STRATEGIC PATENTING: EVIDENCE FROM THE BIOPHARMACEUTICAL INDUSTRY

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Biological drugs account for just two percent of prescriptions filled in the U.S. but fifty percent of prescription-drug spending. To explore the role patents play in explaining high biologics prices, we build the first comprehensive database of patents associated with all FDA-approved biologics. We document robust evidence consistent with two patenting strategies that may block biosimilar competition: thicketing and evergreening, whereby firms supplement primary patents with a dense web of later-expiring patents on secondary drug features—e.g., drug formulations. Whether such strategies actually forestall biosimilar entry is ambiguous for a range of reasons. While it is difficult to construct a counterfactual to explore how much sooner competitors will enter absent such practices, we do demonstrate that the threat of biosimilar entry causes biologics manufacturers to build denser patent portfolios in the first place. For these purposes, we explore responses to a 2009 Act that created an abbreviated pathway for biosimilars to receive FDA approval. Finally, we simulate the degree to which the thickness of patent portfolios and the nominal patent lives of biologics are impacted (under certain assumptions) by various policy proposals currently under consideration.

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I. INTRODUCTION

In the United States, annual costs of prescription drugs exceeded $700 billion in 2023 (Tichy et al. 2024), accounting for 15% of total healthcare spending. Patents are thought to play a key role in explaining this level of spending, offering firms the potential to exclude competitors from the market. Of course, monopoly rents are a key purpose of the patent system, with the promise of such rents encouraging investments in research and development in the first place (Nordhaus 1969). However, there is a growing concern that brand-name manufacturers are strategically engaging in patent practices that allow them to benefit from periods of exclusivity in excess of socially desirable levels (Frakes and Wasserman 2023).

Key to understanding such strategic practices is the fact that most drugs approved by the Food and Drug Administration (FDA) are not simply associated with a single patent on the underlying molecule. Rather, manufacturers acquire multiple patents per drug, particularly with respect to "secondary" drug features, such as routes of administration, methods of use, devices, or manufacturing processes. Some of these additional patents may reflect true innovation along secondary dimensions (Frakes and Wasserman 2023). Some may not and may instead reflect attempts to take advantage of imperfect patentability screening at the U.S. Patent Office (Shapiro 2001).

One specific practice along these lines is known pejoratively as "evergreening," whereby a pharmaceutical firm seeks additional patents years after filing the primary patent (Kesselheim and Avron 2006; Hemphill and Sampat 2013). Given that patent terms run twenty years from filing, these later-filed patents expire later and thereby extend the exclusivity period of the relevant drug. Relatedly, firms may attempt to build "patent thickets" surrounding each drug (Hall et al. 2021). That is, brand-name manufacturers may build a dense web of patents for each drug to ensure that at least some patents survive legal challenges against the patent portfolio (Lemley and Shapiro 2005) and/or, generally, to

compound litigation- or licensing-related expenses for competitors wishing to navigate the associated web of patents. The full extent to which firms engage in these practices and their effects on blocking competitors' entry, however, remains unclear.

Much of what we know about the drug-patent landscape is based on research of "small-molecule" drugs. Such drugs possess simple molecular structures that can be easily reverse engineered—e.g., penicillin and Lipitor. Hemphill and Sampat (2011, 2013) fail to find evidence of substantial thicketing in the small-molecule marketplace, documenting a mean of only 2.7-3.9 patents per drug across different drug samples. Hemphill and Sampat (2013) do find evidence of evergreening behaviors, with secondary patenting extending nominal patent terms of drugs by roughly 3 years. However, they find that litigation challenges by generic manufacturers were effective at notably reining in such extensions.

We know much less regarding the patenting landscape associated with "large-molecule" drugs, also known as "biologics." Biologics have complex molecular structures, often consisting of proteins, antibodies, or cell-based therapies. They are much costlier to manufacture than small-molecule drugs, and, because they are derived from living organisms/cells, they are difficult to reverse engineer and impossible to replicate exactly. Given these replication challenges, biologics face potential competition from what are called "biosimilars," rather than generics—i.e., rather than bioequivalents.[1] There is reason to suspect that biologics may be associated with greater evergreening and thicketing practices given that the complexity associated with manufacturing and delivering biologics brings with it the greater potential for secondary patenting in the first place. A prominent example of a

[1] Throughout, we will refer to the original biologics drug as the "brand-name" and its associated producer as the "brand-name manufacturer." We use this terminology to facilitate comparisons between small- and large-molecule marketplaces. Technically, in the context of biologics receiving FDA approval, the original biologic goes by the term "reference product" and its associated manufacturer goes by the term "reference sponsor."

biologic is the blockbuster drug, Humira, which is used to treat rheumatoid arthritis and a host of other inflammatory conditions.

The little that we do know about biologics patents has come from studies that have attempted to map the patents associated with only the six highest revenue-generating biological drugs using a database developed by the Initiative for Medicines, Access & Knowledge (I-MAK). These studies do suggest a completely different picture between small-molecule and large-molecules drugs. For instance, demonstrating markers of both thicketing and evergreening, Harrow et al. (2024) find that these six biologics are associated with an average of 8 patents when approved by the FDA but an average of 41 patents 13 years after approval. However, Harrow et al. acknowledge that their results may not generalize to the hundreds of other large-molecule drugs that have been approved to date, which remain unstudied. Moreover, the largely descriptive analysis that they set forth fails to fully probe the consequences of, and the strategic nature of, such practices. Further, as we discuss below, the inclusion criteria used by I-MAK is arguably too broad to shed informative light on the blocking potential of biologic patent portfolios.

The literature's failure to offer a complete account of the patenting landscape of biologics and to address the resulting implications for competition is significant given what we do know about observed levels of pricing for biologics. A given biologic can cost a patient on average between $10,000 and $30,000 per year, with costs exceeding $500,000 for the most expensive biologics (Chen et al. 2018). Even with specialty and biologics drugs representing only 2% of prescriptions written (IQVIA 2019), spending on biologics represents close to 50% of net drug spending (IQVIA 2023). Evidence further suggests that biologics' share of overall drug spending will only increase in the years to come, with biologics spending growth rates far exceeding that of traditional / small-molecule drugs (IQVIA 2023).

Why do we know so little about the patents associated with biologics? The answer in part relates to the regulatory structure surrounding these markets. U.S. law has mandated since 1984 that brand-name manufacturers of small-molecule drugs disclose to the FDA patents that would be infringed if generics were to launch before the expiration of the relevant drug's patents. The FDA publicly disseminates the resulting patent lists in something known as the Orange Book.[2] The law works quite differently in the context of biologics. In 2020, Congress initiated a process by which the FDA would publish the Purple Book, a biologics counterpart to the Orange Book. However, the information to be disclosed pursuant to this 2020 Act is first triggered by what is effectively a voluntary process; moreover, the disclosure requirements do not cover all patents that could be potentially infringed by competitors. Our analysis actually demonstrates that the Purple Book identifies less than 1% of the relevant patents associated with approved biologics.

The result is that scholars that have made so much use of the Orange Book to learn about the small-molecule drug-patent landscape lack a corresponding patent reference to study the largest growing segment of the pharmaceutical industry. To fill this much needed gap, we build the first comprehensive patent database associated with all 515 FDA-approved therapeutic biologics. Our key inclusion criterion is to identify patents that would be infringed if a biosimilar were to enter the market to compete with the focal drug. We conduct structured searches of patent texts to identify possible patents associated with each FDA-approved biologic and then read each identified patent to assess it against the stated inclusion criteria, to code the relevant patent type (e.g., device patent), and to collect relevant additional information (e.g., patent expiration date). The resulting database consists of 11,595 drug-patent pairs.

[2] This research has been heavily used by researchers, including health and innovation economists, with the National Bureau of Economic Research housing archived versions of the Orange Book.

We next set forth preliminary evidence indicative of thicketing and evergreening behaviors, in each case using small-molecule patents as a benchmark. Biologic drugs are associated with substantially more patents per drug than small-molecule drugs: 27.7 versus 3.8, on average. Moreover, the extent to which subsequent patents prolong patent lives of drugs is substantially greater in the biologics context. For instance, the median number of years between the expiration date of a given biologic patent and the expiration date of the first-expiring patent associated with the relevant drug is 12 years, notably greater than the 2.7 year median for small-molecule drugs.

