patent term at

[19] 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.

[20] The grant of SPC protection is product-as well as patent-specific (European Commission, 2018). To keep things tractable, we assume possible SPC protection for each drug project unless the first drug-indication project gained market approval before the time of opposition outcome.

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

drug approval and the length of the exclusivity period,[22] i.e.,

$$LoE = \max\Big[\Big(20 \text{ years} - \Big(\widehat{\text{date}_{Approval}} - \text{date}_{PatApp}\Big) - \text{dur}_{DataExcl}\Big); 0\Big].$$

We compute this measure for all patents in our sample irrespective of subsequent invalidation.[23] Strictly speaking, it is a measure of the *potential* loss of exclusivity. Only patent invalidation renders the potential loss an actual loss, which we model using an interaction term between the invalidation indicator and the loss of exclusivity measure. Figure 3 shows the distribution of (potential) loss of exclusivity. In about 45% of all cases in our sample patent invalidation does not reduce the duration of 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.[24] The ratio of potential loss of exclusivity to realized loss of exclusivity is fairly stable along the distribution, which opens up the possibility to implement the loss of exclusivity as a linear treatment variable in the empirical analysis.

Drug and drug development characteristics

We distinguish between drugs on a chemical and a biological basis. In contrast to chemical drugs, biologics are derived from large molecules with therapeutic effect. 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.[25]

About 30% of all drugs in Cortellis list development projects for multiple therapeutic indications. These indications refer to conditions or diseases that may significantly differ in prevalence, clinical trial costs, and the likelihood of regulatory approval. 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.[26] It should be noted that while later-stage clinical trials are conducted separately for different indications, results from pre-clinical trials and phase I clinical trials can – under certain circumstances – be used across multiple indications, saving development cost. 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*

[22] As elaborated in Section 2, data exclusivity was extended from six years (as the lower bound) to ten years in Europe. We assign 10 years of data exclusivity to all cases that had the expected date of approval in November 2005 or later and where patent invalidation occurred after the announcement of the policy change in May 2004.

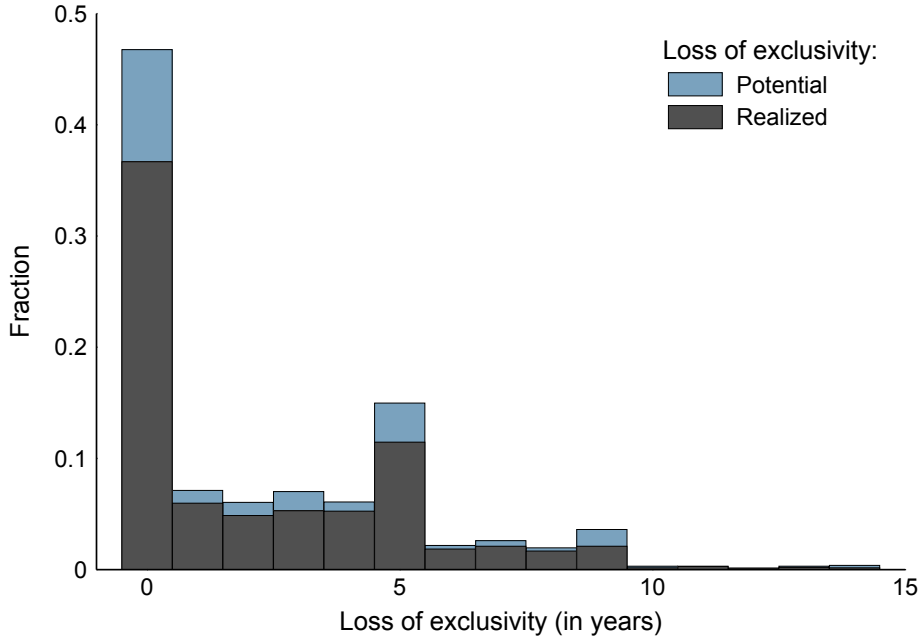
[23] There is reasonable concern that the used drug development times are not fully exogenous. First, the observed order of development projects (at indication level) for the same drug is not random but a strategic choice. Second, trial durations are partly calculated upon averages of the population, even though they can be influenced by the originator. However, if more promising projects are sped up and prioritized, the actual loss of exclusivity will be larger, which ultimately makes the estimated effect size a *lower bound*.

[24] Opponents might have an incentive to challenge granted patents at the EPO in the absence of a loss of exclusivity to the originator company if an invalidation at the EPO improves their legal position in subsequent litigation cases in other jurisdictions.

[25] Unlike in the US, data exclusivity regulations in Europe do not discriminate between chemical drugs and biologics.

[26] The used concordance table has been introduced by Krieger (2017).

Figure 3: Distribution of loss of exclusivity



Notes: This figure shows the distribution of potential and realized loss of exclusivity (in years). Observations are at the drug-indication level with the largest (potential) loss of exclusivity in the sample.

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 pre-clinical trials, phase I, II, or III clinical trials.[27] 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). Most importantly, 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., 30) and large if involved in more. In addition, we distinguish originators as being corporate entity or not (e.g., universities) and based on their *place of incorporation* (European vs. non-European) and include dummy variables in the regressions.

Opponent characteristics

Characteristics of the opposing party may also affect opposition outcomes. We therefore control for whether the opponent is a corporate entity or not and its *place of incorporation* (Europe or

[27] The pre-clinical phase serves as reference group.

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 that form a "patent fence". We operationalize the patent fence simply as the *total number of patents linked to a particular drug* as stated in the Cortellis database.[28] We are further able to distinguish *primary patents* linked to a drug from *secondary patents*.[29]

Moreover, we seek to characterize heterogeneity regarding patent protection of drugs by using correlates to a patent's value and its characteristics. Regarding patent value, we focus on measures that are independent of the examination and opposition proceeding at the EPO. 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.[30] In order to further characterize a patent beyond these value indicators, we include a count of *different IPC4 subclasses*, the number of independent *claims*, the *number of inventors*, the number of *references to patent documents* and the number of *references to non-patent literature*. We also 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

In total, the Cortellis database 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 are 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 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 920 unique drug candidates (column 4, Table 1).

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

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

[30] A discussion of these indicators can be found in Wagner and Wakeman (2016).

Table 1: Drug characteristics

	(1) All drugs $N = 44,764$	(2) All drugs with patent link $N = 14,149$	(3) All drugs with opposition $N = 1,769$	(4) All drugs in oppo. sample $N = 920$
Drug level	Mean	Mean	Mean	Mean
Drug characteristics				
Biologic (d)	0.31	0.33	0.40	0.44
Drug discovery (yr)	2003.04	2000.51	1996.03	1996.86
Latest development (yr)	2008.43	2009.33	2008.38	2011.16
Approval in at least one indication (d)	0.06	0.17	0.57	0.58
# Indications	1.53	2.01	3.46	4.61
# Indications (in opposition sample)				3.03
Patent protection				
# Patent families		3.74	15.35	18.84
# Opposed patents			2.51	3.09
# Invalidated patents			1.85	2.33

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 non-pending 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 all non-pending drug projects with at least one EP patent challenged in opposition proceedings. "All drugs in opposition sample" refers to all non-pending drug projects that are part of our final sample of analysis. Patent families follow the INPADOC patent family definition.

