Patents, Data Exclusivity, and the Development of New Drugs

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ABSTRACT

Firms in the pharmaceutical industry typically rely on a period of market exclusivity derived from patent protection and data exclusivity to recoup their investments in R&D. The invalidation of patent rights during drug development renders data exclusivity the sole source of protection and shifts the period of market exclusivity at the project-level. Invalidation therefore constitutes a natural experiment that allows us to causally identify how the duration of market exclusivity affects firms' incentives to innovate. Our analysis is based on a novel data set that links the development histories of drug candidates with underlying patent data. Our findings from instrumental variables regressions highlight that shorter durations of market exclusivity reduce the likelihood of successful drug commercialization. This main effect is largely driven by patent invalidations during early stages of the drug development process and by large originators. We discuss the policy implications of these results.

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 twelve Pacific Rim states accounting for about 40% of the global economy – took more than five years and have been closely followed by the public.[1] TPP put the discussion on the design of intellectual property rights that protect new drugs against imitation and generic competition back on center stage. 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 data from clinical trials of a drug's toxicology and efficacy submitted to regulatory agencies cannot be relied upon to evaluate applications for marketing approval by generic entrants. As clinical trials are costly, data exclusivity creates entry barriers and hence is a source of market exclusivity independent of patent protection. In fact, the countries with either no (Brunei) or short data exclusivity periods (Australia, Chile, Malaysia, Mexico, New Zealand, Peru, Singapore, Vietnam) were opposing demands for a uniform extension of data exclusivity to up to twelve years. The opponents were pointing 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.

The trade-off between stronger incentives for innovation (stronger protection against imitation) and resulting costs to society (higher drug 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 recent empirical literature increasingly focuses on the incentives of intellectual property rights on inventive activity and analyzes 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 explicitly modeling its complex interplay with data exclusivity.[2] In this paper, we contribute to this literature by relating the overall duration of market exclusivity resulting from both patent protection *and* data exclusivity to the likelihood of successful product commercialization in the pharmaceutical industry. Ultimately, we aim at quantifying the marginal effect of the duration of market exclusivity granted to innovators on their innovation efforts.

The overall duration of market exclusivity derived from patents and data exclusivity is determined by the time period between initial patent filing and market approval of new drugs: Patents

[1] 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. Due to the United States of America's decision to withdraw from the trade agreement in January 2017, however, it is currently renegotiated between the remaining eleven countries.

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

grant exclusive rights to inventions (in our context typically molecules) for a fixed period of time (20 years) starting from the date of the patent application. Data exclusivity, in contrast, is granted for a fixed period of time 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 since its duration exceeds the remaining patent term. 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 can remedy weakened R&D incentives. The results of Budish et al. (2015)'s theoretical analysis of potential policy responses to skewed R&D incentives resulting from fixed patent terms allow a similar 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 risks of invalidation in opposition proceedings at the European Patent Office (EPO): in case a patent has been 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 link this project-specific exogenous variation in the duration of market exclusivity to drug development projects' commercialization outcomes in order to causally identify how duration of market exclusivity determines innovation efforts.

We account for the fact that invalidation might not be random as a company's effort put in defending a patent is 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 is using random variation in the participation of the examiner who granted the patent in the opposition proceedings. Examiner participation is negatively correlated with patent invalidation but uncorrelated with other factors that might determine originators' commercialization efforts. Instrumenting patent invalidations hence creates exogenous variation that allows us to causally identify how innovation outcomes depend on the duration of protection against generic competition. Additionally, we exploit variation in the duration of data exclusivity that originates from a regulatory change in 2005, when the period of data exclusivity in Europe has been harmonized to up to 11 (8+2+1) years from the date of first authorization.[3] Prior to that, the period of data exclusivity was only six years in most EU member states.

[3]For more details, see the Directive 2004/27/EC of the European Parliament.

For our study, we construct a novel data set that links the development histories of pharmaceutical compounds from pre-clinical trials up to European market approval (or the highest development stage reached) with information on the underlying European (EP) 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 890 unique drug candidates and their respective development histories with the underlying 1,142 EP patents subject to opposition. 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 2,613 unique observations at drug-indication-level where the decision on opposition takes place before drug approval or the termination of clinical trials – a prerequisite for our empirical strategy. We 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 and instrument patent invalidation with examiner participation in the opposition proceedings. Our results indicate that a reduction in the overall duration of market exclusivity causally lowers the likelihood of project completion significantly. In fact, we find that the loss of one year of market exclusivity lowers the likelihood of drug approval by about 3.9%. The effect is driven by (i) timing as patent invalidations that occur in early development phases having a stronger effect and (ii) firm size as medium/large originators reacting stronger to reductions of market exclusivity periods than small ones. With regard to the aggregate inventive activity, we find no increase in drug development projects within the same therapeutic area after patent invalidation.

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 controversially but largely in the absence of empirical evidence (Grabowski et al., 2015; Diependaele et al., 2017; Lietzan, 2016). We are able to identify how the duration of market exclusivity affects originators' commercialization efforts and quantify how variations in the durations of exclusivity determine private incentives to complete drug development. Our findings have several implications. First, if a drug is socially desirable yet not commercialized due to insufficient incentives, welfare is likely to be diminished. Data exclusivity can be a policy instrument to provide market exclusivity in cases where the remaining patent term is short relative to the needed clinical trials, or where patent protection is uncertain. It can therefore incentivize the commercialization of pharmaceutical innovations and increase social welfare. Second, existing literature argues that data exclusivity is hampering follow-on innovation (Grabowski, 2008). However, our findings highlight that data exclusivity might in fact be instrumental in incentivizing initial innovations that are prerequisite to follow-on innovation. This trade-off between encouraging "first-round" innovation and discouraging follow-on innovation deserves more attention in subsequent research.

The remainder of this study is structured as follows: Section 2 describes the institutional setting of our study with a particular focus on the regulatory framework in Europe. Section 3 provides details on the data set as well as variables, and Section 4 entails the descriptive statistics. Section 5 discusses our estimation approach and provides a discussion on how we instrument patent invalidation in order to address potential endogeneity problems. It also presents the findings of

our econometric analyses. Section 6 concludes the paper with a discussion of the results and their implications for policy makers, firm strategy and future research.

2 Patents, data exclusivity, and the development of new drugs

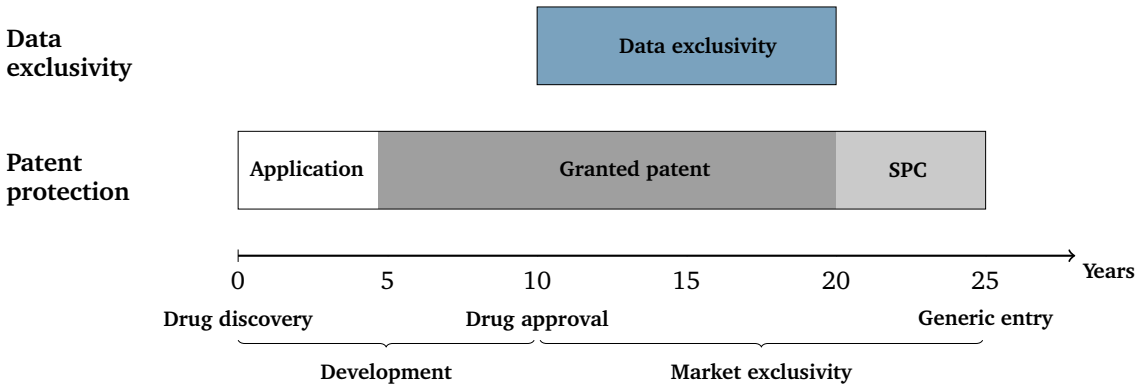
2.1 Institutional background

Context

The commercial life-cycle of a drug consists of three major distinct periods: (i) the development period where R&D and clinical trials take place; (ii) the market exclusivity period where the originator company can solely market and sell a drug; and (iii) a post-exclusivity period where competition by generic products copying the initial drug is possible. The development period is highly regulated and typically consists of discovery, pre-clinical trials, phase I, II and III trials to ascertain the toxicity and efficacy of a molecule. On average, it takes between 8.6 and 11.5 years from discovery to achieve marketing authorization and only a small fraction of all drug candidates (molecules) entering development reach final approval (European Commission, 2009). The originator can then submit the data gathered during the clinical trials and request marketing authorization from the respective regulatory authority (Scherer, 2010). Developing new drugs is a costly endeavor as witnessed by cost estimates in the range of USD 500 million to USD 2.6 billion (Adams and Van Brantner, 2006; DiMasi et al., 2016). The tests and clinical trials are responsible for the majority of the total R&D costs – the European Commission (2009) estimates that research-active pharmaceutical companies spend only 1.5% of their overall revenues on basic R&D (which includes the discovery of novel compounds) but 15.5% on clinical trials, tests and market approval. The decision of companies to make these high upfront investments in developing a drug largely rely on their expected pay-offs during the subsequent period of market exclusivity. Only if companies can expect to recover their R&D investments during the exclusivity period by high mark-ups on prices, initial investments in development will be made.