Are some (or many) of these biologic patents "strategic" as the relevant patent literature has come to use that term? That is, are they patents on less innovative ideas acquired to maximize rents associated with the entire drug product, as distinct from being acquired to recover the expenses associated with developing truly innovative secondary features of the drug? To explore this, we theorize that firms seeking to meet evergreening goals will make sure to secure new patents prior to the expiration of previous patents and as close as possible to the expiration of preceding patents (and even build thickets around these timing points—i.e., not rely on just single patents for such purposes). If firms were acquiring patents on truly innovative secondary drug features, they would be incentivized to do so as those innovations develop, which would not necessarily align at the precise timing points. Estimating event-study specifications in the window around the most salient preceding patent—the primary compound patent associated with the drug—we find evidence suggestive of strategic timing of subsequent patents.

All together, these findings suggest that biologics patent portfolios have the potential to meaningfully forestall entry by biosimilar competitors. Whether such an effect will occur in practice is theoretically ambiguous. After all, the high cost of showing biosimilarity and receiving FDA approval to enter as a biosimilar may be enough to deter entry. While the

competitive blocking effect of biologics patent portfolios is thus an empirical question, it is one that is inherently challenging to answer as it is difficult to construct a counterfactual without such portfolios. Despite this challenge, we do have the ability to answer a related question: was it the threat of biosimilar entry that caused biologics firms to amass the documented patent thickets in the first place?

To be sure, confronting questions of that latter nature is also inherently challenging in patent scholarship, as it is not straightforward to link patents to specific, potentially infringing products and to find plausibly exogenous shocks in the competitive or technological space that may increase the infringement threat (Righi and Simcoe 2022). In our case, we take advantage of an opportunity afforded to us by Congress in 2010 when it passed the Biologics Price Competition and Innovation Act (BPCIA), which created an abbreviated pathway for FDA approval of biosimilars and thus arguably originated the biosimilar marketplace. We find that in response to the creation of the biosimilar threat, biologics firms rapidly accelerated the degree to which they sought patents on existing biologics while finding no corresponding acceleration in the case of existing small molecule drugs.

The fact that we document such an increase in patenting in 2010 for already existing drug products provides further evidence—albeit only suggestive—of strategic behavior. After all, while it is possible that these additional patents were acquired to justify the marginal innovations associated with the relevant secondary drug feature, it is also possible that these patents were acquired to maximize the rents associated with an already existing innovation—i.e., the molecule / brand itself.

We also explore each of the inquiries discussed above separately by patent type. Should the evidence be reflective of strategic patenting—i.e., gamesmanship—one might predict to observe this more frequently with respect to patent types that are more amenable to fabrication. We predict this is more likely the case for device, formulation and

manufacturing patents, as opposed to compound and method of treatment patents, as it is difficult to strategically manipulate an innovation over a protein itself or over the clinical conditions treated by that compound. Indeed, we find systematic evidence that our various markers of strategic patenting are stronger for the predicted types.

Congress and the Patent Office have recently proposed various reforms aimed at curbing evergreening and patent thicketing practices. In a final exercise, we simulate the extent to which these various proposals (subject to certain assumptions) will actually diminish these practices.

Our paper proceeds as follows. In Part II, we offer a brief background on the biologics regulatory process. In Part III, we discuss the construction of the novel biologics patent database. In Part IV, we explore the thicketing and evergreening behaviors of biologics manufacturers. In Part V, we estimate the impact of the origination of the biosimilar threat on these patenting practices. In Part VI, we explore the effectiveness of certain policies aimed at reducing biologics patent thickets. In Part VII, we conclude.

II. Background: Pharmaceutical Regulatory Approval Process

The Hatch-Waxman Act of 1984 created an abbreviated pathway for generics to enter the small-molecule market. To receive FDA approval, generics need not replicate the clinical trials of brand-name drugs (demonstrating safety and efficacy), but, instead, need only demonstrate that their product is bioequivalent to the already FDA-approved small-molecule drug. Whether the generic receives FDA approval also turns on the status on the relevant patents held by the brand-name firm. The HWA requires the brand to provide the FDA with a list of patents that would be infringed if a generic is launched before the expiration of these patents, information which is ultimately included in an FDA publication commonly known

as the Orange List.[3] The FDA can approve the generic after all of the Orange-book listed patents expire or after a thirty month stay during which the generic and brand engage in specialized patent-dispute procedures, which often result in litigation.

The HWA of 1984 did not address the approval and patenting of biologics, perhaps due to the fact that scientists did not meaningfully begin to develop biological drugs until the 1970s. It was not until 2010, with the passage of the Biologics Price Competition and Innovation Act (BPCIA), that the FDA was empowered to develop an abbreviated pathway to approve biosimilars. Similar to the HWA, the goal of this pathway is to obviate the need for biosimilars to demonstrate safety and efficacy through their own clinical trials. However, certain critical differences exist between the HWA and its biologics counterpart, the BPCIA.

First, given the inherent replication challenges associated with biologics, biosimilars seeking approval must demonstrate that there are no clinically meaningful differences between the biosimilar and the original FDA-approved biologic. This demonstration of "biosimilarity" is a considerably more drawn-out and expensive process than that required to show bioequivalence in the generic small-molecule context (Attebury et al. 2019). Second, in contrast to the HWA, the BPCIA neither links FDA approval of biosimilars to the patent rights associated with biologics nor does it require biologic companies to provide patent information to the FDA upon the filing of license application.

Between the BPCIA and follow-on legislation passed in 2020, federal law does create certain patent-disclosure mechanisms for brand-name biologics, culminating with the FDA dissemination of something known as the Purple Book. However, the comprehensiveness of the Purple Book falls far short of that of the Orange Book for several reasons. First, such disclosures are produced though a complicated sequence of negotiations between the brand

[3] However, the HWA does not require the disclosure of manufacturing patents, a reflection of the fact that manufacturing processes are less critical to small-molecule drugs.

and biosimilar known as "the patent dance," but this process is itself only voluntary. Second, the original biologic firm does not need to disclose all the patents that cover its product, as is required in the small-molecule regime, but instead only those that it believes will be infringed by the *specific* biosimilar with which it is engaged in the "patent dance." It is possible that the originating firm might assert a different set of patents against another biosimilar.

Given these realities, there is a growing understanding that the Purple Book fails to provide meaningful information about the patent rights of biologics (Feldman 2024). Our analysis below demonstrates that the vast majority of biologics patents are not represented in the Purple Book.

III. Construction of Biologics Patent Database

One of the key implications of the regulatory structure set forth in Part II is that, while scholars have been able to take advantage of the Orange Book to study the small-molecule drug-patent landscape, they have been unable to benefit from a corresponding resource in the biologics context. To address this gap, we build a database of patents associated with 515 biologics licensed and approved by the FDA. Given that innovation incentives and markets differ considerably between preventives and treatments (Kremer and Snyder 2015), we focus our analysis on therapeutic biological drugs rather than vaccines, leaving the latter for the subject of future study.

Before discussing the search steps that we take to construct the biologics patent database, we first address the theoretical foundations underlying its scope.

A. Inclusion Criterion

The key inclusion criterion that we use to guide our selection of patents is as follows: we identify patents that would likely be infringed if a biosimilar were launched to compete with the focal drug product. Doing so, and consistent with the aims of our analysis, we

capture situations in which the included patent may have a meaningful competitive blocking effect in the relevant market. We do not wish to be overinclusive in this regard to avoid overstating the degree of market interference that biologics patent portfolios actually impose.

Indeed, this discussion is of relevance as not all patents acquired by brand-name firms meet the above inclusion condition. A frequent context in which this criterion fails is when a brand-name firm acquires a patent on a new indication but where the FDA has not approved that indication. To see this more clearly, let us consider several abstract scenarios, beginning with one where the criterion is, in fact, met.

Scenario 1. Consider a biologic, Drug X, that is FDA approved to treat rheumatoid arthritis and that is marketed by Firm A. Moreover, consider a patent held by Firm A that indicates rheumatoid arthritis as a method of use for Drug X. Assume Firm B seeks approval of Biosimilar Y to treat rheumatoid arthritis and demonstrates its biosimilarity to Drug X to the FDA. Though Biosimilar Y may receive approval to enter the market and compete with Drug X, such entry may be blocked by Firm A's assertion of its patent against Firm B. This patent has a meaningful biosimilar-blocking effect and will thus be included in our sample.

Scenario 2. Building on Scenario 1, now assume Firm A receives a patent claiming use of a novel dosage of Drug X to treat Crohn's disease. Further assume the FDA has not authorized Drug X at this new dosage to treat Crohn's. It is illogical to think of biosimilar entry (and thus infringement) for this drug/dosage combination to treat Crohn's, as there is no corresponding originator/reference biologic previously approved to treat Crohn's. In other words, the inclusion criterion fails in this scenario because there is no possible biosimilar that has relevance to this patent. Accordingly, this patent would not be included in our data.