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") to minimize the risk of imitation. Drugs associated with at least one opposed patent are surrounded by an average of 15.35 different patent families and drugs in our final sample (opposition decision prior to project termination) by 18.84 different patent families; see columns 3 and 4 of Table 1. Compared to an average of only 3.74 patent families for all projects with known patent link, 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 58% in the final sample but only 17% for all drugs with a patent link. Finally, drugs with opposed patents have been tested against 3.46 different indications on average compared to 2.01 indications for drugs with known patent link.[31] 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

[31]Drugs in our final sample have been tested against 4.61 different indications. Note that we exclude development histories where the opposition outcome occurs before project start or after its termination. The final sample therefore contains only an average of 3.03 indications per drug.

also constitute an important additional determinant of differences in observed patent characteristics and selection into opposition. Existing literature argues that patents attached to valuable projects are significantly more likely to be challenged. The selection towards more valuable projects renders our results conservative. Given that companies put more effort into developing higher value projects, any negative relation between patent invalidation and project progress in our sample underestimates the unknown population effect.

Drug-indication level statistics

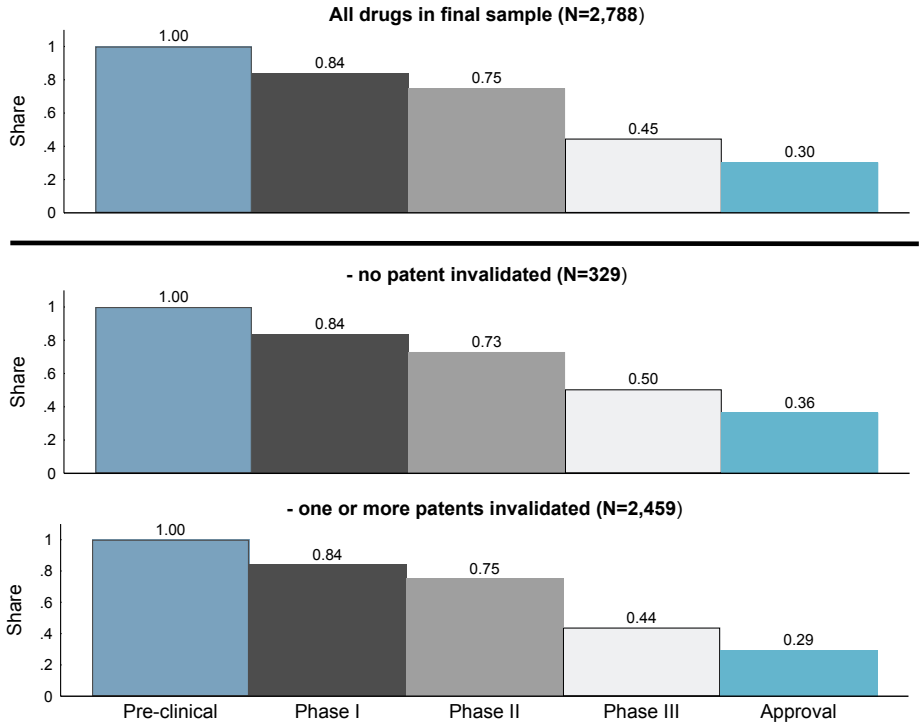
A given drug's efficacy is typically tested against multiple indications independently. In total, Cortellis contains 75,396 different non-pending drug-indication level projects (each of the different 44,764 drug candidates is associated with an average of 1.68 different indications) out of which about 6% are approved for the market while 94% are terminated before approval. Attrition patterns differ by sample definition (see Figure A-4 in the Appendix). The majority of cases (62%) of all drug-indication level projects are terminated after the pre-clinical phase before major investments in clinical trials are due. Development projects with patent link are characterized by higher approval rates (17%) and terminated at later stages compared to the population of non-pending projects. The projects in our final sample (projects associated with opposed patents where a decision on opposition was communicated before termination) follow a similar pattern of comparably late termination and average approval rates of 30%.

4.2 Patent invalidation and development outcomes

We present descriptive evidence on how patent invalidation in opposition proceedings affects drug development outcomes. In Figure 4, we report attrition rates at the drug-indication level and distinguish between cases with no patent invalidated in opposition and cases with at least one patent invalidated in opposition. We find notable differences between these two groups. First, projects with at least one patent invalidation before project termination lead to final drug approval in 29% of cases. In contrast, if no patent was invalidated, average approval rates are significantly higher with 36%. This descriptive evidence is in line with our prediction that patent invalidation reduces approval rates as the incentive to engage in costly development efforts is diminished.

To further explore how the exact 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 development stage at time of opposition outcome in Figure 5a. 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's progress. While this clearly holds for drug approvals, its relation to continuations is not clearly visible in this bivariate graph. Figure 5b 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.

Figure 4: Project advancement at the drug-indication level by opposition outcome

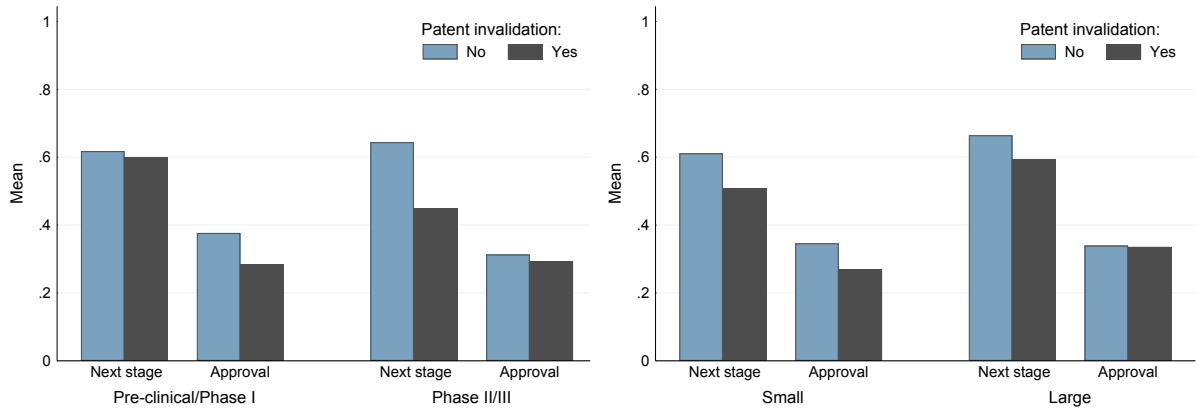


Notes: Observations are at the drug-indication level. "All drugs in final sample" refers to all non-pending drug projects that are part of our final sample of analysis.

Figure 5: 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.

Table 2: Highest development stage by development stage at time of opposition outcome

Development stage at opposition outcome	Development stage reached									
	Pre-clinical		Phase 1		Phase 2		Phase 3		Approval	
No patent invalidated										
Total	**329**	→							**120**	**36.5%**
Pre-clinical	168	*(67.9%)*	*114*		101		80		**70**	**41.7%**
Phase I	–		31	*(29.0%)*	*9*		7		**6**	**19.4%**
Phase II	–		–		63	*(19.0%)*	*12*		**7**	**11.1%**
Phase III	–		–		–		67	*(52.7%)*	***37***	***55.2%***
At least one patent invalidated										
Total	**2,459**	→							**725**	**29.5%**
Pre-clinical	1,446	*(72.8%)*	*1,052*		946		601		**452**	**31.3%**
Phase I	–		168	*(32.7%)*	*55*		36		**31**	**18.5%**
Phase II	–		–		498	*(18.7%)*	*93*		**55**	**11.0%**
Phase III	–		–		–		347	*(53.9%)*	***187***	**53.9%**

Notes: This table presents progression of projects (drug-indication level) conditional on their development stage at time of opposition outcome for the regression sample. Percentages are conditional on having reached the prior development stage.