Market exclusivity, which allows originators to recoup their R&D investments, is derived through two legal mechanisms: patent rights and data exclusivity. Figure 1 presents a stylized life-cycle of a drug and the associated property rights in a schematic way. Upon discovery, companies typically file applications for patents covering the active substance of a drug and obtain a grant decision after a few years by the responsible patent offices. Once clinical trials are completed and the collected data shows the non-toxicology and the effectiveness of a drug, it can be approved for marketing by regulatory authorities. This typically is the starting point of a drug's period of market exclusivity which is determined by the effective patent term (potentially extended by Supplementary Protection Certificates (SPCs), see below for details) and the period of data exclusivity. Longer periods of market exclusivity are typically related to higher pay-offs and hence greater incentives for innovation.

Figure 1: Lifecycle of pharmaceutical products



Notes: Figure stylizes the typical drug lifecycle. SPC protection optional. Generic entry may occur earlier due to authorized entry. Data exclusivity as of 2005 onward.

After expiration of market exclusivity, market entrance from generic manufacturers likely reduces prices and consequently the originator company's profits.

Pharmaceutical companies often seek to increase their R&D productivity either by broadening the market for a molecule by finding additional medical indications or by extending the period of market exclusivity by launching improvements of the original drug. First, they might try to "reposition" existing drugs for new indications (Ashburn and Thor, 2004). The process of repositioning is characterized by a lower risk profile as repositioning candidates have already completed clinical trials and therefore have known toxicological and efficacy profiles. Additionally, existing clinical data often allows pharmaceutical companies to bypass entire steps in the development funnel such as pre-clinical trials (Ashburn and Thor, 2004). The investments needed to reposition an existing drug are therefore significantly lower than those needed to develop a new drug.

Second, research 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 of 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.[4]

Patent rights

Patents surrounding a drug grant the originator company market exclusivity for a fixed term of 20 years from the original filing date (priority date of the patent). They are considered the pri-

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

mary mechanism to appropriate value from innovation in the pharmaceutical industry (Cohen et al., 2000). As crucial patents on active ingredients of a potential drug are typically filed during the basic R&D stage, the duration of exclusivity is directly determined by how much time lapses between the filing of the patent and the market approval of a product. If this period of exclusivity is shorter than 15 years, companies can apply for so-called supplementary protection certificates (SPCs) for medicinal products in Europe according to Council Regulation (EEC) No 1768/92 of 18 June 1992 (see European Commission (2018) for details on the regulation of SPCs).[5] SPCs effectively amount to an extension of the patent right for a maximum of five years as the total time of market exclusivity derived from patent plus SPC is limited to 15 years.[6] Note that SPCs extend only to the specific medicinal product and use which had been authorized – they do not cover subsequent authorizations of the same compound for different indications.

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, formulations, production methods, etc. Secondary patents often result from originator companies' 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 represents 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 test data protection.[7] Data exclusivity (or test data protection) pre-

[5] In the United States of America, the 1984 Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Act") allows some qualifying companies to apply for a partial extension of patent life based on the duration 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 in total (Saha et al., 2006).

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

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

vents 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 has elapsed. In cases where a drug's protection via patents (and SPCs) has lapsed *and* in absence of data exclusivity, generic companies can file abridged applications in which they are not required to provide the results of costly pre-clinical tests or clinical trials but only need 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 to conduct clinical trials, data exclusivity creates a significant barrier to entry for generic companies (Grabowski, 2004; Branstetter et al., 2017). In the majority of cases (and as in our example in Figure 1), the data exclusivity period term 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 periods (European Commission, 2009).

The duration of data exclusivity in Europe varied considerably across countries ranging from six to ten years before the Directives 2001/83/EC and 2004/27/EC of the European Commission harmonized data exclusivity regulations in Europe with legal effect in November 2005 (European Commission, 2009).[8] For marketing authorization applications made from November 2005 onward, the period of data exclusivity in Europe has been harmonized as eight years from the date of first authorization in Europe with an additional period of two years of "market exclusivity".[9] After a total period of ten years from the grant of the innovator company's marketing authorization, generic companies can also market their product.[10]

2.2 Market exclusivity and the incentives for drug development

As shown above, the development of new drugs is risky and requires a significant investment of time and money. As profits are realized only after approval and 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 (Scherer, 2010). Everything else equal, increasing future profits should increase firms' willingness to invest.

A major determinant of expected future profits are IP rights awarded to originator companies. Market exclusivity allows pharmaceutical companies – in the most extreme case – to extract monopoly rents for a certain period and is typically considered a major incentive for firms to in-

[8]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.

[9]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).

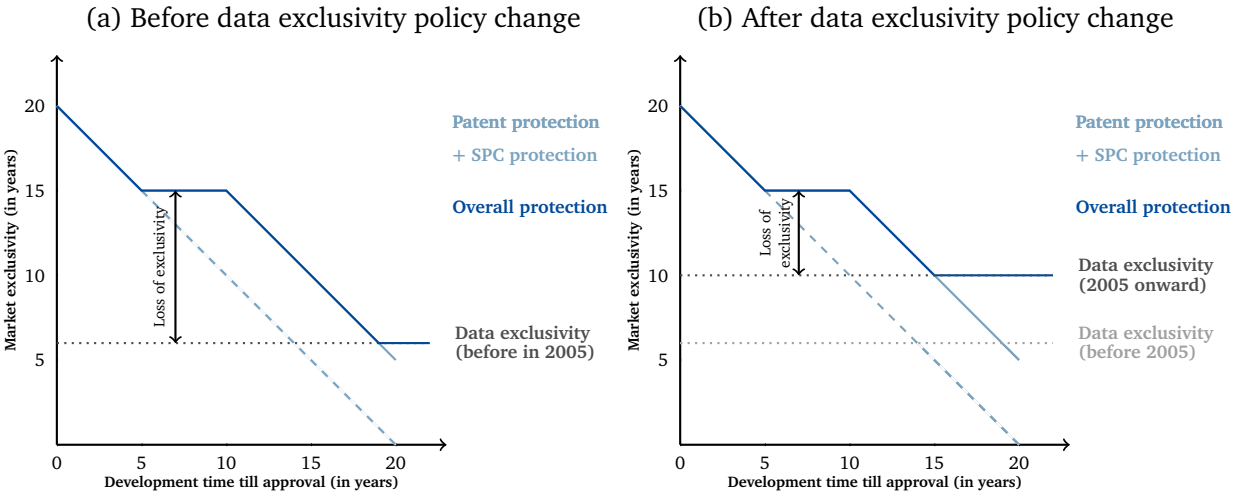
[10]The originator's product may qualify for one further year of exclusivity. This additional year can be obtained in a number of circumstances, such as where the innovator company is granted a marketing authorization for a significant new indication for the relevant medicinal product. For these reasons, 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).

vest in risky drug development projects (Cohen et al., 2000; Mansfield, 1986; Levin et al., 1987). Additional determinants of future profits include market size, level of market saturation and the competitive dynamics in the targeted therapeutic area (Acemoglu and Linn, 2004; Krieger, 2017; Rao, 2018). In this paper, we abstract from competitive dynamics and competition by new drugs in the same indication and focus on the link between the design of IP rights and firms' innovation efforts and drug development outcomes.

The universal existence of harmonized IP systems renders empirical studies of the effect of IP rights on the development of new drugs challenging. So far, only limited evidence exists on how firms' investment decisions relate to IP regulations. Most relevant, Budish et al. (2015) argue that, in contrast to the fixed patent length, the effective duration of patent protection varies: innovations that can be commercialized at the time of invention receive a full patent term, whereas innovations that have a long time lag between invention and commercialization (such as pharmaceuticals) receive only a substantially reduced period of patent-based market exclusivity. This distorts investments as firms disproportionately invest in projects with longer effective patent protection. Budish et al. (2015) highlight negative welfare effects in cases where socially desirable drugs have long development lags. Wagner and Wakeman (2016) provide additional evidence on the link between patent protection and the hazards of successful drug commercialization. Exploiting variation in the duration until patents are granted, they find that once the uncertainty regarding the patent grant and its ultimate legal delineation is resolved, the likelihood and the speed of successful drug development are increasing significantly. Wagner and Wakeman (2016) argue that firms are less likely to invest in projects until they are certain about the patent protection available. Existing empirical work therefore suggests that firms take the expected duration of market exclusivity into account when allocating resources to drug development projects. This is in line with theoretical models of firms' dynamic decision making that take into account future profits. Shorter durations of market exclusivity render development projects less attractive as they *ceteris paribus* reduce the time during which monopoly rents can be earned (Budish et al., 2015).