Scenario 3. Continuing from Scenario 2, while no biosimilar can be approved to treat Crohn's—i.e., an abbreviated approval pathway is not possible—another firm may proceed through full clinical trials to get approval for the relevant drug/dosage combination for

Crohn's. Assume Firm C does so. In this event, the patent from Scenario 2 does have relevance as Firm A could sue Firm C for patent infringement. However, in this instance, we would no longer be discussing Firm A's patent blocking *biosimilar* entry, in which case this patent still fails the inclusion criterion. Rather, Firm C in this latter example would be considered an originator of a *new biologic*, not a biosimilar.

Discussion. We acknowledge that Scenario 3 only raises the question as to why we do not broaden our inclusion criterion to capture patents that not only block biosimilar entry but also block entry of new biologics. We elect not to extend matters this far as Firm A's patent is likely doing little direct work to discourage Firm C's entry in Scenario 3. That is, what is likely to block Firm C from actually entering this Crohn's market is not the threat of a patent infringement suit from Firm A, but instead the considerable expenses needed to conduct the relevant clinical trials showing safety and efficacy of using the relevant drug to treat Crohn's. Firm C is unlikely to undertake these expenses as (i) Firm C, by assumption, is not the party holding the relevant patent and thus lacks the ability to exclude biosimilars from competing against its new Crohn's biologic and (ii) Firm C cannot prevent physicians from prescribing Firm A's Drug X off-label for the treatment of Crohn's.

Putting this all together, to focus our attention on those biologics patents that may meaningfully forestall competition, we focus on those patents that are specifically relevant to *biosimilar* infringement. Moreover, to recap the point of the above demonstrations, when patents claim drug features that require FDA approval—e.g., new indications, routes of administration, etc.—and when the FDA has not approved such features, we exclude such patents.[4] On a final note regarding the reasonableness of these inclusion choices, we note that our decisions here largely track those taken by Congress in calling for the construction

[4] For similar reasons, if the FDA had only approved the biologic drug alone, we did not include combination patents that claimed an FDA-approved biologic to be used in combination with another chemical compound.

of the Orange Book in the small-molecule context, of course substituting "patents likely to be infringed by biosimilar entry" with "patents likely to be infringed by generic entry."

B. Search Process

To identify biologics patents meeting this criterion, we follow these steps: (1) identify patents listed in the FDA's Purple Book, (2) identify patents asserted in litigation in the United States (or at a Patent Trial and Appeal Board proceeding) in relation to any FDA-approved therapeutic biologic, (3) conduct structured patent searches utilizing Orbit Intelligence patent analytic and search software (discussed further below).[5] The patents captured in the first two steps are immediately included in our data as patents identified through these steps ostensibly capture patents that would be infringed by entering biosimilars.[6] However, the vast majority (over 90%) of the biologics patents that we identify are produced through the third step, where no such straightforward means of assessing the suitability of the patents for our database exists.

Indeed, a key challenge in implementing this search is that public patent documents do not contain text fields that directly speak to our inclusion criterion. For instance, imagine that a search over Humira's chemical name "adalimumab" flags a patent with "adalimumab" in its claims text. It would be inaccurate to include that patent as a Humira patent if a careful read reveals that the claims speak to using adalimumab in ways not authorized by the FDA. Relatedly, it would be inaccurate to include the patent in our database if a careful read reveals that adalimumab was not actually the functional subject of the claims.

[5] One benefit of Orbit Intelligence software is that it allows for the easy grouping of assignees of patents based on the responsible corporate entity—i.e., the entity that filed the biologics license application, including all subsidiaries that may have a different name. For example, searches for biologics owned by Johnson & Johnson would include results for Janssen Pharmaceuticals, Centocor, and Acelion among others. Including all corporate entities with direct ties to the responsible marketing party gives the highest likelihood of finding relevant publications.

[6] For instance, as discussed in Part II, the Purple Book's inclusion criterion is a subset of our own—i.e., the Purple Book is underinclusive but not overinclusive for our purposes.

To avoid the risk of otherwise misapplying our inclusion criteria through an attempt to automate detection of these kinds of failures, we read and hand-code all patents before including them in our database. Nonetheless, we design a search protocol to manage the scope of this validation exercise, attempting to cast a net that is wide enough to capture all likely patents, but not too wide so as to sacrifice tractability.

To fine-tune this targeting process, we operationalize this protocol in different stages, across which we trade off on different search parameters. That is, in a first stage, we start with a narrow framing of one parameter—mainly, limiting the search to the corporate entity who filed for FDA approval—while searching broadly across other search parameters—e.g., searching across all patents held by that entity in the drug class of the focal biologic. Reading the patents identified by this search allows to further narrow down to the specific patents associated with the focal biologic. In the next stage, we take a broader framing on that first parameter—now searching over all possible assignees (e.g., to capture subsidiaries of the origin firm)—but a narrower framing on the other parameters—e.g., searching only for patents with the same Trade name, chemical name, chemical identifier code, or biosequence. In the Online Appendix, we discuss other aspects of the resulting searches and provide greater detail regarding this staging process.

We emphasize that this protocol is designed to capture the full scope for patenting associated with each biologic. As discussed in the Introduction, originating firms may seek patents on the active compounds, on the routes of administration, on associated devices, on methods of treatment, on methods of manufacturing, etc. As part of this process, we also coded each included patent for its type.

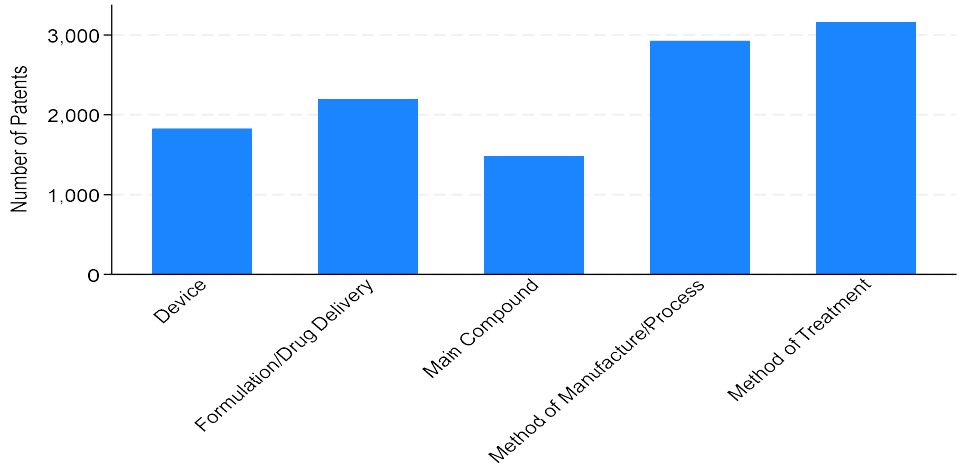
Our primary results will include pending patent applications in the associated patent portfolios.[7] We do so given that biologic patenting activity has particularly accelerated in recent years and the vast majority (over 75%) of these applications will ultimately issue, in which case their inclusion is consistent with our goals of depicting the degree to which biologics patenting activity may forestall competitors moving forward. Moreover, we note that our goal is not necessarily to provide a snapshot of biologics patent portfolios at the present but rather to provide a sense of the blocking effects of portfolios when they were active. As such, we include patents that have expired to provide a sense of the portfolios associated with older biological drugs.

The resulting dataset consists of 11,595 drug/patent pairs across the 515 therapeutic biologics approved by the FDA to date. Six of these biologics do not have any patents (issued or pending) in their portfolios. Roughly 73% of biologics patents are unique to a single drug product, whereas 27% of biologics patents are associated with more than one drug—e.g., the same patented manufacturing process is associated with more than one approved biologic.

Figure 1 breaks down the drug/patent pairs into patent type. Main/primary compound patents comprise 13% of the sample. The remainder represent different types of secondary drug patents, including device patents (16%), manufacturing process patents (25%), formulation patents (19%), and method of treatment patents (27%).

[7] Nonetheless, we exclude applications that have been formally abandoned with the Patent Office, as they will ostensibly never issue and have blocking effect.

Figure 1. Number of Patents by Patent Type, Across Sample of Drug/Patent Pairs



Data are from 11,595 patent/drug pairs associated with 516 biologics approved by the FDA.