Finally, we report the advancement through the development funnel for all projects in our final sample (drug-indication level) in a life-table-like fashion. Table 2 tabulates the development stage in which opposition was decided (rows) against the subsequent stages reached by the respective development projects (columns).[32] In total, our final sample contains 329 development projects where no underlying patent has been invalidated before project termination or approval with 120 (36.5%) of these cases leading to final approval in a given indication (first line of Table 2). For a subset of 168 projects, the opposition outcome "valid" was communicated while the drug was still in pre-clinical trials. The second line of Table 2 reports how these 168 projects advance through the development funnel with 70 projects (41.7%) eventually being approved. Additionally, we report the number and share of projects that start the next stage after communication of the opposition outcome – in this case 114 projects (67.9%).

Table 2 further reveals differences in progress patterns for projects by opposition outcome. While early patent invalidations during pre-clinical trials have no different effect on the likelihood of taking the drug to the next stage, final approval rates of 29.5% are significantly lower compared to 36.5% for cases where patents are upheld. Moreover, oppositions leading to patent invalidation only during clinical trials are associated with lower drug approval rates as well as lower probabilities of starting

[32]Due to the life-table logic, the left-most number in each row of Table 2 denotes the overall number of projects for which the opposition proceeding has been decided in a given stage. Moving right in a given row lists how many projects survive the transition to the subsequent stage in the development funnel.

the next development stage. These differences are more pronounced during phase I and phase II but remain present in phase III. One explanation is that once phase III trials have been initiated, the additional investments needed for market approval are lower than in situations in which invalidation is communicated before the start of phase III trials.

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 in opposition proceedings, 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:

$$\begin{aligned} Approval \;=\; & \gamma\,(Invalidation \times LoE) + \\ & +\; \beta_0 \;+\; \beta_1\, Invalidation \;+\; \beta_2\, LoE + \beta_3\, X + \epsilon. \end{aligned}$$

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. A finding of $\gamma = 0$ would indicate that the period of market exclusivity does not affect 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 our regressions.[33]

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 outcome of the opposition procedure might be determined by unobservable characteristics (such as early

[33] A comprehensive list of the control variables can be found in Table B-1 in the Appendix.

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. Such a situation would generate a positive correlation between ϵ and *Invalidation* in our regression equation and therefore bias the OLS estimate of γ upwards. To address potential endogeneity of the outcome of the opposition proceeding, 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. (2017), we use the granting patent examiner's participation in the opposition proceeding as the basis for instrumentation. Specifically, we instrument the opposition outcome (*Invalidation*) as well as its interaction with *LoE* with the predicted probability of invalidation obtained from a probit model $\widehat{\text{Prob}(\textit{Invalidated})} = \Phi(\gamma_1 \textit{Examiner participation} + \gamma X)$. Note that this estimator is asymptotically efficient in the class of estimators based on instruments being a function of examiner participation and other independent variables (Wooldridge, 2010). 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* $\times$ *LoE*. Based on this reasoning we estimate the following two-stage model:

$$
\begin{aligned}
\textit{Invalidation} &= \alpha\, \widehat{\text{Prob}(\textit{Invalidated})} + \theta\, X + u \\
\textit{Approval} &= \gamma\, \widehat{(\textit{Invalidation} \times \textit{LoE})} + \\
&\quad + \beta_0 + \beta_1\, \widehat{\textit{Invalidation}} + \beta_2\, \textit{LoE} + \beta_3\, X + \epsilon.
\end{aligned}
$$

Our instrument exploits variation in the participation of the patent examiner who initially granted the patent in the opposition division. Although the rules and regulations of the EPO allow some personnel overlap in the examination and opposition procedure, they do not require the involvement of the initial patent examiner in the opposition division. In fact, the average examiner participation rate is about 68% across all opposition proceedings at EPO, with continuous variation over time and technology fields. The variation in examiner participation has been described as a result of the temporary non-availability of other examiners with expertise in the particular technology area and can be considered random to the focal patent (Gaessler et al., 2017). Figure A-3 in the Appendix presents the annual number of opposition proceedings and the annual rate of examiner participation.

Gaessler et al. (2017) 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. This finding is in line with views expressed by EPO officials and patent attorneys that the participation of the examiner is independent of the opposed patent and beyond the influence of the patent holder or the opponent. The exclusion restriction of the instrument prevails given that the patent holder (in our context, the originator company) 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

Table 3: 1^{st}-stage regression: Examiner participation and opposition outcome

	(1)	(2)	(3)
Estimation method	Probit	Probit	Probit
Dep var	Invalidated	Invalidated	Examin. partic.
Exam. participation (d)	−0.051**	−0.055***	
	(0.021)	(0.018)	
Potential LoE (in yrs)			0.000
			(0.005)
Drug characteristics	No	Yes***	Yes*
Development characteristics	No	Yes*	Yes
Patent characteristics	No	Yes***	Yes***
Technology effects	No	Yes***	Yes***
Disease effects	No	Yes***	Yes***
Examination characteristics	No	Yes	Yes
Age effects	No	Yes	Yes*
Originator characteristics	No	Yes**	Yes
Opponent characteristics	No	Yes***	Yes
Year effects	No	Yes***	Yes***
Model degrees of freedom	1	112	110
χ^2-statistic	5.8	479.0	299.8
Pseudo-R^2	0.004	0.197	0.129
Observations	5,959	5,959	5,936
Observations (weighted)	903	903	903

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 Appendix. 23 observations dropped due to perfect prediction in column (3) and (4). 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.

rather follow a normal distribution around the overall participation rate (as shown in Gaessler et al. (2017)). Second, the opposition division members are disclosed only during the oral proceeding, which typically results in a final decision on the opposition case. Hence, neither applicant nor opponent has time to adjust their strategy during the opposition proceeding.

Table 3 presents the results from probit regressions relating examiner participation to opposition outcomes controlling for other sources of heterogeneity. The dependent variable is at the patent level and patents might be associated with more than one development project if the associated drug is tested against multiple indications. For this reason, we include all observed patent-indication observations in the regressions 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 903 unique patents that are associated

with an average of 3.01 different indications resulting in 2,719 observations at drug-indication level and 5,959 observations at drug-indication patent level.[34] 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 3, column 2). Opposition divisions are less likely to invalidate a patent if the initial examiner participates. As can be seen from column 3, examiner participation is not only orthogonal to our key explanatory variable *Potential LoE*, but also to various other aspects of the opposition proceeding, including characteristics of the drug, the drug development process, the originator or the opponent.

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. In line with Roin (2008), we argue that patentability is hardly related to a drug's (social) value and its chance of market approval.[35] 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 characteristics of a drug candidate – 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.

5.2 Results

Before discussing the results from our regressions in detail, we provide an overview of the main findings. First, our findings indicate that an increase in the loss of exclusivity leads to a significant reduction of the likelihood of drug approval and continuation. Second, taking the timing of patent invalidation into account, we find that a loss of exclusivity at an early stage of product development has a more significant negative effect on commercialization outcomes compared to later stages. Third, splitting our sample between small/medium and large originator companies, we find evidence for differential effects of patent invalidation by firm size. Large originators are considerably more likely to abandon projects after a reduction in the expected duration of market exclusivity. These findings are robust to various subsamples and alternative operationalizations of the dependent as

[34] The small difference to the overall sample is due to perfect prediction of the first stage outcome.

[35] In fact, patent invalidation in opposition proceedings at the EPO may result from a lack of novelty, insufficient inventive step, insufficient disclosure of the invention or the undue broadening of the patent scope beyond the initial application. These criteria are not related to a drug's efficacy and toxicology which ultimately determine its value.

well as the key independent variables (see Section 5.3). We discuss these findings in detail below.