As described in Section 2.1 (Figure 1) the exact duration of market exclusivity for new drugs is determined by development time as well as the period of data exclusivity. Figure 2 illustrates how the duration of market exclusivity declines in development time from its theoretical maximum of twenty years in case of immediate commercialization to a minimum set by the period of data exclusivity. First, the effective patent term is linearly decreasing in development time. Second, if a drug is approved only after five years of development or later, a company can obtain an SPC which extends market exclusivity for another five years (limited to a maximum total duration of market exclusivity of 15 years). Finally, 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. The dark blue lines in Figure 2 represents the total period of market exclusivity as a function of development time, where Figure 2a is based on six years (before 2005) and Figure 2b on ten years (2005 onward) of data exclusivity in Europe.

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



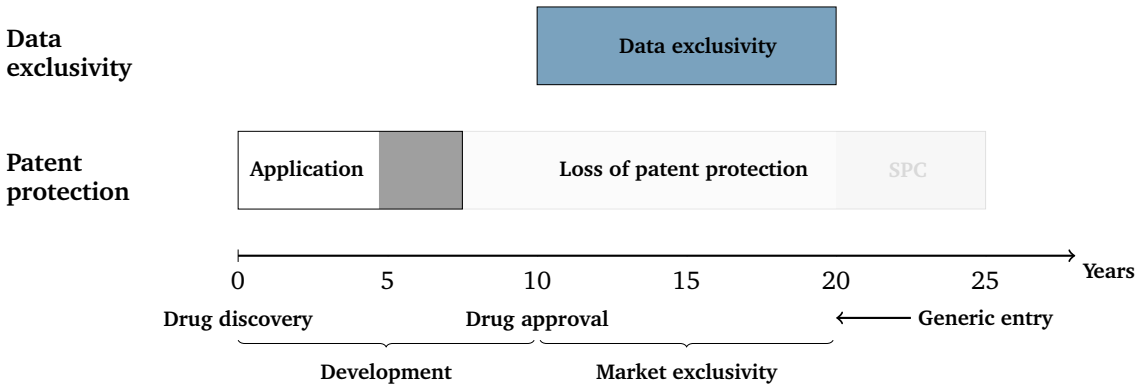
Notes: SPC protection optional. Loss of exclusivity refers to loss of exclusivity due to patent invalidation.

2.3 Patent invalidation and its effect on market exclusivity

In our empirical analysis, we link the duration of market exclusivity for a new drug to development outcomes on the level of individual projects in order to study the effect of IP design on companies' innovation efforts. As we elaborate below, we use a development project's successful completion of subsequent stages in the development funnel (pre-clinical, phase I, phase II and phase III trials) and the eventual marketing authorization as correlates for innovation effort. Any empirical analysis that simply links the outcomes of drug development to expected periods of market exclusivity, however, will be plagued by selection biases. For this reason, we base our analysis on a natural experiment and focus on drug development projects for which at least one of the underlying patents has been at risk of invalidation during opposition at the EPO. The fact that some of the opposed patents are invalidated while others are upheld allows us to compare commercialization outcomes for development projects that have been treated (patent invalidated) with projects where opposed patents have been upheld (control group).

As Figure 3 demonstrates, patent invalidation renders data exclusivity the sole source of market exclusivity for a new drug and has the potential to shift the duration of market exclusivity. If the remaining patent term at approval is greater than the period of data exclusivity, the overall duration of market exclusivity is reduced in case of patent invalidation. The longer the remaining patent term at approval, the greater the potential reduction of market exclusivity due to patent invalidation. In the following, we refer to this reduction due to patent invalidation simply as *loss of exclusivity*. As an illustration, consider a development project with expected approval after eight years of development. Market exclusivity based on patent protection and the associated SPC – if granted – is 15 years in

Figure 3: Lifecycle of pharmaceutical products – patent invalidated



Notes: Figure stylizes the typical drug lifecycle. SPC protection optional. Generic entry may occur earlier due to authorized entry. Data exclusivity as of 2005 onward.

total[11] and exceeds the period of data exclusivity. In case of patent invalidation, market exclusivity is entirely determined by the duration of data exclusivity which is either six years (pre 2005) or ten years (post 2005). In this example, patent invalidation leads to a loss of exclusivity equal to nine (pre 2005, Figure 2a) or five years (2005 onward, Figure 2b). In general, loss of exclusivity due to patent invalidation is a function of project-specific development time.

In our empirical analysis, we exploit project-level variation in development times to quantify to what extent a reduction in the duration of market exclusivity is related to the likelihood of project continuation and drug approval. An institutional feature of the EPO allows us to identify validity challenges on a large scale: The EPO offers third parties the option to challenge patents within nine months after the grant – which on average takes place about four years after application (Harhoff and Wagner, 2009). 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).[12] Finally, and as we discuss below, patent invalidation cannot be expected to be exogenous to unobservables also affecting innovation efforts. We therefore resort to an instrumental variable approach in our regressions that allows us to identify how changes the duration of market exclusivity are causally related to drug commercialization outcomes.

[11] The duration of patent based exclusivity is determined by the remaining patent term at drug approval (here after eight years) plus additional up to five years from an SPC. The total duration of exclusivity derived from patent and SPC cannot be greater than 15 years and hence in this example, the duration of exclusivity is determined by $\max[(20-8)+5;15]=15$.

[12] In the United States of America, 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.

3 Data and variables

3.1 Data sources and sample construction

To assess how changes in the expected duration of market exclusivity affect innovation incentives, 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 (October 2017), that provides curated information on patent-drug relationships such as associated patents' priority filings and their classification in primary and secondary patents. Cortellis has been used before in a similar fashion in Krieger (2017) and Krieger et al. (2018). We augment this data with further patent indicators extracted from EPO's PATSTAT database.

Cortellis reports for each development project when it started, whether it entered and completed clinical trial phases, and whether it achieved marketing authorization. We rely on Cortellis' information on discontinuation of drug development to distinguish truncation from actual project termination at a given development stage.[13] Based on this information, we exclude pending development projects from our analyses.

In order to identify the effect of changes in the duration of market exclusivity on development outcomes, we focus on drug development projects that are linked to at least one opposed EP patent with a decision on the opposition case between the start of drug development (discovery) and its completion (either drug approval or abandonment), and 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 either succeeded the end of drug development or preceded the start 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 6,123 unique development histories at drug-indication-level. For 2,613 of these observations (890 at drug-level), the opposition outcome was published while the drug development

[13] 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.

was ongoing. Our analysis will focus on these cases.

3.2 Variables

Dependent variable

For each drug we observe whether it 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, phase II and phase 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 and zero otherwise.[14] 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 is put into clinical trials phase II and zero otherwise.

Independent variables

Opposition outcome

Opposition at the EPO leads to one of three outcomes: the opposed patent is declared valid with no changes requested (*valid*), the opposed patent is upheld but its scope is narrowed (*valid in amended form*), or the opposed patent is declared invalid (*invalid*). In line with prior literature (cf. Galasso and Schankerman, 2015), 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.[15]

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* 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:

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

[14] 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 predominant route since the harmonization of data exclusivity terms in 2005.

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

Note that SPC protection – if granted – increases LoE by up to five years. We calculate SPC protection for all drug-indication cases and adjust our measure of LoE accordingly.

Note further that LoE is fully determined only once the date of market approval of a drug is known. 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 a patent is invalidated. We derive these estimates from median development times of the Cortellis universe of all drugs for different indications. 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 (up to the stage a project reached before opposition is decided) are added to the population median of the duration of subsequent stages till approval. For a patent that has been invalidated while the associated drug is in phase I clinical trials, we approximate the drug's expected date of approval by adding the median durations of phase II and phase III trials in the same indication to the actual development time until patent invalidation.

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 drug approval and the length of the exclusivity period[16], i.e.

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

We compute this measure for all patents at risk of invalidation irrespective of subsequent invalidation. 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 A-1 in the Appendix 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; in these cases, the remaining patent term at expected market approval is less or equal the duration of data exclusivity.

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.[17]

[16] As elaborated in Section 2, data exclusivity was extended from six years (as the lower bound) to ten years in Europe. We assigned 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.

[17] Unlike in the U.S., data exclusivity regulations in Europe do not discriminate between chemical drugs and biologics.

About 30% of all drugs in Cortellis list development projects for multiple therapeutic indications. While later stage clinical trials are conducted separately for different indications, results from pre-clinicals trials and phase I clinical trials often can be used across multiple 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.[18] We also construct a count variable of the *number of indications* per drug and include it in our analyses. Finally, we create a variable indicating whether at the time of opposition outcome the drug has been already *approved for another therapeutic indication* than the one of the focal observation.

A drug's *development stage at opposition outcome* is captured by a set of indicator variables equaling one when the opposition was decided in either pre-clinical trials, phase I, phase II and phase III trials or zero otherwise.[19] We further compute 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 (Dranove et al., 2014) and their behavior in opposition proceedings (Harhoff and Reitzig, 2004; Harhoff et al., 2016). We distinguish originators according to their *sector* (corporate entity or not) and their *place of incorporation* (European vs. non-European). We further control for the size of the originator by including indicator variables for originators involved in fewer than five development projects, originators involved in five to 19 development projects and originators involved in 20 projects or more over the observational period. These categories approximately reflect the 33% and the 66% quantiles of the size distribution.