IV. Descriptive Analysis of Patent Thicketing and Evergreening Behaviors

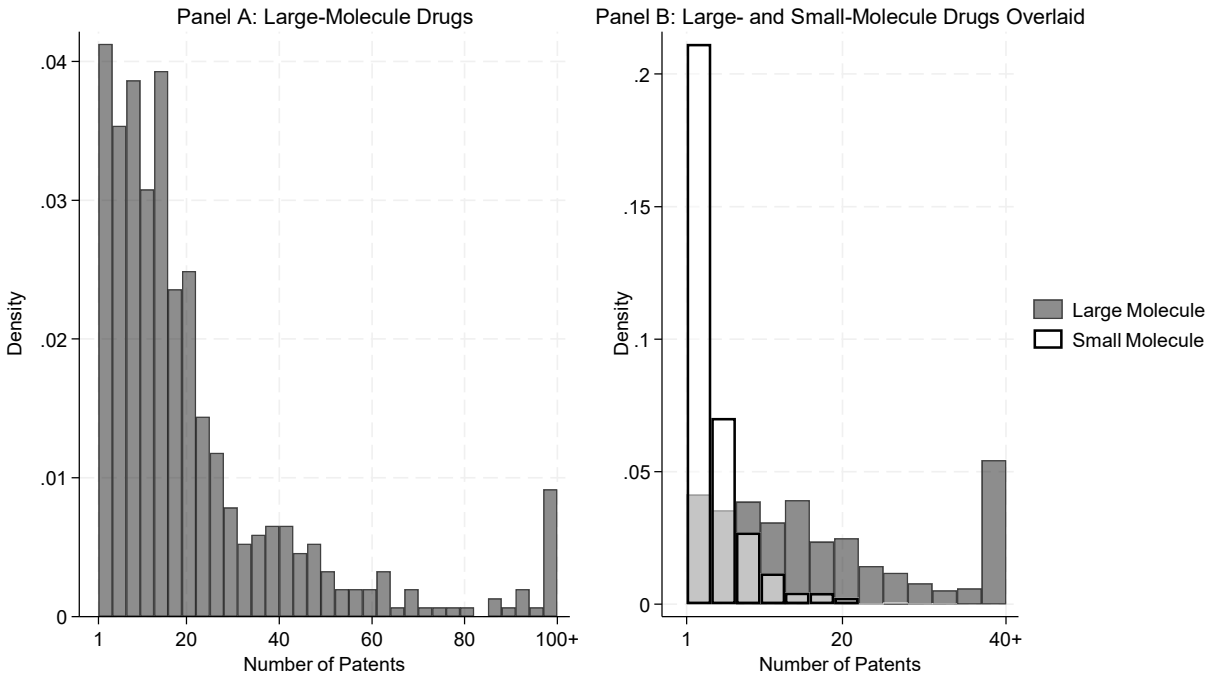
A. Patent Thicketing

To begin to shed light on the strategic patenting practices of brand-name manufacturers of large-molecule drugs, we demonstrate in Panel A of Figure 2 the distribution of per-drug patent counts across all FDA-approved biologics. To offer a frame of reference, we show in Panel B the large-molecule distribution overlaid with the corresponding distribution of per-drug patent counts across all small-molecule drugs represented in the FDA's Orange Book (past and present).[8] As is evident from Panel B, large-molecule drugs tend to have substantially more patents than small-molecule drugs. Whereas virtually none—less 1 than percent—of the small-molecule distribution is beyond 20 patents-per-drug, a substantial portion of large-molecule drugs—roughly 35 percent—

[8] For the Orange Book data, we use the small-molecule dataset compiled in Frakes and Wasserman (2023) and update it to reflect the most recent Orange Book data from the FDA. These data amount to a series of snapshots of the Orange Book over time to ensure that we collect information from patents that were ever listed in the Orange Book (even if delisted at some point).

have over 20 patents. Seven percent of biologics have more than 50 patents and 3 percent have more than 100. The average patent-per-drug of biologics is 22.7, in comparison with 3.8 for small-molecules.[9]

Figure 2. Histogram of Number of Patents Per Drug Across FDA-Approved Biologics, with and without Overlay of Small-Molecule (Orange Book) Patents-Per-Drug Histogram



Notes: Panel A is from our hand-collected and coded data on biologics patents across all 509 large-molecule drugs with at least one patent (excluding 6 drugs with no patents). Panel B overlays the distribution from Panel A with the corresponding small-molecule distribution, using data from Frakes and Wasserman (2023) on 2,032 small-molecule drugs represented in the FDA's Orange Book. In each case, each observation represents a given trade-name as registered with the FDA.

[9] We acknowledge there is a comparability challenge inherent in Figure 2 in that Congress did not require that manufacturers list certain patents in the Orange Book, mainly manufacturing patents. Unfortunately, we are not aware of a comprehensive database in the small-molecule context that was constructed through a search process similar to that taken in this paper. Nonetheless, we do not believe the omission of small-molecule manufacturing patents from the FDA's Orange Book impacts the effective comparison we are attempting to make in Figure 2. After all, manufacturing processes are simply less critical in small-molecule contexts in the first place. For further validation, we turn to the I-MAK database, which provides patent information on the top four selling small-molecule drugs, including those listed and not listed in the Orange Book. There are 59 Orange Book patents collectively across these four drugs, and I-MAK finds that these drugs are associated with 16 method of production / process patents. Accordingly, the small-molecule patents missing from the Orange Book cannot likely account for the over five-fold difference in mean patents depicted in Figure 2 between small- and large-molecule drugs. Moreover, considering our aim in this paper of assessing the degree to which drug patents may block competitive entry, we note that the Orange Book patents identified in the I-MAK data were nearly eight times more likely to be asserted in litigation than the non-Orange Book patents.

In the Online Appendix, we show counterparts to Panel A of Figure 2 that separately depict the distribution of patent counts across biological drugs by the different patent types depicted in Figure 1. With respect to each of method-of-treatment, manufacturing process, and formulation patents, the mean per-drug patent count of the indicated type exceeds that of the total per-drug patent count of small-molecules. Altogether, the number of patents that biosimilars need to navigate before entering the large-molecule market greatly exceeds that of generics in the small-molecule context.

B. Evergreening

Of potentially greater significance is the degree to which patents in these dense portfolios extend the exclusivity periods associated with the relevant drugs. To begin to show this, we calculate the difference in years between the first- and last-expiring patent for each biologic and then show a histogram in Figure 3 of this term-extension across all 509 biologics associated with patents. The distribution has both a substantial mean and spread. The mean gap between first and last expiring patents per drug is 17.4 years with a standard deviation of 11.4 years. Nearly 40% of biologics have at least a twenty-year gap between their first- and last-expiring patent.

Figure 3 gives a potentially inflated sense of the extent of evergreening as it places substantial weight on just two patents—the first and last expiring—and it is possible that one of these is an outlier within the given portfolio. In Figures 4 and 5, we provide a sense of the evergreening potential of the average biologic patent itself. We start in Figure 4 by taking a sample of drug-patent pairs and plotting a histogram of the duration between a given biologic patent's expiration date and the date of the last expiring patent associated with

the relevant drug. In Figure 5, we take the same sample and instead show a histogram of the distance in years between a patent's expiration and the expiration of the first-expiring patent associated with the focal drug, providing an even more direct sense of the degree to which a given patent is prolonging the drug's patent life on average. In Panel B of both such figures, we overlay this large-molecule histogram with its small-molecule counterpart.

Between Figures 4 and 5, we continue to document evidence of both a high level of evergreening potential for a given biologic patent and substantial heterogeneity across patents, in addition to evidence of notably stronger markers for evergreening in larger relative to small molecule drugs, For instance, we find that the average number of years between a patent's expiration and the relevant drug's first patent expiration is 12.7 years, with a standard deviation of 8.2 years and a median of 12.0. The corresponding small-molecule numbers are as follows: mean of 4.7, standard deviation of 5.5 and median of 2.7 years.

All told, our evidence suggests that, in the process of building dense patent thickets, biologics manufacturers are also filing much of these patents at different periods of time, resulting in substantial extensions in the duration over which patents protect biologics from biosimilar competition. In Figures __ of the Online Appendix, we show a counterpart of Panel A of Figures 4 and 5 by patent type and demonstrate that these behaviors may extend to all types of patents, even follow-on main-compound patents. However, we do find that the average degree to which patents expire after first-expiring patents is smallest among main-compound patents (9.9 years) and method of treatment patents (___ years), while strongest among device patents (17.9 years), formulation patents (13 years), and manufacturing patents (12.6 years).