Main specification

In Table 4, we report results from regressions relating loss of exclusivity due to patent invalidation to market approval and the starting of the next stage in the development process using linear probability models as well as linear IV estimators in which we instrument patent invalidation and its interaction term. In columns 1, 2 (approval) and 5, 6 (next stage) of Table 4, we do not account for the loss of exclusivity but focus merely on the effect of patent invalidation. The OLS and IV estimate of the effect of patent invalidation on drug approval is statistically indistinguishable from zero both for approval as well as next stage. The coefficients of patent invalidation, however, do not relate to the resulting loss of exclusivity and that – in case of patent invalidation – the implied loss of exclusivity varies considerably across projects. In cases where the remaining patent term at market approval is lower than the period of data exclusivity, the duration of a drug's market exclusivity is entirely determined by data exclusivity and patent invalidation does not degrade the legal position of the originator company. The estimated coefficients of patent invalidation presented in columns 1, 2, 5, and 6 of Table 4 therefore do not reflect a loss of exclusivity, which likely explains the high standard errors of the coefficient estimates.

In order to quantify how a loss of exclusivity affects the likelihood of successful drug commercialization, we include the potential loss of exclusivity measured in years (*LoE*) and its interaction with patent invalidation in the regressions (Table 4, 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 compared to the OLS specifications. 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 3.5 percentage points (Table 4, column 4). This an economically meaningful effect given that the average likelihood of successful drug commercialization in our sample is 30.5% and the average market exclusivity length is about 10 years.[36]

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 reported in column (8) of Table 4 imply that a one-year reduction in the expected market exclusivity of a new drug leads to an average decrease in the likelihood of project continuation of 4.7 percentage points. Compared to an average continuation rate of 50.7% across all development stages, this again is an economically 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 com-

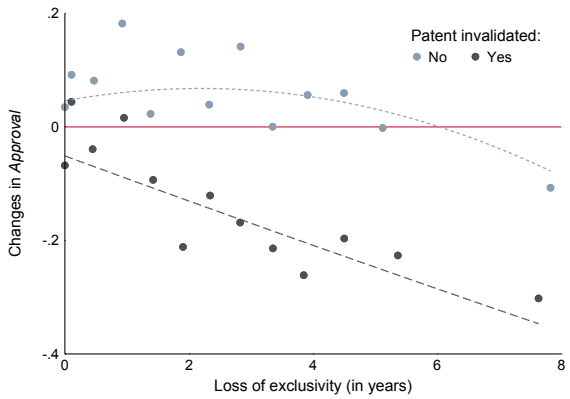
[36]Note that the potential loss of market exclusivity, as a strong correlate of the overall length of market exclusivity, positively affects drug approval.

mercialization efforts in response to *ceteris paribus* lower expected profits due to a shorter duration of the market exclusivity period. Figure 6 shows binned scatter plots of the residuals for two of our regressions (column 4 and column 8 in Table 4, respectively). These figures confirm the linearity of the effect of the realized market exclusivity loss on drug development outcomes.

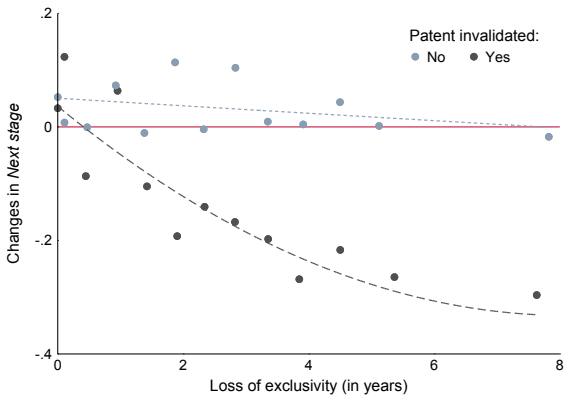
All regression specifications include a comprehensive set of control variables capturing characteristics of the drug, the development project, the originator, the opponent, and the underlying patent, as well as time and disease fixed effects. We do not report coefficients for these variables but briefly 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 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.

Figure 6: Effects of market exclusivity loss (in years) on drug development

(a) Drug approval



(b) Next stage



Notes: These figures plot market exclusivity loss (in years) on the change in drug development outcome (approval or continuation of drug development). The figure hereby distinguishes between cases where the patent was invalidated, so loss of exclusivity occurred, and where the patent survived, so no loss of exclusivity occurred. To construct this binned scatterplot, we predict the residuals from the estimated regressions in column 4 and column 8 in Table 4 and plot these by the instrumented variable *Loss of exclusivity (in years)*.

Timing of invalidation

In this subsection, we report results from specifications that account for the timing of patent invalidation. We have argued above that originator companies face a sequential decision-making process when developing new drugs. Early losses of exclusivity should have a more pronounced effect on firm decision making. As argued before, this result can be explained by the sequential nature of the (then sunk) investments in the different clinical trial stages (Dixit and Pindyck, 1994; Pindyck, 1991).

In order to test the prediction regarding the timing of invalidation (early vs. late), we split the sample in development projects with opposition decisions at an early stage (pre-clinical/phase I trials) and at a late stage (phase II/phase III trials). About 64% of the projects in our final sample had the opposition outcome of the underlying patent(s) during pre-clinical/phase I trials and 36% at later stages. In columns 1 to 4 in Table 5, we report the effect of a loss of exclusivity due to patent invalidation on drug approval and next stage based on this sample split. While the coefficient on the interaction carries the expected 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 eventual drug approval by 4.6 percentage points and the likelihood of starting the next stage of clinical trials by about 6.1 percentage points, which are slightly larger effects compared to our baseline effects reported in Table 4. A reduction in the exclusivity period affects firm behavior more significantly when received early, i.e., 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 now further investments to reach approval.

Table 4: 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	0.305	0.305	0.305	0.305	0.507	0.507	0.507	0.507
Invalidated	−0.018	−0.151	0.021	−0.076	0.011	−0.129	0.044	0.006
	(0.030)	(0.121)	(0.031)	(0.124)	(0.034)	(0.125)	(0.039)	(0.139)
Invalidated × Potential LoE (in yrs)			−0.015*	−0.035**			−0.014*	−0.047***
			(0.009)	(0.017)			(0.009)	(0.015)
Potential LoE (in yrs)			0.037***	0.052***			0.000	0.025**
			(0.008)	(0.013)			(0.008)	(0.012)
Drug characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes**	Yes**	Yes**	Yes**	Yes**	Yes**	Yes**	Yes***
Technology effects	Yes	Yes*	Yes	Yes**	Yes	Yes	Yes	Yes
Disease effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Examination characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age effects	Yes	Yes**	Yes	Yes***	Yes	Yes	Yes	Yes
Originator characteristics	Yes**	Yes*	Yes**	Yes**	Yes**	Yes**	Yes**	Yes**
Opponent characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Underidentification test		36.5		33.9		36.5		33.9
Weak identification test		52.8		24.6		52.8		24.6
Observations	5,959	5,959	5,959	5,959	5,959	5,959	5,959	5,959
Observations (weighted)	2,719	2,719	2,719	2,719	2,719	2,719	2,719	2,719

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, as reported by Stata's ivreg2 command (Baum et al., 2010). A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the 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.