Opponent characteristics

Characteristics of the opposing party may also affect opposition outcomes (Harhoff and Reitzig, 2004; Harhoff et al., 2016). Therefore, we likewise control for the opponent's *sector* (corporate entity or not) and the *place of incorporation* (Europe or not). Oppositions can be filed by multiple independent parties. We include a variable capturing the *number of opponents*. In case of multiple opponents, we set the respective indicator to one if at least one party is a corporate entity or European.

Patent characteristics

Drugs typically are surrounded by more than one patent 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. We are further able to distinguish *primary patents* linked to a drug from secondary patents (see Section 2).

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

[19] Pre-clinical phase serves as reference group.

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

In order to further characterize a patent beyond these value indicators, we also 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*. Furthermore, we 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 45,918 unique drug candidates with non-truncated development information (column 1, Table 1). About one third (14,201) 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 890 unique drugs candidates (column 4, Table 1).

Table 1 presents summary statistics of selected drug and patent characteristics for the different subsamples of the Cortellis data. Judging on observables, our final sample is skewed towards high-value drugs. Most importantly, the number of different patent families associated with a drug is an indicator of a drugs 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 20.03 different patent families and drugs in our final sample (opposition decision prior to project termination) by 26 different patent families, see columns 3 and 4 of Table 1. Compared to an average of only 5 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 55% in the final sample but only 15% for all drugs with a patent link. This difference is an additional sign of a positive association between opposition and value. Finally, drugs with opposed

Table 1: Drug characteristics

	(1) All drugs $N = 45,918$		(2) All drugs with patent link $N = 14,201$		(3) All drugs with opposition $N = 1,769$		(4) All drugs in final sample $N = 890$	
Drug-level	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Drug characteristics								
Biologic (d)	0.31	0.46	0.33	0.47	0.40	0.49	0.43	0.50
Drug discovery (yr)	2003.25	6.74	2000.58	6.97	1996.09	6.31	1996.88	5.75
Latest development (yr)	2008.39	5.23	2009.14	5.46	2008.13	6.19	2010.95	4.90
Approval in at least one indication (d)	0.05	0.23	0.15	0.36	0.55	0.50	0.56	0.50
Number of indications	1.81	2.03	2.68	3.23	4.01	5.65	5.43	7.14
Number of indications (in sample)							2.94	3.77
Patent protection								
Number of inpadoc families			5.05	17.26	20.03	44.19	26.06	57.88
Number of opposed patents			1.31	13.29	10.54	36.34	16.90	50.04
Number of invalidated patents			1.03	10.83	8.26	29.69	13.44	40.92

Notes: "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 final sample" refers to all non-pending drug projects within at least one opposition case decided before market approval.

patents have been tested against 4.01 different indications on average compared to 2.68 indications for drugs with known patent link.[20] These differences are partly driven by cohort effects, as drugs associated with opposed patents are on average older in terms of discovery year. However, value may also constitute an important additional determinant of differences in observed patent characteristics and selection into opposition. Existing literature argues that patents attached to valuable projects are significantly more likely to be opposed (Harhoff and Reitzig, 2004; Harhoff et al., 2016). This selection towards more valuable projects renders our results conservative. Granted companies put more effort in 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

As described above, a given drug's efficacy is typically tested against multiple indications independently. Table 2 reports how different drugs progress through the development funnel at the level of drug-indication project. In total, Cortellis contains 75,840 different non-pending drug-indication-

[20] Drugs in our final sample have been tested against 5.65 different indications. Note that we exclude development histories where the opposition outcome is observed only before project start or after its termination. The final sample therefore contains only an average of 2.94 indications per drug.

Table 2: Project advancement at the drug-indication-level by sample

	(1) All drugs $N = 75,840$		(2) All drugs with patent link $N = 32,560$		(3) All drugs with opposition $N = 6,123$		(4) All drugs in final sample $N = 2,613$	
Drug-indication-level	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Highest stage reached:								
Pre-clinical	0.64	0.48	0.40	0.49	0.18	0.38	0.18	0.38
Phase I (d)	0.11	0.31	0.14	0.35	0.09	0.29	0.10	0.30
Phase II (d)	0.14	0.35	0.25	0.43	0.25	0.44	0.32	0.47
Phase III (d)	0.04	0.20	0.07	0.26	0.11	0.32	0.15	0.36
$\sum$ *Terminated (d)*	*0.93*	*0.25*	*0.86*	*0.35*	*0.64*	*0.48*	*0.75*	*0.44*
Approved (d)	0.07	0.25	0.14	0.35	0.36	0.48	0.25	0.44

Notes: "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 could be identified. "All drugs with at least one 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 within at least one opposition case decided before market approval.

level projects (each of the different 45,918 drug candidates is associated with an average of 1.81 different indications) out of which about 7% are approved on the market while 93% are terminated before approval. The majority of cases (64%) of all drug-indication-level projects is terminated after the pre-clinical phase, so before major investments in clinical trials are due.

Attrition patterns, however, differ across subsamples. Development projects with patent link are characterized by higher approval rates (15%) and get terminated at later stages compared to the population of non-pending projects. The share of approved development projects associated with at least one opposed patent is even higher (36%) with project termination primarily taking place during clinical trials, in particular after phase II trials. These differences can at least partially be attributed to cohort effects. Opposition has to be initiated within nine months after patent grant and projects terminated before opposition outcome are by definition excluded from these statistics.

Finally, while the timing of project termination in our final sample (decision on opposition before termination) follows a similar pattern of comparably late termination, average approval rates are lower compared to all projects with opposition (25% vs. 36%, see columns 4 and 3 of Table 2 respectively). We suspect that higher approval rates for development 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. Krieger (2017), for instance, provides a decision model in which firms update their expectations on future profits based on signals they receive at each stage of a project's advancement through different test phases. Patent invalidation is a negative signal and likely lowers anticipated future profits as well as a firm's willingness to continue to invest. For the

majority of all projects with opposed patents in our sample opposition outcomes are communicated only after investment decisions have been made and development has been completed. In case opponents select promising projects, a higher approval rate for these cases can be expected. In contrast, if opposition outcomes are communicated while development is still ongoing (our final sample) companies can update their beliefs on future profits before making investment decisions. If patent invalidation reduces the duration of market exclusivity and hence lowers the expected profits, continuation becomes less likely.

4.2 Patent invalidation and development outcomes

We present descriptive evidence on how patent invalidation in opposition proceedings affects drug development outcomes. In Table 3, we report project progress at the drug-indication level for all development projects associated with at least one opposed patent and for development projects in our final sample. We further distinguish whether the opposition led to the invalidation of at least one patent or not.

Similar to Table 2, we find striking differences between our final sample (opposition outcome before project termination) and projects tied to at least one opposed patent. First, projects with at least one patent invalidation before project termination lead to final drug approval in 24% of cases (column 6, Table 3). In contrast, if no patent was invalidated, average approval rates are significantly higher with 36% (column 5, Table 3). This supports our argument that patent invalidation reduces approval rates as the incentive to engage in costly development efforts is diminished. Second, and interestingly, in the more comprehensive sample of projects associated with at least one opposed patent (irrespective of the opposition outcome's timing, cf. columns 1 to 3 in Table 3), we observe the reverse effect: the share of projects that reach market approval is 32% if none of the opposed patents has been invalidated, but increases to 37% if at least one of the opposed patents has been invalidated. In the majority of these cases, the opposition outcome is known only after project termination or market approval. As argued above, we expect oppositions to have little effect on project outcomes if their outcome is communicated only after completion or termination of development. Higher approval rates in these cases are likely driven by opponent behavior. If a project is terminated before market approval there is little incentive for third parties to pursue invalidation efforts against associated patents. Such a behavior can explain the positive correlation between patent invalidation and drug approval in cases of opposition outcome after drug approval.

To further explore how the timing of the opposition outcome affects project success, we report the advancement through the development funnel for all projects in our final sample (drug-indication-level) in a life-table like fashion. Table 4 tabulates the development stage in which opposition was decided (rows) against the subsequent stages reached by the respective development projects (columns).[21] The top part of Table 4 relates to projects where none of the opposed patents

[21] Due to the life-table logic, the most left number in each row of Table 4 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.