Figure 3: First-to-last expiring histogram

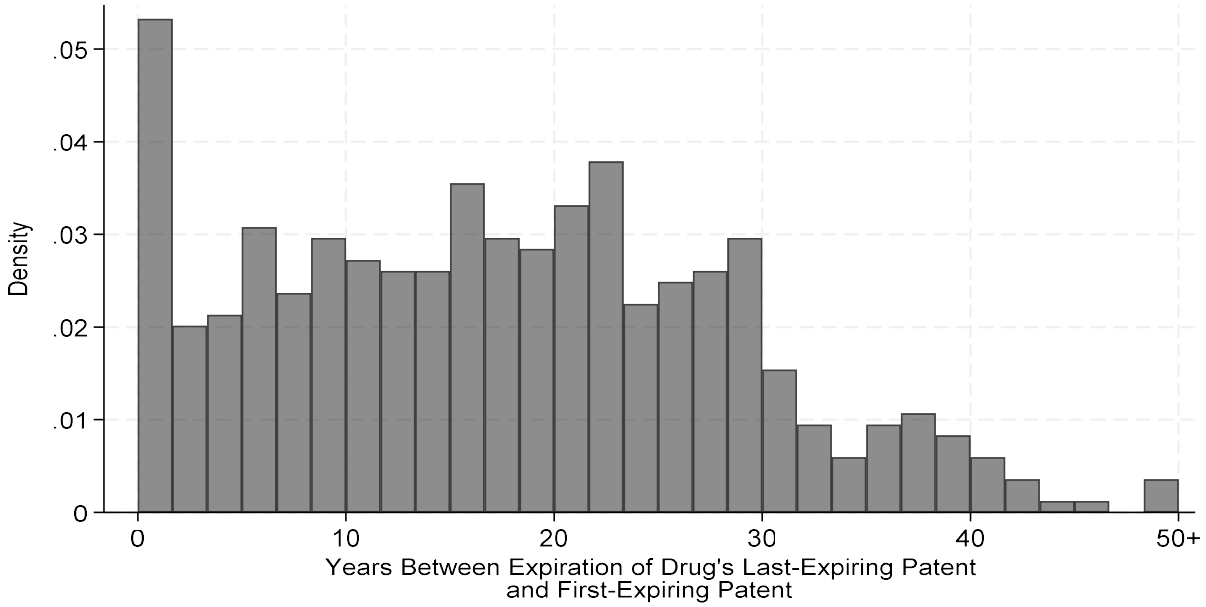


Figure 4

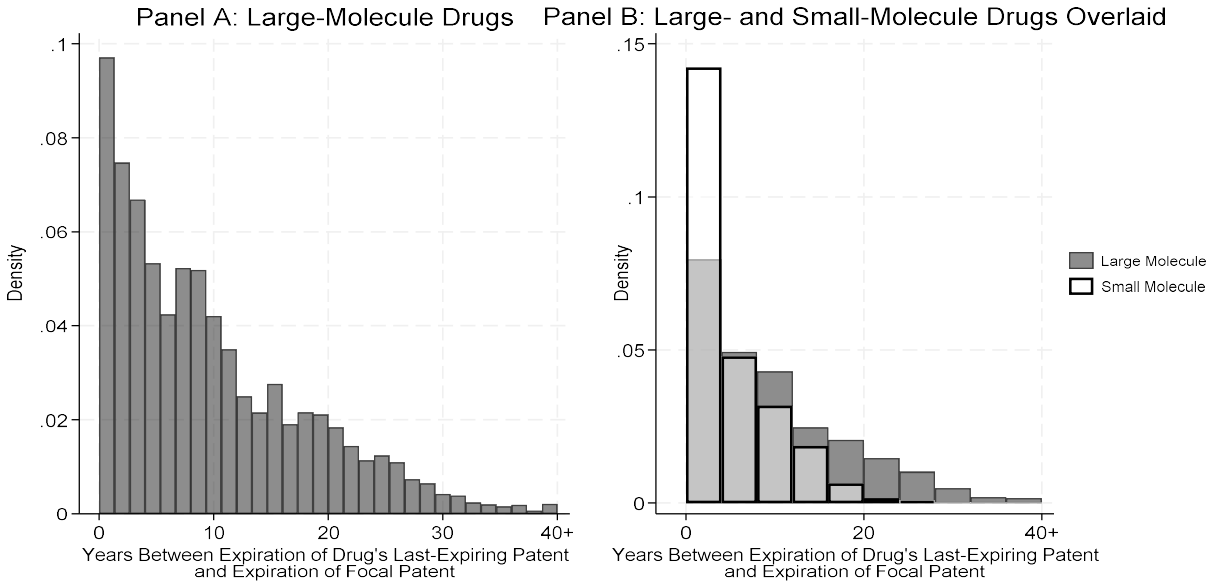
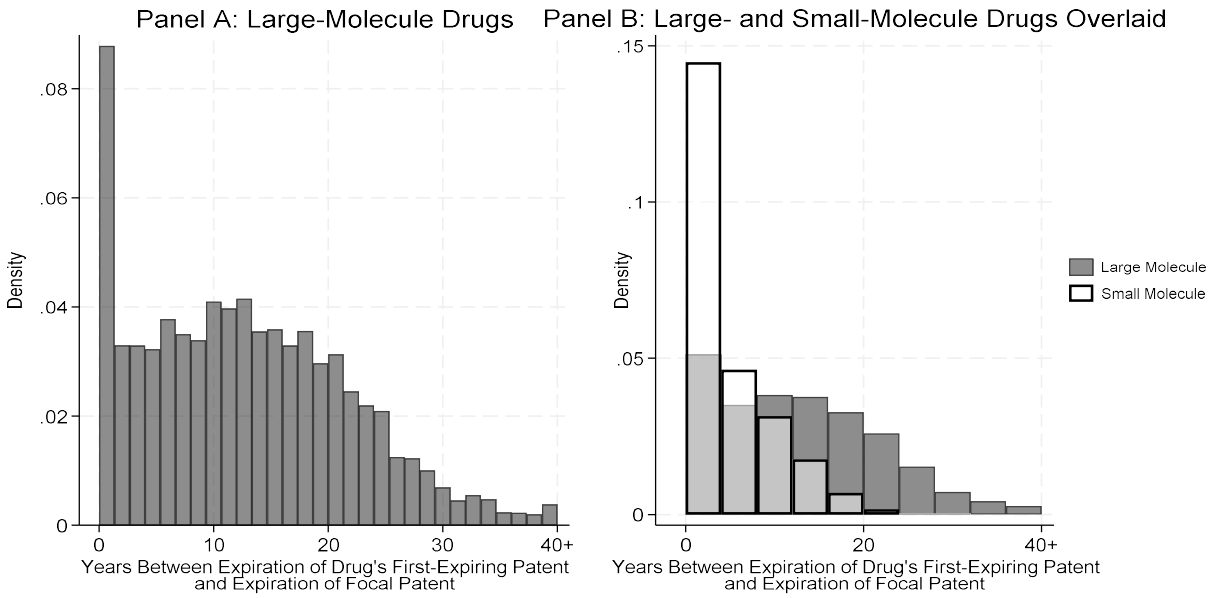


Figure 5



V. Additional Markers of Strategic Behavior

The terms "evergreening" and "thicketing" are often used with a strategic connotation. "Strategic patenting" itself is generally defined to capture patenting practices that go beyond that necessary to incentivize the innovation associated with the particular patent in the first place (Moser 2013). To be sure, some later-filed secondary patents that prolong the patent life of the drug may not perfectly meet this strategic definition. For instance, a biologics manufacturer may invest in developing a truly innovative delivery mechanism and seek a patent on that innovation to help recover the development expenses associated with the new mechanism. Other secondary patents, however, may be more consistent with the strategic labeling—that is, they may be less innovative patents acquired primarily to maximize revenues associated with the whole drug itself (which nonetheless get by the imperfect patentability screens at the Patent Office).

A. Additional Markers of Strategic Evergreening Behavior

In this Part, we begin by further unpacking our evergreening findings above by testing for markers suggestive of strategic evergreening behaviors. To begin this analysis, consider a firm that wishes to file patents to satisfy two strategic objectives: (1) ensure that the relevant drug never goes without some patent protection and (2) maximize the duration over which some patent covers the drug. The firm may meet these objectives by filing subsequent patents prior to the expiration of the preceding patents (meeting objective 1) and as close as possible to the expiration of the preceding patents (meeting objective 2, considering that patent terms toll from filing). A non-strategic patent that is acquired to justify its specific innovation—e.g., a truly innovative formulation—would not necessarily follow such timing and would instead be expected to arise in the due course of its development.[10]

Accordingly, to illuminate the more strategic aspects to the evergreening statistics set forth above, we test whether firms' subsequent patenting activity is concentrated prior to the expiration of the preceding patents and strongest just short of that preceding-patent expiration. To get analytical traction on this prediction, we explore patenting activity in an event window surrounding the expiration of the most significant preceding patent: the primary patent covering the main molecule associated with the biologic. We flag the primary patent by identifying the first-expiring "Main Compound" patent recorded in our database.