Table 5: 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/III	Pre-clinic/Phase I	Phase II/III	Small	Large	Small	Large
Dep var mean	0.302	0.307	0.505	0.507	0.302	0.307	0.505	0.507
Invalidated	−0.060	−0.068	0.071	−0.098	−0.268	−0.011	−0.221	0.142
	(0.143)	(0.193)	(0.164)	(0.216)	(0.204)	(0.190)	(0.221)	(0.205)
Invalidated × Potential LoE (in yrs)	−0.046**	−0.025	−0.061***	−0.025	−0.007	−0.048**	−0.026	−0.058***
	(0.018)	(0.026)	(0.018)	(0.028)	(0.025)	(0.022)	(0.032)	(0.018)
Potential LoE (in yrs)	0.079***	0.003	0.041***	−0.010	0.023	0.062***	0.003	0.033**
	(0.015)	(0.022)	(0.015)	(0.023)	(0.021)	(0.017)	(0.027)	(0.014)
Drug characteristics	Yes***	Yes	Yes***	Yes	Yes***	Yes**	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes***	Yes	Yes**	Yes	Yes**	Yes*	Yes**	Yes***
Technology effects	Yes**	Yes***	Yes*	Yes***	Yes*	Yes***	Yes	Yes***
Disease effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes**	Yes***	Yes***
Examination characteristics	Yes**	Yes	Yes***	Yes	Yes	Yes	Yes	Yes
Age effects	Yes***	Yes***	Yes	Yes***	Yes**	Yes***	Yes	Yes
Originator characteristics	Yes**	Yes	Yes***	Yes	Yes***	Yes	Yes***	Yes
Opponent characteristics	Yes	Yes	Yes	Yes	Yes***	Yes	Yes**	Yes
Year effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Underidentification test	28.2	20.6	28.2	20.6	14.3	22.6	14.3	22.6
Weak identification test	20.6	11.9	20.6	11.9	10.5	13.9	10.5	13.9
Observations	4,311	1,648	4,311	1,648	2,345	3,614	2,345	3,614
Observations (weighted)	1,757	962	1,757	962	1,076	1,643	1,076	1,643

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 pre-clinical phase or in clinical phase I. Likewise, the samples used in columns (2) and (4) include drug projects only if the patent opposition outcome occurred during clinical phase II or III. 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. 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, as reported by Stata's ivreg2 command (Baum et al., 2010). A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the 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.

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.[37] About 38% of the projects are associated with small orginators and 62% with large originators. In columns 5 to 8 of Table 5, we report the effect of a loss of exclusivity due to patent 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 patent invalidation is comparable to the baseline results in Table 4, we do find differences 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 5). In contrast, projects of large originators are significantly affected by the realized loss of exclusivity. A one-year reduction in exclusivity lowers the likelihood of drug approval by 4.8 percentage points and the likelihood of starting the next stage by 5.8 percentage points (see columns 6 and 8 of Table 5). We argue that portfolio considerations are a likely explanation of the observed size differences.[38] Large companies are more likely to drop a project as they can reallocate their resources to alternative drug projects in their portfolio. In contrast, the marginal value for a given project is higher for firms with smaller portfolios (and hence fewer outside options) (Girotra et al., 2007).[39]

Although not a central question of our paper, these insights also inform the ongoing debate to what extent innovation incentives from IP rights are more important for small companies than for large ones (Galasso and Schankerman, 2018). Galasso and Schankerman (2018) report that small and medium sized companies significantly reduce their innovation efforts after patent invalidation, whereas large firms are not affected. However, their study focuses on patenting activities in a five-year time-window after patent invalidation as an indicator of innovative activities, while we focus on a different aspect: Conditional on having started a development project, small/medium originators are less likely than larger ones to reduce their innovation efforts after patent invalidation. In this regard, our findings complement Galasso and Schankerman (2018), who focus on the start of new projects, whereas we focus on the completion of existing projects.

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. Equally, results from unweighted regressions correspond well with the results reported above. Additionally,

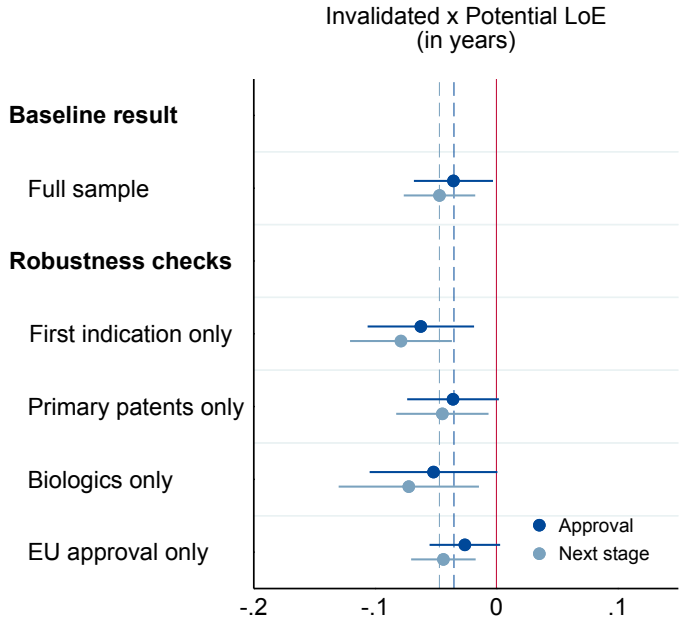
[37] We split the sample at the median, which is 30 drug projects.

[38] In Table B-2 in the Appendix, we split up our sample by timing *as well as* the originator's portfolio size. The results correspond to our findings in the main text: the effect on drug commercialization is most significant for the sample of large firms subject to patent invalidation in the early stages of the development process.

[39] In line with this, Arora et al. (2009) find that large firms are more selective when evaluating drug projects.

we investigate to what extent various institutional details of the drug development process affect our results (see Figure 7 for an overview of these results).

Figure 7: Overview of robustness checks



Notes: This figure depicts the estimated coefficients of our main independent variable of interest, *Invalidated* × *Potential LoE (in years)*, on the dependent variable *Approval*, respectively *Next stage*. The regressions for the main results are reported in Table 4. The corresponding regression tables for the robustness check results (in the Appendix) are the following: First indication only: Table B-3, Primary patents only: Table B-4, EU approval only: Table B-5, Biologics only: Table B-6. Horizontal lines represent 95% confidence intervals. Dashed vertical lines represent the baseline effects from the full sample.

First, we restrict our regressions to the first indication a drug candidate is tested against and limit the sample to the first indication for each drug candidate. 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 slightly larger effects, though the precision of some estimates is lower due to a reduced sample size (see Table B-3 in the Appendix). Likewise, restricting the analyses to the primary patent underlying a drug leads to results that compare well to the main findings reported above (see Table B-4 in the Appendix).[40]

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-5 reports the results where we focus exclusively on drug approvals in Europe. Again, the results remain largely unchanged, though the effect is smaller in magnitude and 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 (5

[40]For drugs with no opposed primary patent, we choose the patent with the largest patent family.

years). As a result, market exclusivity lengths in Europe and 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, which may differ from those in other economically relevant pharmaceutical markets. Table B-6 in the Appendix reports the findings of a reduced sample containing development projects related to biological drugs exclusively. The effect of the realized loss of exclusivity is highly significant and notably larger in magnitude than in our baseline model. 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-7 in the Appendix, but measure the loss of exclusivity this time in relative terms, i.e., 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 but 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 with the granting examiner's participation in opposition proceedings allows for causal identification. Our regression results highlight that a reduction in the expected duration of market exclusivity upon drug approval by one year significantly reduces the likelihood of drug approval in our sample by 3.5 percentage points relative to a mean approval rate of 30.5%. 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 regulatory changes at the *extensive margin*. We note that firms can be expected to respond even stronger at the extensive margin as both uncertainty as well as the necessary investments for successful commercialization are higher; our baseline effect sizes therefore should be interpreted as lower bound. However, our estimates for the responses of large firms with exclusivity loss in early stages of drug development provide an 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. 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 in opposition proceedings. Future research may complement our results by explicitly modeling competitive dynamics.