Table 3: Project advancement at the drug-indication-level by opposition outcome

	All drugs with opposition			All drugs in final sample		
	(1)	(2)	(3)	(4)	(5)	(6)
	All	No patent invalidated	≥ 1 patent invalidated	All	No patent invalidated	≥ 1 patent invalidated
Drug-indication-level	N=6,123	N=943	N=5,180	N=2,613	N=298	N=2,315
	mean	mean	mean	mean	mean	mean
Highest stage reached:						
Pre-clinical	0.18	0.22	0.17	0.18	0.17	0.18
Phase I (d)	0.09	0.11	0.09	0.10	0.10	0.10
Phase II (d)	0.25	0.23	0.26	0.32	0.21	0.33
Phase III (d)	0.11	0.12	0.11	0.15	0.15	0.15
$\sum$ *Terminated (d)*	*0.64*	*0.68*	*0.63*	*0.75*	*0.64*	*0.76*
Approval (d)	0.36	0.32	0.37	0.25	0.36	0.24

Notes: "All drugs with at least one 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 within at least one opposition case decided before market approval. Note that pending drug projects are excluded in all samples. Primary patents refer to all patents with a claim concerning the formulation or product to at least one drug.

has been declared invalid and the bottom half refers to those with at least one patent invalidation before project termination. We report final drug approval (last column) as well as the likelihood that the next stage in the development funnel is started after the communication of the opposition outcome. These are the dependent variables in the subsequent regressions (*approval* and *next stage*).

In total, our final sample contains 298 development projects where no underlying patent has been invalidated before project termination/approval with 108 (36.2%) of these cases leading to final approval in a given indication (first line of Table 4). For a subset of 150 projects, the opposition outcome "patent upheld" has been communicated while the drug was still in pre-clinical trials. The second line of Table 4 reports how these 150 projects advance through the development funnel with 60 projects (40.0%) 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 98 projects (65.3%).

Table 4 reveals differences in progress patterns for projects by opposition outcome. While early patent invalidations during pre-clinical trials do not have a different effect on the likelihood of taking the drug to the next stage, final approval rates of 25.4% are significantly lower compared to 40.0% 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 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 compared to situations in which

Table 4: 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	**298**	→							**108**	**36.2%**
Pre-clinical	150	*(65.3%)*	*98*		88		70		**60**	**40.0%**
Phase 1	–		30	*(30.0%)*	*9*		7		**6**	**20.0%**
Phase 2	–		–		54	*(20.4%)*	*11*		**7**	**13.0%**
Phase 3	–		–		–		64	*(54.7%)*	***35***	***54.7%***
At least one patent invalidated										
Total	**2,315**	→							**554**	**23.9%**
Pre-clinical	1,187	*(65.5%)*	*777*		689		412		**301**	**25.4%**
Phase 1	–		181	*(22.7%)*	*41*		19		**15**	**8.3%**
Phase 2	–		–		540	*(12.8%)*	*69*		**36**	**6.7%**
Phase 3	–		–		–		407	*(50.4%)*	***205***	**50.4%**

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.

invalidation is communicated before the start of phase III trials.

To summarize, the descriptive evidence presented above hints at a negative association between patent invalidation and the likelihoods of project continuation and final drug approval. In order to establish causality and to include the loss of exclusivity an originator company incurs in case of patent invalidation, we resort to a multi-variate regression framework. This allows us to relate the loss of exclusivity to project outcomes while controlling for additional sources of heterogeneity.

5 Multivariate analysis

5.1 Identification

Estimation approach

In our multivariate analyses we relate measures of intellectual property protection, most importantly the loss of exclusivity after patent invalidation in opposition proceedings, to the outcome of product commercialization. As our dependent variable is a binary variable indicating whether a drug candidate reaches marketing authorization (*approval*) or launches the next stage after the opposi-

tion case was decided for each drug development process (*next stage*), we report results from linear probability models at the drug-indication-level. 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 and originators' innovation incentives. To control for heterogeneity in the underlying drug development projects, originators and patents, we include a set of additional independent variables X as described above in our regressions.

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 signs of a drug's efficacy or potential market size) that affect (i) the effort put in 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 into the drug *Approval* equation.

Following Gaessler et al. (2017), we use the granting patent examiner's participation in the opposition proceeding as basis for instrumentation. Specifically, we instrument the opposition outcome (the *Invalidation* variable) as well as its interaction with *LoE* with the predicted probability of invalidation obtained from a probit model $\widehat{\text{Prob}(Invalidated)} = \Phi(\gamma_1 Examiner\ participation + \gamma X)$. 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). Based on

this reasoning we estimate the following two-stage model

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

Our instrument exploits variation in the participation of the patent examiner who initially granted the patent in the opposition division which decides on the opposition against a patent's validity. 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 rates is about 68% across all opposition proceedings at EPO, with continuous variation over time and technology fields. The variation in examiner participation rates has been described as a result of the non-availability of other examiners with expertise in the particular technology area (Gaessler et al., 2017). Figure A-2 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 rather follow a normal distribution around the overall participation rate. 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 have time to adjust their strategy during the opposition proceeding.

Table 5 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 indications per patent as weights and report standard errors clustered at the level of individual patents. In total, these regressions are based on 1,111 unique patents that are associated with an average of 4.81 different indications resulting in 5,344 observations. 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 5, column 2). Opposition

Table 5: Examiner participation and opposition outcome

	(1)	(2)	(3)	(4)
Estimation method	Probit	Probit	Probit	Probit
Dep var	Invalidated	Invalidated	Examin. partic.	Examin. partic.
Exam. participation (d)	−0.056**	−0.056***		
	(0.022)	(0.018)		
Potential LoE (in years)			0.001	0.002
			(0.005)	(0.005)
Approval (d)			0.039	
			(0.031)	
Next stage (d)				0.019
				(0.030)
Drug characteristics	No	Yes	Yes	Yes
Development characteristics	No	Yes	Yes	Yes
Patent characteristics	No	Yes**	Yes**	Yes**
Technology effects	No	Yes	Yes*	Yes*
Disease effects	No	Yes***	Yes*	Yes*
Examination characteristics	No	Yes	Yes	Yes
Age effects	No	Yes	Yes	Yes
Originator characteristics	No	Yes*	Yes	Yes
Opponent characteristics	No	Yes***	Yes	Yes
Year effects	No	Yes***	Yes***	Yes***
Model degrees of freedom	1	110	110	110
χ^2-statistic	6.6	390.3	277.3	274.6
Pseudo-R^2	0.005	0.187	0.125	0.124
Observations	5,344	5,344	5,327	5,327
Observations (weighted)	1,111	1,111	1,105	1,105

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. Columns (3) and (4) show 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. 17 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 indications per patent. Significance levels: * p<0.1, ** p<0.05, *** p<0.01.

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 dependent variables as well as key explanatory variable *LoE*, but also to various other aspects of the opposition proceeding, including characteristics of the drug, the originator or the opponent. We therefore feel confident to use examiner participation as instrument for patent invalidation in the main regressions presented in the following section.

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 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 unrelated to a drug's (social) value and its chance of market approval. In fact, patent invalidation in opposition proceedings at the EPO are results of a lack of novelty, insufficient inventive step, insufficient disclosure of the invention or undue broadening of the patent scope beyond the initial application. These criteria are not related to a drug's efficacy and toxicity which ultimately determine its value. 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. Again, 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 Main Results

We use examiner participation as instrument in a set of regressions in which we highlight different facets of the relation between a loss of exclusivity due to patent invalidation and the outcome of drug commercialization projects. Before discussing the results in detail, we provide an overview of the main findings. First, we focus on drug approval as dependent variable in Table 6. Our findings suggest that the likelihood of drug approval is lowered by patent invalidation but the estimate is imprecise. Specifications including the interaction between patent invalidation and the loss of exclusivity indicate that an increase in the loss of exclusivity leads to significant reductions of the likelihood of drug approval. We find a comparable pattern for project continuations (see Table 7). In these specifications, patent invalidation lowers the chances of a project entering the next stage after the opposition outcome, however the respective coefficient estimates are not significant. Including measures of the loss of exclusivity reveals that the likelihood of continuation is not affected by patent invalidation *per se* but again is determined by the resulting loss of exclusivity. 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 stronger negative effect on commercialization outcomes compared to later stages where we do not find a significant effect (see Table 8). Third, we split our sample between small and medium/large originator companies in order to capture firm size differences. We find evidence for differential effects of patent invalidation as only medium/large originators are more likely to abandon projects in the face of a reduction in the duration of market exclusivity while we do not find a similar effect for smaller originators (see Table 9). Finally, and more tentatively, we address the question whether patent invalidation affects aggregate inventive activity in a given

therapeutic area. Looking at the number of new drug projects within three years after the focal drug was subject to patent opposition, we do not find a significant effect of patent invalidation (or the realized loss of exclusivity) on aggregate inventive activity (see Table 10). We discuss these findings in detail below.

Drug approval and project continuation

In Table 6, we report results from different regression specifications in which we relate patent invalidation and the induced loss of exclusivity to market approval as dependent variable using both linear probability models and linear IV estimators. In the first two columns of Table 6, we do not account for the exact loss of exclusivity that results from patent invalidation but focus on the effect of patent invalidation. The OLS estimate of the effect of patent invalidation on drug approval is statistically indistinguishable from zero. Instrumenting invalidation renders the effect negative albeit only at a significance level of 10%. This difference might be driven by unobserved variables (such as early signs of efficacy or commercial attractiveness of an indication) that affect patent invalidation and drug approval similarly thus leading to an upward bias in the OLS estimate.