We acknowledge that, at the moment when the primary patent expires, it may not necessarily be the last expiring patent associated with the relevant drug. Consider, for instance, a patent, Patent B, that is filed several years after the primary patent. Patent B would then expire several years after the primary patent. However, considering evidence that primary patents are more likely to survive legal scrutiny ([add cite]), the primary patent

[10] Of course, a firm could strategically delay on filing such truly innovative patents. However, delaying on novel and nonobvious innovations until later dates runs the risk of prior art—e.g., other patents or scientific articles—emerging in the interim and invalidating the relevant patent.

may remain the last expiring patent with confident legal validity. In this case, the primary patent's expiration remains particularly salient, and firms may wish to target much of their evergreening timing around this expiration date. If firms wait longer—e.g., for the expiration of Patent B—they run the risk of Patent B being invalidated in the courts and a consequent gap in patent coverage for the relevant drug.[11]

Altogether, in building their thickets, we predict that biologics manufacturers will target a disproportionate share—though not necessarily the entirety—of their subsequent patent filings in the period just before the expiration of the primary patent. Some lead time is necessary to give time to the Patent Office to review the associated application. Accordingly, we center our event-window around the year prior to the primary patent's expiration and track patent-filing activity in the four years leading up to and following that centered year (for a 9-year window in total). In particular, we focus on the filing of non-continuation patents, as continuation patents keep the expiration date of their earlier parent application, thereby serving primarily thicketing rather than evergreening goals.[12]

We also focus on event windows in the post-2010 period. As discussed in Part VI below, Congress effectively created the biosimilar competitive threat at this time, leaving strategic evergreening motivations less relevant prior to this time.[13] Considering the above-stated construction of the 9-year event window, we thus focus on biologics whose primary patent expires between 2015 and 2021, allowing us to track post-2010 patent filings

[11] Our analysis here generalizes and builds upon the analysis set forth by Tu et al. 2024, which documented an uptick in patenting near the end of the term of Humira's primary patent.

[12] Continuation patent applications are new applications that allow applicants to see new claims based on inventions disclosed in previous "parent" applications that have not yet issued (Righi and Simcoe 2023). The continuations share the parent's expiration date. Continuations are common in the pharmaceutical industry as they afford applicants the ability secure early priority dates while waiting to draft claims once they garner a better understanding of the relevant innovation.

[13] The event-time patterns we present are robust to including drugs with primary patents expiring pre-2010; however, not surprisingly given the weakened incentives pre-2010, the magnitudes of the findings are less pronounced. Ultimately, there are only a small number of drugs (12) that could serve the basis for a pre-2010-only analysis, limiting the power to formalize a test of a weaker primary-patent-expiration response in the pre-2010 period.

throughout the entirety of the relevant windows—e.g., for the first cohort (2015 expirations), we follow patenting behavior between 2010 and 2018, and for the last cohort (2021 expirations), we follow patenting behavior between 2016 and 2024. These sample restrictions leave us evaluating 80 treatment biologics. We estimate event-time trends after first stacking the event-windows for each such treatment biologic on top of one another. Stacking in this manner and centering our temporal focus in event-time allows us to avoid the various concerns raised by Goodman-Bacon (2019).

We take two approaches to account for possible confounding of event and calendar time. First, we take advantage of the fact that calendar and event time do not perfectly overlap given staggering of primary-patent expirations and estimate a simple stacked event study design over the treatment drugs. Second, we take a more comprehensive approach that draws inspiration from the stacked event-study difference-in-difference literature (Wing et al. 2024; Cengiz et al. 2019; Desphande and Li 2019) and include control drugs within each layer of the stack to account for calendar-time trends, which we discuss further below. In each approach, our unit of observation is a drug-by-time period—where time is measured with reference to the timing of patent filings—and our key dependent variable is the number of patents recorded in our database for that drug-by-time cell. Our primary analysis estimates Poisson specifications, though our results are virtually unchanged when estimating Ordinary Least Squares specifications, as we demonstrate in the Online Appendix. We begin with the simple event-study specification without control drugs:

(1) $$Patent_Count_{eit} = \exp\left(\alpha + \boldsymbol{\delta_i} + \sum_{\boldsymbol{e=-4}}^{\boldsymbol{4}} \boldsymbol{\beta_1 EXPIRE_e} + \varepsilon_{eit}\right)$$

where e indexes the treatment time (centered, as above, around the year prior to the primary patent expiration), t the calendar time and i the biologic. $\mathbf{EXPIRE_e}$ represents a set of dummy variables capturing the event-time associated with the incidence of the treatment drug's primary-patent expiration. Drug fixed effects are captured by $\boldsymbol{\delta_i}$.[14]

We present results from this preliminary specification in Panel A of Figure 6. Consistent with the predictions of the strategic-evergreening behavior set forth above, we find a precipitous increase in non-continuation patent filings as we near the expiration of a drug's primary patent, followed by a sharp decline in patenting frequency following the primary patent's expiration.

Next, we include control drugs within each stack layer. We seek a control drug that is i) actively patenting over this time-period but (ii) will not have a primary-patent expiration until a future time outside of the event window. Since the essence of our exercise is one that predicts heightened patenting prior to the treatment event and a retreat thereafter—i.e., we predict both pre- and post-treatment effects—it is important in order to produce "clean" controls (Desphande and Li 2019) that we impose sufficient distance between the post-treatment period of our treatment windows and the years prior to the future primary-patent expiration of the control group. For the 2015 treatment cohort (first primary expiring in 2015), we choose a control set of drugs whose primary patent expires between 2027 and 2031. For the 2016 cohort, we choose a control set with the primary set to expire between 2028 and 2032, and so on. This approach provides a 4-year gap between the end of the treatment-event window and what would be the beginning of the treatment event window for the control,

[14] In this specification and in the specification below that includes control drugs, we follow Wing et al. (2024) and Deshpande and Li (2019) and cluster standard errors at the unit level—i.e., drug level—though our analysis is robust to two-way clustering at the drug and event level.

while still ensuring that the control drug has begun its patenting by the beginning of the treatment drug's event window.

With the stacked sample designed as such, we follow Wing et al. (2024) and estimate the following specification (specifically, estimating a Poisson regression and including the regression weights recommended by Wing et al. 2024):

$$(1) \qquad Patent_Count_{eit} = \exp\left(\alpha + \boldsymbol{\delta_i} + \gamma D_i + \sum_{e=-4}^{4} \boldsymbol{\beta_1 \mathbf{EXPIRE}_e} + \boldsymbol{\beta_2} D_i \, \mathbf{X} \, \mathbf{EXPIRE}_e + \varepsilon_{eit}\right)$$

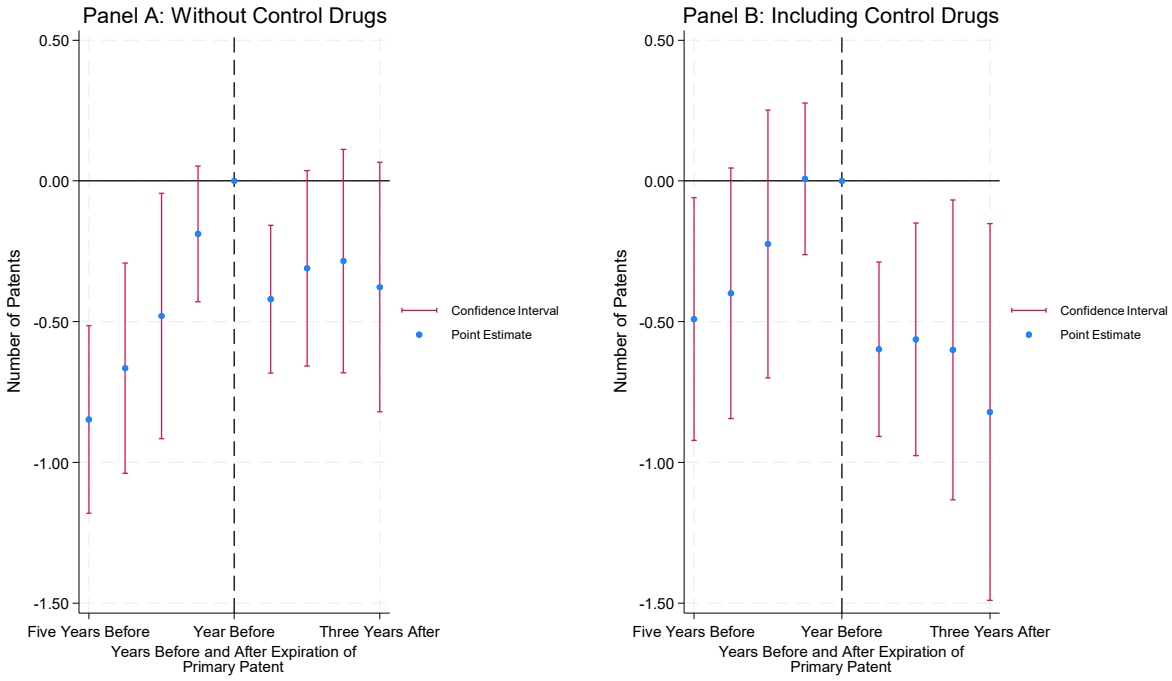
where D_i is an indicator for the treatment group and other parameters are as above. Control drugs are assigned the same event-time indicators as the corresponding treatment drugs within the relevant layer of the stack. The coefficients of the interactions between these event-time indicators and an indicator for the treatment drug, $\boldsymbol{\beta_2}$, represent the coefficients of interest. This specification is intuitive and essentially estimates a classic dynamic difference-in-difference-like specification within each layer of the stack—centering in event time—and then effectively averaging those estimates over all layers of the stack.[15]