The effect of the duration of market exclusivity periods on the likelihood of drug approval has important 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 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. 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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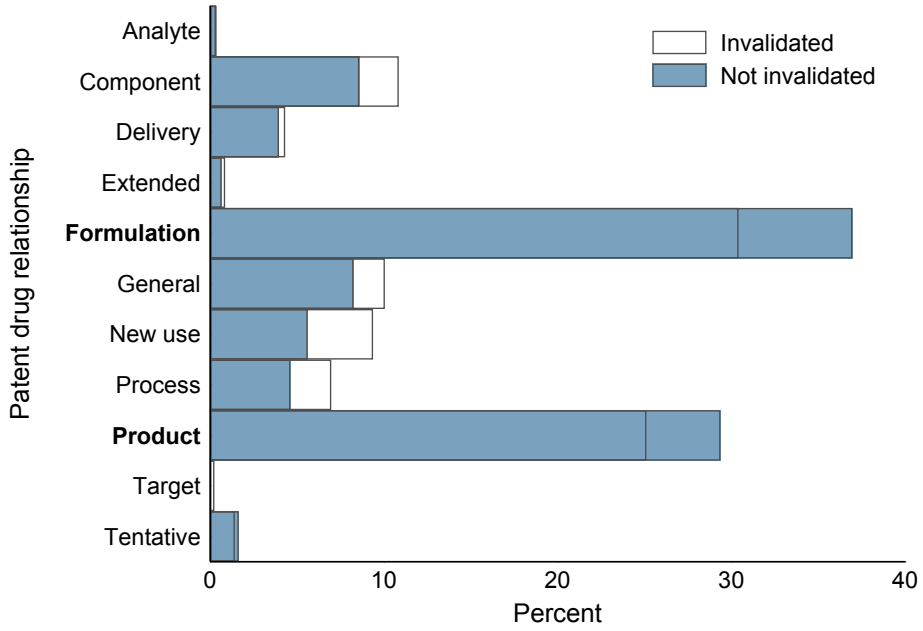
A Appendix: Figures

Figure A-1: Distribution of clinical trials lengths

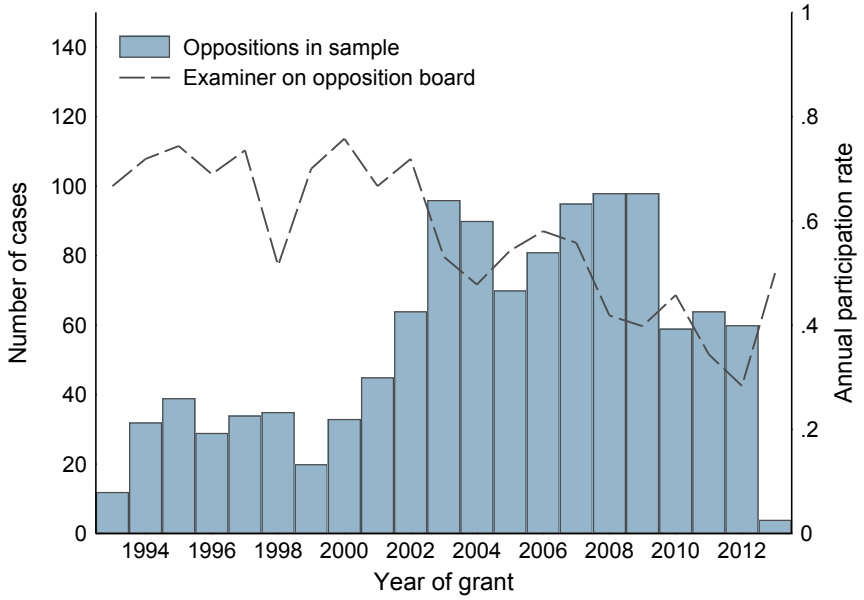
Notes: This figure shows the distribution of lengths of clinical trials by phase at aggregated indications level. Observations are at the aggregated indications level. Lengths calculated as the medians of the full sample of clinical trials in Cortellis. Only aggregated indications that are part of the opposition sample included.

Figure A-2: Distribution of patent-drug relationships by opposition outcome



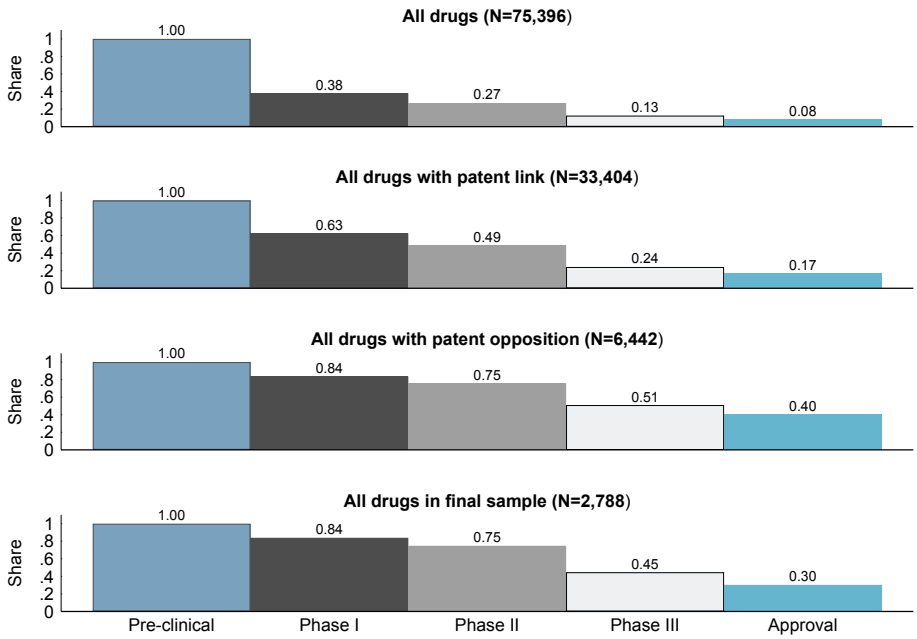
Notes: This figure shows the distribution of patent-drug relationships by opposition outcome. Patent-drug relationship as stated in Cortellis. Observations are at the drug-patent level. Bold relationships indicate "primary patent status". The null-hypothesis that the two distributions are equal can be rejected with a p-value of 0.143 ($Chi^2 = 14.712$).

Figure A-3: Annual number of opposed patents and rate of examiner participation



Notes: This graph includes all opposition proceedings (at the patent-level) in the regression sample. Based on the same sample, the figure also shows the annual rate of examiner participation in opposition proceedings.

Figure A-4: Project advancement at the drug-indication level by sample



Notes: Observations are at the drug-indication level. "All drugs" refers to all non-pending drug projects with development information in the Cortellis database. "All drugs with patent link" refers to all non-pending drug projects where a link to a patent family was identified. "All drugs with patent opposition" refers to all non-pending drug projects with at least one patent challenged in opposition proceedings. "All drugs in final sample" refers to all non-pending drug projects that are part of our final sample of analysis. Higher approval rates for drug projects with opposed patents compared to our final sample are due to the fact that companies adapt their innovation efforts only conditional on opposition outcome.