The negative effect of patent invalidation on market approval is a first indication that originator companies put less effort in commercializing a drug candidate once patent protection has been weakened. When interpreting these results we need to consider that the estimated coefficients do not relate to the actual loss of exclusivity due to patent invalidation and that – in case of patent invalidation – the implied loss of exclusivity varies considerably across projects. As we have argued above, 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 deteriorate the legal position of the originator company. The estimated coefficients of patent invalidation presented in columns 1 and 2 of Table 6 therefore do not reflect the effect of a loss of exclusivity, which likely explains the high standard errors of the coefficient estimates.

In the remaining four columns of Table 6, we therefore consider the effect of the loss of exclusivity on the likelihood of successful product commercialization. In a first coarse specification, we simply interact patent invalidation and an indicator variable equaling one if the expected patent term exceeds the duration of data exclusivity at approval (*Potential LoE* > 0) and zero otherwise. *Potential LoE* > 0 implies that patent invalidation reduces the expected duration of market exclusivity. Interacting *Potential LoE* > 0 with the patent invalidation dummy therefore identifies all cases in which an originator's expected duration of market exclusivity has been reduced due to patent invalidation. The regression specifications including this interaction term reveal that patent invalidation alone does not affect commercialization outcomes as its coefficient becomes insignificant. Only invalidations that lead to an actual loss of exclusivity have a negative and significant effect on approval as indicated by the negative coefficient of the interaction term (see Table 6, columns 3 and 4). Again, the IV estimates point to a stronger effect and are more precisely estimated.

In order to fully quantify how a loss of exclusivity affects the likelihood of successful drug com-

mercialization, we include the potential loss of exclusivity measured in years (LoE) and its interaction with patent invalidation in the regressions (Table 6, columns 5 and 6). While not significant in the OLS regression, we find a significant negative coefficient of the interaction term after instrumentation which indicates that a realized loss of exclusivity leads to a reduction in the likelihood of drug approval. As before, patent invalidation alone has no significant effect. The results from the instrumented regression suggest that a one-year reduction of expected market exclusivity reduces the likelihood of drug approval by 3.9 percentage points. This an economically meaningful effect given that average likelihood of successful drug commercialization in our sample is only 25.4% at the drug-indication-level. We argue that firms reduce their commercialization efforts as response to *ceteris paribus* lower expected profits.

All regression specifications include a comprehensive set of control variables capturing characteristics of the drug, the development project, the originator, the opponent, the underlying patent as well as time and disease fixed effects.[22] 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. Furthermore, we find heterogeneity in approval rates across disease areas.[23]

In Table 7, we model the probability that a given development project starts the next development stage after the opposition case was decided. The results regarding the likelihood of project continuation are comparable to the findings obtained in models of market approval as reported in Table 6 above. Patent invalidation alone does not affect the likelihood of project continuation and the estimated coefficient of the *Invalidated* indicator is statistically indistinguishable from zero in all specifications presented in Table 7. As before, 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 (6) of Table 7 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 5.4 percentage points. Compared to an average continuation rate of 47.5% across all development stages, this again is an economically meaningful effect. These models of project continuation, however, do not take into account at what stage of a development project patent invalidation occurred. For this reason, we report results from specifications that account for the timing of patent invalidation in the following subsection.

[22] A comprehensive list of the control variables contained in the indicated groups can be found in Table B-1 in the appendix.

[23] Development projects concerning diseases of the respiratory system, of the skin and subcutaneous tissue, and of the musculoskeletal system and connective tissue have the highest approval rates.

Table 6: Impact of invalidation as opposition outcome on drug development (drug approval)

	(1)	(2)	(3)	(4)	(5)	(6)
Estimation method	OLS	IV	OLS	IV	OLS	IV
Dep var	Approval	Approval	Approval	Approval	Approval	Approval
Dep var mean:	0.254	0.254	0.254	0.254	0.254	0.254
Invalidated	−0.037	−0.202*	0.006	−0.046	0.003	−0.084
	(0.030)	(0.119)	(0.033)	(0.124)	(0.032)	(0.126)
Invalidated × Potential LoE > 0			−0.077*	−0.241**		
			(0.047)	(0.116)		
Potential LoE > 0			0.137***	0.276***		
			(0.047)	(0.105)		
Invalidated × Potential LoE (in years)					−0.015	−0.039**
					(0.010)	(0.017)
Potential LoE (in years)					0.022**	0.041***
					(0.009)	(0.015)
Drug characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes**	Yes**	Yes**	Yes**	Yes***	Yes**
Technology effects	Yes*	Yes	Yes*	Yes*	Yes*	Yes*
Disease effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Examination characteristics	Yes	Yes	Yes	Yes	Yes	Yes
Age effects	Yes*	Yes*	Yes	Yes	Yes*	Yes**
Originator characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Opponent characteristics	Yes	Yes	Yes	Yes	Yes	Yes
Year effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Underidentification test		33.7		36.0		31.0
Weak identification test		47.1		24.6		21.6
Observations	5,344	5,344	5,344	5,344	5,344	5,344
Observations (weighted)	2,544	2,544	2,544	2,544	2,544	2,544

Notes: Columns (1) and (2) as well as (3) and (4) provide a comparison between the OLS and the 2SLS regressions for the impact of invalidation on drug development (here: approval) when accounting for the actual loss of exclusivity. Columns (1) and (2) include an interaction term capturing in binary form all cases with non-zero loss of exclusivity. Columns (3) and (4) 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 7: Impact of invalidation as opposition outcome on drug development (next stage reached)

	(1)	(2)	(3)	(4)	(5)	(6)
Estimation method	OLS	IV	OLS	IV	OLS	IV
Dep var	Next stage	Next stage	Next stage	Next stage	Next stage	Next stage
Dep var mean:	0.475	0.475	0.475	0.475	0.475	0.475
Invalidated	−0.023	−0.185	0.043	0.085	0.020	0.013
	(0.033)	(0.126)	(0.044)	(0.129)	(0.036)	(0.136)
Invalidated × Potential LoE > 0			−0.100*	−0.430***		
			(0.055)	(0.114)		
Potential LoE > 0			−0.077	0.199**		
			(0.050)	(0.099)		
Invalidated × Potential LoE (in years)					−0.016*	−0.054***
					(0.009)	(0.015)
Potential LoE (in years)					−0.022**	0.009
					(0.009)	(0.014)
Drug characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Technology effects	Yes	Yes	Yes	Yes	Yes	Yes
Disease effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Examination characteristics	Yes	Yes	Yes	Yes	Yes	Yes
Age effects	Yes	Yes	Yes	Yes	Yes	Yes
Originator characteristics	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Opponent characteristics	Yes	Yes	Yes*	Yes*	Yes	Yes
Year effects	Yes***	Yes***	Yes***	Yes***	Yes***	Yes***
Underidentification test		33.7		36.0		31.0
Weak identification test		47.1		24.6		21.6
Observations	5,344	5,344	5,344	5,344	5,344	5,344
Observations (weighted)	2,544	2,544	2,544	2,544	2,544	2,544

Notes: Columns (1) and (2) as well as (3) and (4) provide a comparison between the OLS and the 2SLS regressions for the impact of invalidation on drug development (here: next stage) when accounting for the actual loss of exclusivity. Columns (1) and (2) include an interaction term capturing in binary form all cases with non-zero loss of exclusivity. Columns (3) and (4) 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.

Timing of invalidation

When developing new drugs, originator companies face a sequential decision making process. Having completed a given stage of the development funnel, originators have to decide whether investments in further development are made. At each decision point, firms update their beliefs on the likelihood of success based on the data gathered in previous tests as well as expected future profits conditional on reaching market approval (Krieger, 2017). The outcome of opposition proceedings removes uncertainty regarding the expected duration of market exclusivity and hereby also regarding future profits. Originators may learn about the opposition decision at early stages of the development funnel or at later stages. As a comprehensive model of originators' staged decision making is beyond the scope of this study, we refrain from *a priori* predictions on whether originators react stronger to opposition decisions at early or later stages of drug development. Instead, we present empirical evidence from regression analyses that take timing into account.

In Table 8, we provide IV regression results where we examine how patent invalidation at different stages of the development process affects the probability that a drug candidate reaches approval (columns 1 and 2) or starts the next stage after the opposition case was decided (columns 3 and 4). For this purpose, we split the sample in development projects with opposition decisions during pre-clinical/phase I trials and projects with opposition decisions during phase II/phase III trials. About 65% of the projects in our final sample had the opposition outcome of the underlying patent(s) during pre-clinical/phase I trials and 35% at later stages.