In Figure 6, we present the estimated $\mathbf{B_2}$ coefficients, allowing us to trace the frequency of biologics patenting for treatment drugs relative to control drugs in the years leading up to and following the year before the expiration of the focal biologic's primary compound patent. The estimated pattern is highly similar to that without control drugs included. We document an increase in patenting activity leading up to the one-to-two-year period prior to primary patent expiration—giving the Patent Office time to review the

[15] In the Online Appendix, we show substantially similar results from the Cengiz et al. (2019) specification, which tracks the same intuition but follows a slightly different specification that includes certain high-dimensional fixed effects.

application (which generally takes 1-2 years)—followed by a sharp drop in patenting activity once the primary patent expires (reflecting that the incentives are in place to patent prior to this time). Moreover, the magnitudes of these swings are considerable, with the Poisson regression coefficients suggesting a nearly 40% increase in patenting frequency in the four years leading up to the year prior to primary-patent expiration followed by an over 50% fall upon expiration.

Figure 6



Note. Panel A. N = 720 observations. 80 drugs with 9 obs per drug. Panel b. N = 3429 observations. 80 treatment drugs and 301 control drugs.

Further, as a falsification exercise, in Figure __ of the Online Appendix, we demonstrate no clustering of patenting near primary-patent expirations in the case of continuation patents—that is, based on the timing of when the continuation patent

application is filed. Again, continuation applications have no marginal impact on the patent term of the focal drug given that they share the priority/expiration date of their parent patents. Accordingly, one would not expect firms to file continuation patents in a direct attempt to extend the drug's patent life.

In the Online Appendix, we also explore the behaviors explored in this Part by patent type. For reasons of power, as we discuss in the Online Appendix, we focus that exercise more on the binary question—rather than the year-by-year question—of whether firms make sure to avoid gaps in patent coverage by concentrating their follow-on patent in the time period before primary-patent expiration. Consistent with the preliminary evergreening evidence from Part IV, we find the strongest evidence of strategic evergreening with respect to device patents and then next with formulation and manufacturing patents. These heterogeneous effects are intuitive. It is easier to make modifications to existing devices and attempt to patent this development than it is to innovative over new proteins themselves and innovative over new clinical indications of existing proteins. This makes devices more suitable to strategic use of patenting relative to main-compounds and method-of-treatment patents. Similar arguments can be made for formulation and manufacturing patents. Accordingly, these heterogeneous findings lend confidence to an interpretation of the evergreening findings depicted thus far as being strategic in nature.

Altogether, the findings from this Part suggest that biologics manufacturers may be designing and timing their patenting portfolios in part to ensure and prolong the duration of patent protection covering their approved biologics.

C. Additional Strategic Patent-Thicketing Markers

We now build on the strategic analysis just set forth by considering continuation patents in a different light. When continuations are filed, they may not serve evergreening goals directly as they have no immediate marginal impact on the length of time over which a patent is covering a drug, as above. However, they may serve thicketing goals that complement the evergreening strategy just discussed in Part A above.

To see this, consider two original, non-continuation patents: Patents X and Y, which were filed 1 and 2 years, respectively, before the primary patent expires. While each of these may serve the evergreening goals depicted in Figure 6 above, they run the risk of being invalidated by the courts, thus compromising those goals. A biologic manufacturer may protect against this risk by filing subsequent applications at later times that "continue" the applications associated with Patents X and Y. These continuation applications do not directly add additional patent life as they share the expiration date of their parent application, but they "thicken" the protection afforded to the expiration dates associated with Patents X or Y by providing an additional set of patents that courts and/or challengers would need to clear (Carrier and Tu 2024).

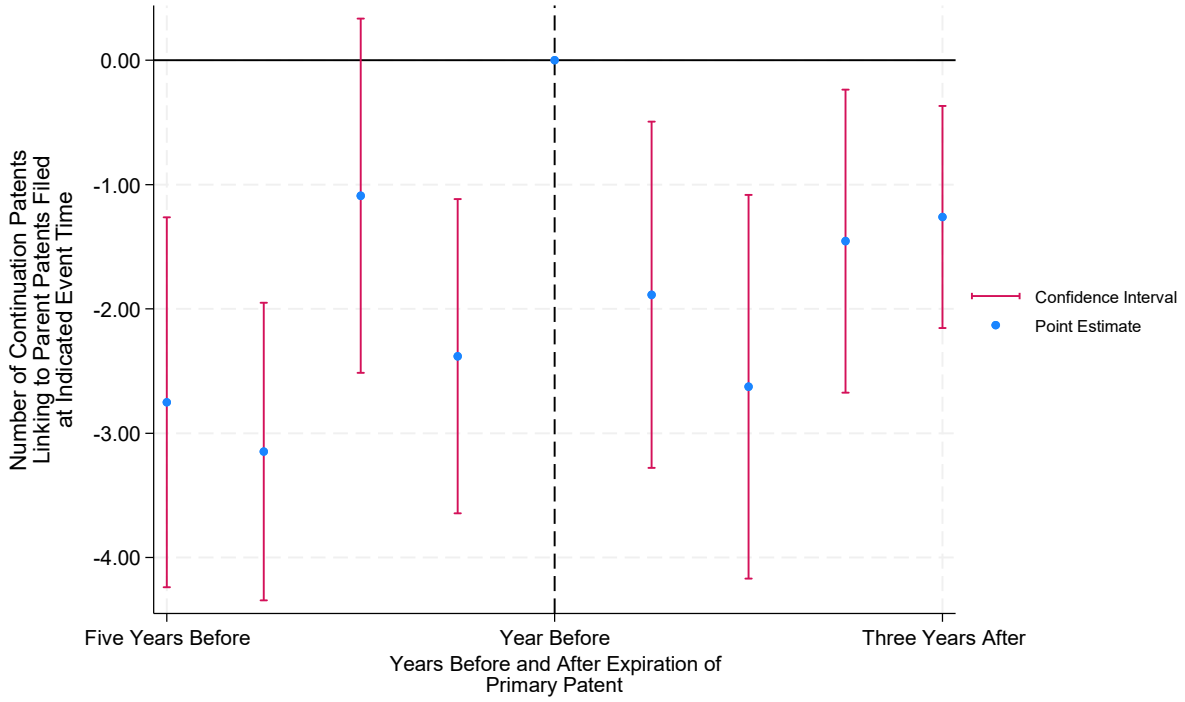
Now, importantly, consider a biologics manufacturer in the year(s) following the primary-patent expiration that is considering seeking a continuation application. As between the two possible parents (X or Y), targeting Patent X for continuation activity may be more sensible from a strategic perspective given that it expires later than Patent Y. More generally, among those original, non-continuation patents filed in the window leading up to the primary-patent's expiration, we predict that those filed just prior to the primary patent expiration will serve as the parent for the most continuation applications.

Testing this prediction requires but a simple modification of the Wing et al. (2023) stacked-event-study specification from above, where the unit of observation is now a given original, non-continuation patent that is filed in the window surrounding the relevant drug's primary patent expiration. The dependent variable of interest is now the number of continuation patents later filed whose parent is the focal non-continuation patent. We show results from our most robust approach that includes the control drugs set forth above within each layer of the stack. Our coefficients of interest are again the interaction between the treatment-drug indicator and the event-time dummies, which we plot in Figure 7. As demonstrated, and consistent with the above prediction, we find that among those original non-continuation patents filed in the period of time leading up to the primary patent's expiration, those filed immediately prior to the relevant expiration date are the most likely to be the parent of a subsequent continuation filing.