B Appendix: Tables

Table B-1: Groups of control variables

Group name	**Variables in group**
Patent characteristics	Dummy for PCT application Dummy for accelerated examination Dummy for examination in Munich Dummies for publication language Size of docdb family Number of IPC classes Number of claims Number of inventors log(1 + Number of patent literature references) log(1 + Number of patent literature 3yrs forward citations)
Patent examination characteristics	Duration of examination Duration of wait until examination
Patent age effects	Dummies for age in years
Year effects	Dummies for patent grant year Dummies for opposition outcome year
Drug characteristics	Number of indications Dummy for prior approval Number of patents Dummy for orphan drug status Dummy for paediatric use status
Development characteristics	Time since discovery Dummies for current development stage
Disease effects	Dummies for aggregated ICD-9 levels (19)
Technology effects	Dummies for technology class (34) Dummy for biologics
Originator characteristics	Dummies for originator country Dummy for originator corporation Dummies for originator portfolio size: small – large
Opponent characteristics	Number of opponents Dummies for opponent country Dummy for opponent corporation

Table B-2: Impact of patent invalidation on drug development by timing as well as portfolio size

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Dep var	Approval				Next Stage			
Sample	Small		Large		Small		Large	
	Pre-clinic/Phase I	Phase II/III	Pre-clinic/Phase I	Phase II/III	Pre-clinic/Phase I	Phase II/III	Pre-clinic/Phase I	Phase II/III
Dep var mean	0.311	0.287	0.599	0.336	0.311	0.287	0.599	0.336
Invalidated	−0.301*	0.329	0.023	0.047	−0.302	0.612	0.393	−0.261
	(0.179)	(0.530)	(0.342)	(0.206)	(0.198)	(0.693)	(0.357)	(0.231)
Invalidated × Potential LoE (in yrs)	0.006	−0.073	−0.065**	−0.035	−0.021	−0.082	−0.081***	−0.015
	(0.037)	(0.055)	(0.030)	(0.028)	(0.042)	(0.064)	(0.030)	(0.031)
Potential LoE (in yrs)	0.041	0.037	0.099***	0.022	0.011	0.030	0.059**	−0.015
	(0.026)	(0.049)	(0.024)	(0.024)	(0.031)	(0.055)	(0.024)	(0.026)
Drug characteristics	Yes**	Yes***	Yes***	Yes	Yes***	Yes***	Yes***	Yes
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes***	Yes***	Yes	Yes***	Yes**	Yes***	Yes**	Yes**
Technology effects	Yes	Yes*	Yes***	Yes	Yes*	Yes***	Yes***	Yes
Disease effects	Yes***	Yes***	Yes	Yes***	Yes***	Yes***	Yes**	Yes***
Examination characteristics	Yes	Yes	Yes	Yes	Yes	Yes*	Yes**	Yes
Age effects	Yes***	Yes***	Yes***	Yes	Yes*	Yes***	Yes	Yes***
Originator characteristics	Yes**	Yes***	Yes	Yes	Yes***	Yes**	Yes	Yes
Opponent characteristics	Yes***	Yes	Yes	Yes	Yes**	Yes	Yes**	Yes*
Year effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Underidentification test	15.7	6.8	10.8	16.5	15.7	6.8	10.8	16.5
Weak identification test	11.5	3.9	6.2	9.2	11.5	3.9	6.2	9.2
Observations	1,668	677	2,302	1,312	1,668	677	2,302	1,312
Observations (weighted)	672	404	890	753	672	404	890	753

Notes: Columns (1) to (8) 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 and the size of the originator. The samples used in columns (1), (3), (5) and (7) include drug projects only if the patent opposition outcome occurred during the pre-clinical phase or in clinical phase I. Likewise, the samples used in columns (2), (4), (6) and (8) include drug projects only if the patent opposition outcome occurred during clinical phase II or III. The samples used in columns (1), (2), (5) and (6) include drug projects only if the drug originates from small entities. Likewise, the samples used in columns (3), (4), (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, as reported by Stata's ivreg2 command (Baum et al., 2010). A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the 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.

Table B-3: Impact of patent invalidation on drug development – first indication only

	(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	0.422	0.422	0.422	0.422	0.559	0.559	0.559	0.559
Invalidated	−0.053	−0.230	−0.020	−0.012	−0.009	−0.103	0.028	0.143
	(0.041)	(0.148)	(0.050)	(0.190)	(0.042)	(0.151)	(0.052)	(0.198)
Invalidated × Potential LoE (in yrs)			−0.007	−0.047*			−0.014	−0.063**
			(0.011)	(0.026)			(0.011)	(0.026)
Potential LoE (in yrs)			0.029**	0.058***			−0.003	0.035
			(0.012)	(0.022)			(0.011)	(0.022)
Drug characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes***	Yes***	Yes***	Yes***	Yes**	Yes***	Yes**	Yes***
Technology effects	Yes	Yes***	Yes	Yes***	Yes	Yes***	Yes	Yes***
Disease effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Examination characteristics	Yes	Yes	Yes	Yes	Yes*	Yes*	Yes*	Yes
Age effects	Yes	Yes	Yes	Yes**	Yes	Yes*	Yes	Yes**
Originator characteristics	Yes**	Yes*	Yes**	Yes*	Yes**	Yes**	Yes**	Yes*
Opponent characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Underidentification test		37.4		28.6		37.4		28.6
Weak identification test		43.0		16.5		43.0		16.5
Observations	1,566	1,566	1,566	1,566	1,566	1,566	1,566	1,566
Observations (weighted)	901	901	901	901	901	901	901	901

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. First indication refers to the drug-indication project that was first initiated for a particular compound. 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, as reported by Stata's ivreg2 command (Baum et al., 2010). A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the 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.

Table B-4: Impact of patent invalidation on drug development – primary patent only

	(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	0.305	0.305	0.305	0.305	0.503	0.503	0.503	0.503
Invalidated	−0.055	−0.143	−0.021	−0.067	−0.007	0.097	0.016	0.197
	(0.034)	(0.140)	(0.036)	(0.156)	(0.036)	(0.165)	(0.042)	(0.191)
Invalidated × Potential LoE (in yrs)			−0.013	−0.036*			−0.010	−0.045**
			(0.010)	(0.019)			(0.010)	(0.019)
Potential LoE (in yrs)			0.037***	0.055***			−0.003	0.024
			(0.010)	(0.017)			(0.010)	(0.017)
Drug characteristics	Yes***	Yes***	Yes**	Yes***	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes**	Yes**	Yes**	Yes***	Yes**	Yes**	Yes**	Yes**
Technology effects	Yes	Yes*	Yes	Yes**	Yes	Yes	Yes	Yes
Disease effects	Yes***	Yes***	Yes**	Yes**	Yes***	Yes***	Yes***	Yes***
Examination characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age effects	Yes**	Yes***	Yes***	Yes***	Yes	Yes	Yes	Yes
Originator characteristics	Yes**	Yes**	Yes**	Yes**	Yes**	Yes***	Yes**	Yes***
Opponent characteristics	Yes*	Yes*	Yes	Yes	Yes	Yes	Yes	Yes
Year effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Underidentification test		22.5		19.0		22.5		19.0
Weak identification test		28.7		12.1		28.7		12.1
Observations	2,522	2,522	2,522	2,522	2,522	2,522	2,522	2,522
Observations (weighted)	2,522	2,522	2,522	2,522	2,522	2,522	2,522	2,522

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. Primary patent refers to patents that protect the formulation or product of the underlying drug. 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, as reported by Stata's ivreg2 command (Baum et al., 2010). A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the 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.