Similar to the main results presented in Tables 6 and 7, patent invalidation alone has no effect on the likelihood of approval or project continuation irrespective whether the opposition outcome was communicated during pre-clinical/phase I trials or later. Timing does matter, however, for the effect of the realized loss of exclusivity (interaction effect). 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 and stronger than the effect of late invalidations. 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 5.9 percentage points. Compared to the unconditional approval and continuation rates of 25.1% and 55.8% respectively, these effects are meaningful in terms of magnitude.

5.3 Extensions

Originator size

There is an ongoing debate to what extent innovation incentives from IP rights are more important for small companies than for large ones (Galasso and Schankerman, 2018). Although not a central question of our paper, we can draw further insights into the role of IP rights for companies of different sizes in drug development. For this purpose, we split our sample into originator companies with less than five development projects reported in Cortellis during our observational period (*small originator*) and companies with five and more development projects (*medium/large originators*).

Table 8: Impact of invalidation as opposition outcome on drug development – by development stage at opposition outcome

	(1)	(2)	(3)	(4)
Estimation method	IV	IV	IV	IV
Dep var	Approval	Approval	Next Stage	Next Stage
Sample (by development stage)	Pre-clinical/Phase I	Phase II/III	Pre-clinical/Phase I	Phase II/III
Dep var mean	0.251	0.260	0.558	0.299
Invalidated	−0.176	−0.013	0.013	0.012
	(0.152)	(0.226)	(0.160)	(0.256)
Invalidated × Potential LoE (in years)	−0.046**	−0.016	−0.059***	−0.014
	(0.020)	(0.027)	(0.019)	(0.029)
Potential LoE (in years)	0.060***	−0.011	0.010	−0.022
	(0.018)	(0.024)	(0.016)	(0.025)
Drug characteristics	Yes***	Yes*	Yes***	Yes
Development characteristics	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes**	Yes	Yes***	Yes
Technology effects	Yes	Yes***	Yes	Yes***
Disease effects	Yes**	Yes***	Yes***	Yes***
Examination characteristics	Yes*	Yes	Yes**	Yes
Age effects	Yes***	Yes	Yes	Yes
Originator characteristics	Yes***	Yes	Yes***	Yes
Opponent characteristics	Yes	Yes	Yes	Yes
Year effects	Yes***	Yes***	Yes***	Yes***
Underidentification test	26.2	15.8	26.2	15.8
Weak identification test	18.4	8.2	18.4	8.2
Observations	3,809	1,535	3,809	1,535
Observations (weighted)	1,652	892	1,652	892

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. 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.

About 37% of the projects in our sample are associated with small originators while the majority of 63% with large originators. Table 9 reports IV regression results for the two subsets of companies.

First, we model drug approval (project continuation) for small and medium/large originators in columns 1 and 2 (columns 3 and 4) of Table 9. While overall the direction of the effects of patent invalidation as well as the induced loss of exclusivity is comparable to the results in Tables 6 and 7, we do find differences by originator size. Our findings suggest drug candidates associated with small originators are less likely to be approved if an underlying patent is invalidated albeit the effect is significant only at the 10% level. The actual loss of exclusivity has no significant effect for small originators (see column 1 of Table 9). In contrast, projects of medium/large originators are not affected by patent invalidation *per se* but by the realized loss of exclusivity. Here, a one-year reduction in exclusivity lowers the likelihood of drug approval by about 5.7 percentage points. Second, immediate continuation decisions after the opposition decision are not affected by patent invalidation or the induced loss of exclusivity for small originators and all estimated coefficients are insignificant (see column 3 of Table 9). In contrast, a one year loss of exclusivity due to patent invalidation lowers the likelihood that medium/large originators continue a project by approximately 6.9 percentage points.

Taken together, these results imply that the effects identified in our main regressions in Tables 6 and 7 are largely driven by large originators' reactions to a reduction in the duration of market exclusivity due to patent invalidation. Portfolio considerations are a potential explanation of size differences with large originators by definition having a larger pipeline of development projects and being more willing to abandon a given project in favor of an alternative candidate. In contrast, small originators may not have alternatives and therefore be reluctant to give up a project. Also, experience may explain the size differences. Large firms with more experience in bringing drugs to the market may be more capable to apprehend the full effect of patent invalidation and the implied loss of exclusivity than inexperienced firms. Independent of the underlying mechanism, these findings are important as they add to a growing literature concerned about differential effects of IP rights for small and large companies. Most recently, Galasso and Schankerman (2018) use a similar identification strategy based on instrumenting patent invalidation and report that small and medium sized companies significantly reduce their innovation efforts after patent invalidation whereas large firms are not affected. Their study focuses on patenting activities in a five year time-window after patent invalidation as an indicator of innovative activities. Our findings highlight a different aspect. Conditional on having started a development project, small originators are less likely to reduce their innovation efforts after patent invalidation in comparison to larger ones. In this regard, our findings complement Galasso and Schankerman (2018), who focus on the impact of patent invalidation on new projects whereas we focus on completion of existing projects.

Aggregate inventive activity

Patenting may not only affect the focal originator's innovation efforts but also innovation activities by competitors. We present empirical evidence linking patent invalidation after opposition to subse-

Table 9: Impact of invalidation as opposition outcome on drug development – by originator size

	(1)	(2)	(3)	(4)
Estimation method	IV	IV	IV	IV
Dep var	Approval	Approval	Next Stage	Next Stage
Sample (by originator size)	Small	Medium/Large	Small	Medium/Large
Dep var mean	0.207	0.282	0.434	0.499
Invalidated	−0.258*	0.137	−0.185	0.300
	(0.145)	(0.187)	(0.176)	(0.183)
Invalidated × Potential LoE (in years)	−0.017	−0.057***	−0.026	−0.069***
	(0.028)	(0.019)	(0.026)	(0.016)
Potential LoE (in years)	0.036	0.051***	−0.006	0.020
	(0.025)	(0.017)	(0.022)	(0.015)
Drug characteristics	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes***	Yes***
Patent characteristics	Yes***	Yes***	Yes***	Yes***
Technology effects	Yes***	Yes**	Yes**	Yes***
Disease effects	Yes*	Yes***	Yes***	Yes***
Examination characteristics	Yes	Yes	Yes	Yes
Age effects	Yes**	Yes***	Yes***	Yes
Originator characteristics	Yes***	Yes*	Yes***	Yes
Opponent characteristics	Yes*	Yes	Yes	Yes**
Year effects	Yes***	Yes***	Yes***	Yes***
Underidentification test	19.1	20.7	19.1	20.7
Weak identification test	14.7	13.4	14.7	13.4
Observations	1,899	3,445	1,899	3,445
Observations (weighted)	946	1,598	946	1,598

Notes: Columns (1) to (4) 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 (1) and (3) include drug projects only if the drug originates from small entities. Likewise, the samples used in columns (2) and (4) include drug projects only if the drug originates from medium-sized or 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.

quent aggregate innovative activity in a given therapeutic area. Separating therapeutic indications should enable us to identify whether patent invalidation increases the number of drug candidates that are tested within this indication. It will not enable us, however, to disentangle whether this effect comes from competitive effects or increased freedom to operate. On the one hand, patent invalidation increases the chances of project abandonment making the market more attractive for other originators which anticipate less competition. On the other hand, patent invalidation might facilitate follow-on innovation as it increases freedom to operate.

In Table 10, we present the results from both OLS and IV regressions in which we use the total number of new drug candidates that entered pre-clinical trials within three years after patent invalidation as our dependent variable. We interpret the total number of new drug candidates as a measure of aggregate innovative activity in a given therapeutic area and regress it on a set of explanatory variables, most importantly patent invalidation and the realized loss of exclusivity.

The results from these regressions (see Table 10) reveal a strong intertemporal correlation of innovation activity within given indications. The coefficient on the total number of new drug candidates that entered pre-clinical trials within three years *before* opposition outcome is positive and highly significant. A 10% increase in the number of new drug candidates before opposition outcome is associated with a robust 9.2% increase *after* opposition outcome in a given indication. Moreover, the IV estimates in Table 10, column 2, highlight a decrease in the overall number of new drug projects within three years after a patent has been invalidated as the coefficient on patent invalidation is negative and significant. Our first – and tentative – interpretation of this effect is that companies active in a given therapeutic area anticipate difficulties in obtaining strong protection rights for their own inventions and therefore reduce their own activities. A related argument has been made in Krieger (2017) who studies what companies learn from project failures of competitors in the same therapeutic area. He finds that project abandonment after phase II trials increases the likelihood that competitors relying on related technologies are more likely to stop own ongoing projects. Note, however, that our specification is very coarse as we control for neither competitor characteristics nor market structure. Moreover, once we include the potential loss of exclusivity and its interaction with invalidation into the regression, this result becomes insignificant.

5.4 Robustness tests

Our regressions are based on several assumptions regarding the regression models we use. In order to assess the robustness of our results against deviations from these assumptions, we conduct comprehensive robustness tests. We briefly summarize the results from these additional regressions. The full set of results can be obtained from the authors upon request.

First, we replicate the regressions presented above but employ biprobit models in order to account for the binary nature of the outcome variable while still instrumenting patent invalidation. Our results are qualitatively comparable and the coefficients are estimated with higher precision. Equally, results from unweighted regressions are comparable with the results reported above.

In a second set of robustness tests, we focus only on the first indication a drug candidate is tested

Table 10: Impact of invalidation as opposition outcome on new drug project for same indication

	(1)	(2)	(3)	(4)
Estimation method	OLS	IV	OLS	IV
Dep var	log(Number of drug candidates (3 years after))			
Invalidated	0.018	−0.258**	0.026	−0.221
	(0.029)	(0.127)	(0.035)	(0.136)
log(Number of drug candidates (3 years before))	0.924***	0.924***	0.924***	0.923***
	(0.010)	(0.010)	(0.010)	(0.010)
Invalidated × Potential loss (in years)			−0.003	−0.014
			(0.009)	(0.017)
Potential loss (in years)			0.012	0.021
			(0.008)	(0.014)
Drug characteristics	Yes***	Yes***	Yes***	Yes***
Development characteristics	Yes***	Yes***	Yes**	Yes**
Patent characteristics	Yes**	Yes**	Yes**	Yes**
Technology effects	Yes	Yes	Yes	Yes
Disease effects	Yes*	Yes*	Yes*	Yes**
Examination characteristics	Yes	Yes	Yes	Yes*
Age effects	Yes**	Yes**	Yes**	Yes**
Originator characteristics	Yes	Yes	Yes	Yes
Opponent characteristics	Yes**	Yes**	Yes**	Yes**
Year effects	Yes***	Yes***	Yes***	Yes***
Underidentification test		34.0		31.5
Weak identification test		47.9		22.0
Observations	5,344	5,344	5,344	5,344
Observations (weighted)	2,544	2,544	2,544	2,544

Notes: Columns (1) and (2) show 2SLS regressions for the impact of invalidation on the number of new drugs for the same indication. 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.

against and reduce the sample to the first indication for each drug candidate. In these specifications, we can rule out that our findings are driven by originators' decisions whether to reposition a drug in additional indications depending on patent invalidation. Focusing on first indications exclusively, our results remain largely unchanged albeit the precision of the estimates is lower due to the reduced sample size.

Finally, we restrict the analyses to primary patents only. In the regressions reported above, we included all patents that were at risk of invalidation before project completion/termination irrespective of whether they protect the active ingredient of a drug (molecule) or some peripheral aspect, such as the dosage or the means of drug delivery. The results obtained from regressions based on primary patents exclusively are comparable to key findings presented in the main regressions above. Due to the reduced sample size, the precision of some estimates is reduced.

6 Discussion and Conclusion

We estimate 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 significantly reduces the likelihood of successful drug commercialization. In particular, the loss of one year of market exclusivity reduces the likelihood of drug approval in our sample by 3.9%. This result is in line with survey results from Mansfield (1986), who finds that 60% of pharmaceutical products would not have been introduced if patent protection could not have been obtained at all. Our data allows us to further disentangle this effect. We find that early loss of exclusivity has a stronger impact compared to a loss at later stages of the drug development process. Moreover, the negative effect of a loss of exclusivity on the likelihood of successful drug commercialization is driven by medium/large originators whereas small originators seem much less affected.

This finding is consistent with a broad range of theoretical models that argue that intellectual property rights create incentives for innovation by allowing companies to charge monopoly-like prices during the limited period of market exclusivity granted at market entry. Shorter periods of market exclusivity reduce expected profits and therefore lower the incentives to engage in innovation activities. Our paper contributes to this line of research by providing a direct causal link between changes in the duration of market exclusivity and innovation outcomes that has so far not been exploited.

The findings of this study bear important implications for practitioners and policy makers alike. In particular, the ongoing discussion on the design of data exclusivity in the pharmaceutical industry can be informed by our findings. We find that loss of exclusivity lowers the chances of successful drug

commercialization. If a drug candidate, however, has socially desirable characteristics, the erosion of private incentives goes hand in hand with welfare loss as we see fewer drugs entering the market. Data exclusivity may be one way to restore incentives for innovation as it increases the expected duration of market exclusivity – in particular after patent invalidation. However, data exclusivity as a policy instrument is not uncontested as it might limit follow-on innovation and cause redundant clinical trials. Moreover, our study is mute on the optimal duration of data exclusivity periods or how to derive them. Nevertheless, we provide a first quantification of innovators' responses to changes in the duration of market exclusivity as a function of data exclusivity and patent protection.

Finally, we also neglect questions pertaining to the competitive landscape originator companies are acting in. First, our models of project outcome do not include measures of market size, growth or the availability of competing original drugs and generics. Second, we do not consider the incentives to challenge a granted patent in opposition proceedings. Studying which companies, competing originators or generic manufacturers, have an incentive to engage in costly opposition proceedings is beyond the scope of this paper. Future research can complement our initial results by explicitly modeling competitive dynamics that affect opposition against an originator's patent(s) and subsequent development outcomes.

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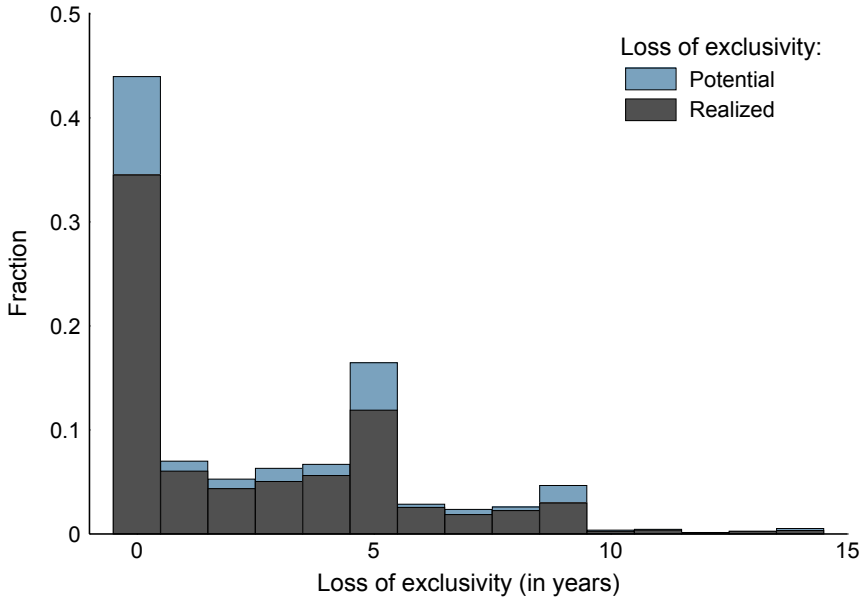
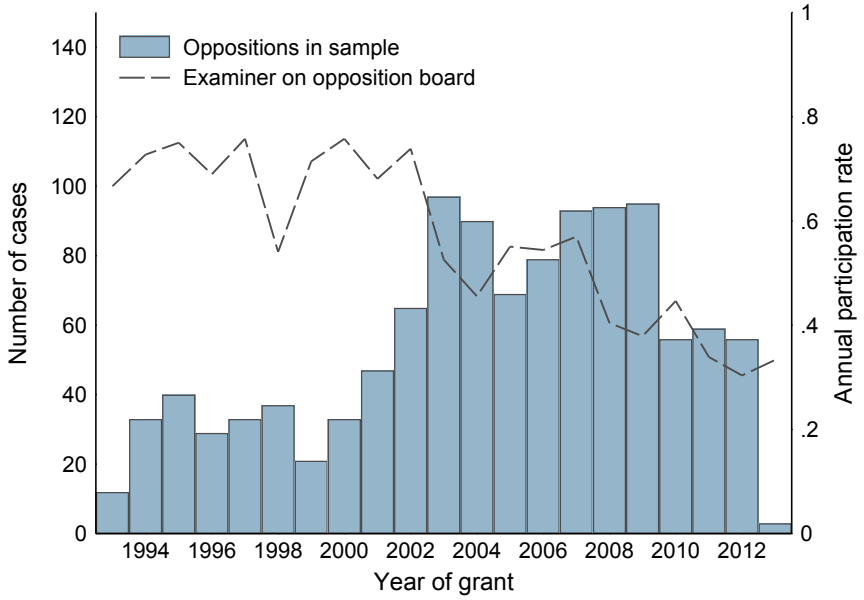
A Appendix: Figures

Figure A-1: Distribution of loss of exclusivity



Notes: This figure shows 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.

Figure A-2: 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.

B Appendix: Descriptive 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 year effects	Dummies for grant year
	Dummies for opposition outcome year
Patent age effects	Dummies for age in years
Technology effects	Dummies for technology class
	Dummy for biologics