Table B-5: Impact of patent invalidation on drug development – approval in Europe

	(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	0.129	0.129	0.129	0.129	0.459	0.459	0.459	0.459
Invalidated	0.005	−0.019	0.033	0.049	0.011	−0.068	0.047	0.058
	(0.021)	(0.096)	(0.021)	(0.099)	(0.030)	(0.123)	(0.036)	(0.135)
Invalidated × Potential LoE (in yrs)			−0.011	−0.026*			−0.015*	−0.044***
			(0.007)	(0.015)			(0.008)	(0.014)
Potential LoE (in yrs)			0.021***	0.032***			0.007	0.029***
			(0.007)	(0.013)			(0.008)	(0.011)
Drug characteristics	Yes**	Yes**	Yes**	Yes**	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes	Yes	Yes	Yes	Yes*	Yes**	Yes**	Yes**
Technology effects	Yes	Yes	Yes	Yes***	Yes	Yes	Yes	Yes
Disease effects	Yes*	Yes*	Yes	Yes*	Yes**	Yes***	Yes**	Yes***
Examination characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Originator characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Opponent characteristics	Yes*	Yes*	Yes*	Yes*	Yes	Yes	Yes	Yes
Year effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Underidentification test		36.5		33.9		36.5		33.9
Weak identification test		52.8		24.6		52.8		24.6
Observations	5,959	5,959	5,959	5,959	5,959	5,959	5,959	5,959
Observations (weighted)	2,719	2,719	2,719	2,719	2,719	2,719	2,719	2,719

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. Drug projects that have not reached approval in Europe have the dependent variable set to 0. 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, as reported by Stata's ivreg2 command (Baum et al., 2010). A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the 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.

Table B-6: Impact of patent invalidation on drug development – biological drugs only

	(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	0.261	0.261	0.261	0.261	0.477	0.477	0.477	0.477
Invalidated	0.050	0.013	0.089**	0.061	0.090*	0.027	0.123**	0.142
	(0.039)	(0.109)	(0.045)	(0.119)	(0.049)	(0.132)	(0.057)	(0.148)
Invalidated × Potential LoE (in yrs)			−0.023	−0.052*			−0.022	−0.072**
			(0.017)	(0.027)			(0.017)	(0.030)
Potential LoE (in yrs)			0.036**	0.060**			−0.003	0.040
			(0.018)	(0.026)			(0.015)	(0.027)
Drug characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes	Yes	Yes	Yes*	Yes***	Yes***	Yes***	Yes***
Technology effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Disease effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Examination characteristics	Yes*	Yes	Yes*	Yes	Yes	Yes	Yes	Yes
Age effects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Originator characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Opponent characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year effects	Yes***	Yes***	Yes***	Yes***	Yes**	Yes***	Yes***	Yes***
Underidentification test		31.6		31.7		31.6		31.7
Weak identification test		49.6		27.4		49.6		27.4
Observations	2,326	2,326	2,326	2,326	2,326	2,326	2,326	2,326
Observations (weighted)	1,138	1,138	1,138	1,138	1,138	1,138	1,138	1,138

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. The sample includes only drug projects on large molecule drugs ("biologics"). 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, as reported by Stata's ivreg2 command (Baum et al., 2010). A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the 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.

Table B-7: Impact of patent invalidation on drug development – relative loss of exclusivity

	(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	0.305	0.305	0.305	0.305	0.507	0.507	0.507	0.507
Invalidated	−0.018	−0.151	0.022	−0.035	0.011	−0.129	0.043	0.029
	(0.030)	(0.121)	(0.032)	(0.125)	(0.034)	(0.125)	(0.040)	(0.141)
Invalidated × Potential LoE (relative)			−0.226*	−0.658***			−0.186	−0.726***
			(0.126)	(0.244)			(0.131)	(0.230)
Potential LoE (in yrs)			0.586***	0.930***			−0.011	0.419**
			(0.121)	(0.203)			(0.124)	(0.194)
Drug characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes**	Yes**	Yes**	Yes**	Yes**	Yes**	Yes**	Yes***
Technology effects	Yes	Yes*	Yes	Yes***	Yes	Yes	Yes	Yes
Disease effects	Yes***	Yes***	Yes**	Yes***	Yes***	Yes***	Yes***	Yes***
Examination characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Age effects	Yes	Yes**	Yes	Yes***	Yes	Yes	Yes	Yes
Originator characteristics	Yes**	Yes*	Yes**	Yes**	Yes**	Yes**	Yes**	Yes**
Opponent characteristics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Year effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Underidentification test		36.5		34.1		36.5		34.1
Weak identification test		52.8		24.8		52.8		24.8
Observations	5,959	5,959	5,959	5,959	5,959	5,959	5,959	5,959
Observations (weighted)	2,719	2,719	2,719	2,719	2,719	2,719	2,719	2,719

Notes: Columns (1-8) 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 as a share of the total market exclusivity. Columns (3) and (4) as well (7) and (8) include an interaction term capturing the relative 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, as reported by Stata's ivreg2 command (Baum et al., 2010). A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the 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.

C Appendix: Incentives to invest in innovation

We present the incentives to invest into R&D in a highly stylized model which has its roots in the model by Nordhaus (1969). In this model, investments in R&D need to be made which stochastically yield successful innovations before the innovator can earn profits conditional on having been successful in innovating. We rely on this highly simplified model to analyze how changes in the duration of exclusivity an innovator enjoys before imitation can occur affect her incentives to invest in R&D.

Investments in R&D: We denote the amount of risky R&D as I that has to be invested in $t = 0$ and the probability of successfully innovating in $t = 0$ as p. p is a concave function of a firm's investments I with $p'(I) > 0$ and $p''(I) < 0$. (This implies that the firm's cost function $I(p)$ is strictly convex with $I'(p) > 0$ and $I''(p) > 0$).

We acknowledge that the assumption of investments and innovation outcomes happening instantaneously in $t = 0$ is an abstraction from the lengthy R&D process in the pharmaceutical industry that we describe in Section 2 of this paper. Budish et al. (2015) provide a more nuanced model that takes the commercialization lag (i.e., the time between discovery and drug approval) into account; regarding the incentive effect of the duration of exclusivity, it leads to the same conclusions as the simple model presented here.

Returns from R&D: In case of successful innovation, the profits of an innovator depend on the level of exclusivity of the innovation. In case of full exclusivity (no imitation is possible for competitors), the innovator earns monopoly profits assumed to equal π^m. If (partial) imitation is possible, the innovator earns some competitive return π^c with $0 \leq \pi^c < \pi^m$. The duration of exclusivity in case of successful innovation is T. As described in Section 2, T is derived from patent protection as well as data exclusivity and depends on the project specific speed of commercialization. Abstracting from the obsolescence of an innovation (a drug might be replaced by a more efficient drug in which case profits would be reduced to zero; see Budish et al. (2015)) and assuming a discount rate of r, a successful innovator therefore earns a total profit $\Pi(T)$ of

$$\Pi(T) = \int_0^T e^{-rt}\pi^m dt + \int_T^\infty e^{-rt}\pi^c dt.$$

Private incentives to invest in R&D: The firm's problem is to choose p so as to maximize the expected pay-off from investing into R&D $p\Pi(T) - I(p)$. The FOC to this problem is given by

$$I'(p^*) = \Pi(T).$$

The optimal likelihood of successful innovation $p^*(T)$ clearly increases in the duration of exclusivity T during which monopoly profits π^m can be earned. Since $\pi^c < \pi^m$, $\Pi(T)$ increases in T with $\frac{\partial \Pi(T)}{\partial T} > 0$. The longer the period of exclusivity, the higher the innovator's return and, hence, its incentive to invest into R&D. Since $p(I)$ is concave, the FOC holds for increasing T only for rising I. The opposite holds as well. A loss of exclusivity will reduce a firm's incentives to invest in R&D.