To parallel our analysis from sub-Part A, we also show dynamics in the period of time following the focal drug's primary patent expiration. To lay out our predictions here, compare Patent X from above with a new patent, Patent Z, which is an original, non-continuation patent filed in the year after the primary expiration. Thicketing a later-expiring patent—in this case, Patent Z—is appealing all else equal, as just set forth. However, recall from sub-Part A that we theorized that firms would not only want to extend the patent lives associated with their drugs as much as possible, but they would also want to ensure no temporal gaps in patent coverage. Accordingly, in the time around the primary-patent expiration, we theorized and found that firms disproportionately focus their patenting activity prior to the primary-patent expiration. To complement that gap-filling goal, firms may also wish to use subsequent continuation patents to build thickets around those original patents that were filed for such purposes. Consistent with such a prediction, we indeed find that original, non-

continuation patents filed right before—versus after—the primary's expiration are more likely to be the parent to subsequent continuation applications.[16]

Figure 7



D. Concluding Thoughts Regarding Strategic Evergreening and Thicketing

All told, our analysis across sub-Parts A and B finds evidence suggestive of strategic evergreening practices in which firms are ensuring no temporal gaps in patenting by

[16] We acknowledge that it is possible that original, non-continuation patents filed right after the primary expiration may be expected to generate more follow-on continuations for other non-strategic reasons. The analysis from sub-Part A tends to suggest that firms may be strategically filing patents prior to the primary patent expiration, and in doing so, those patents serving these strategic goals may be less innovative on average. As such, those original patents filed after the primary expires may be more innovative on average and may, thus, mechanically lead to more follow-on continuation patents considering the non-strategic role that continuations play. Despite this possibility, Figure 7 demonstrates that the original patents filed right after the primary expires garner less continuations than those filed right before, suggesting that the strategic uses of continuation patenting may overwhelm the non-strategic uses of continuations within this event window.

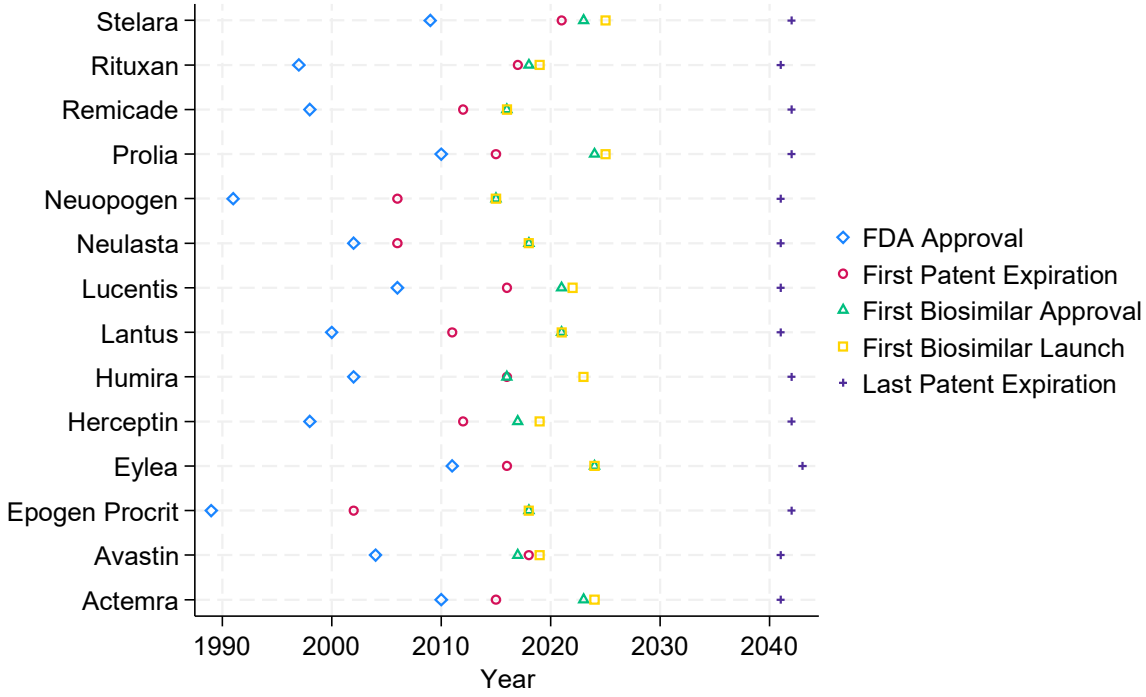
concentrating follow-on patenting practices in time periods prior to the expiration of previous patents associated with the biologic while concentrating such practices as close as possible to the previous patent's expiration date so as to maximize the amount of time in which patents protect the focal drug. Moreover, we find suggestive evidence that firms may be using subsequent continuation patents to build a thicket around this strategy and insure against the possibility that the patents used for these evergreening purposes may be legally invalidated.

VI. Relationship between Patenting and Biosimilar Entry/Threat

A. Challenges in Assessing Whether Thicketing and Evergreening Forestall Competition

The markers of thicketing and evergreening set forth above demonstrate that the patent portfolios of brand-name biologics manufacturers have the potential to meaningfully forestall competition from biosimilars. Perhaps reflective of this potential, only a small number of biosimilars have entered the market to date in the United States—that is, 61 biosimilars with respect to 17 reference (original) biologics. Moreover, as demonstrated by Figure 8, among those small number of drugs with biosimilars to date, the timing of biosimilar entry came some years after the first expiring patent of the brand, suggesting a possible role for patent-induced delays (moveover, biosimilar launch also sometimes occurs after biosimilar approval by some amount of years due to the terms of patent litigation settlements, further suggesting a delay effect of patents).

Figure 8



It may be premature, however, to draw meaningful inferences from this modest entry to date and from the patterns in Figure 8. After all, the biosimilar product space itself is just too new, with the first biosimilar being approved in 2015 and a quarter of them being approved in 2024 alone.

A more fundamental challenge is that alternative theories may explain this limited entry to date. First, the costs of receiving FDA approval to enter the market as a biosimilar—i.e., roughly $100-$200 million—may be enough alone to deter entry (Atteberry et al. 2019, Pfizer 2018). Second, new biologics manufacturers receive a statutory, non-patent-related twelve-year period of exclusivity before the FDA will approve entry of a biosimilar. After that

twelve-year period ends, it may be uncertain whether a viable market still exists for patents to have a marginal effect.

B. Second-Best Empirical Strategy

Ultimately, the delaying effects of biologics patent portfolios on biosimilar entry is an empirical question, but one that is difficult to test as there is no straightforward way to construct a counterfactual without biologics patent portfolios. That being said, to shed light on the blocking potential of biologics patents, we can at least test whether the amassing of these patent portfolios in the first place was caused by the *threat* of biosimilar entry.[17] To be sure, questions of this latter nature have also vexed innovation researchers. To quote Righi and Simcoe (2023) regarding this challenge, "it is hard to link patents to potentially infringing technologies, and (ii) it is difficult to observe clear milestones in the development of those technologies that provide incentives for applicants to seek new claims."

The construction of our database already overcomes the first such challenge identified by Righi and Simcoe, as we are able to link specific patents to specific drug products. To overcome the second challenge and to identify a relevant milestone that provides a fundamental incentive for biologics manufacturers to patent, we take advantage of an unusual opportunity afforded to us by Congress in March, 2010 when it passed the Biologic Price Competition and Innovation Act (BPCIA) as a component to the Affordable Care Act. The BPCIA authorized an abbreviated pathway for biosimilar approval, allowing firms wishing to create and market biosimilars to rely on the clinical trials associated with the originator biologic. This development obviated the need for competitors wishing to enter the market to go through the considerable expense of demonstrating to the FDA the safety and

[17] At first blush, this might seem obvious—that is, the fact that we observe robust portfolios themselves must reveal that they were acquired with the motivation to exclude competitors. However, we note that the literature has discussed motivations to patent beyond simply desires to exclude competitors, including information-based and signaling motivations (Farre-Mensa et al. 2019, Harhoff 2009, Czarnitzki et al. 2007, Long 2002) and desires to improve bargaining positions in attempts to secure licenses (Carrier and Tu 2024).

efficacy of the relevant drug, an expense biosimilar firms are thought to be unwilling to occur considering that they would ostensibly face immediate competition over the same active ingredient form the originator. Instead, the BPCIA simply requires a showing of biosimilarity to the original, already-approved biologic. Effectively, this development provides us with an opportunity to explore how biologics manufacturers' practices responded to the very initiation of the competitive biosimilar threat.

In particular, we aim to explore how the BPCIA incentivized firms to engage in strategic patenting in order to stem off the new biosimilar threat, which again captures patenting practices that go beyond that necessary to incentivize the innovation associated with the relevant patent in the first place. As we discuss further below, it is inherently difficult to isolate those specific patents that meet this exact definition. Nonetheless, to head in this direction, we will explore the patenting response to the BPCIA with respect to manufacturers of original biologics that were already approved—and thus ostensibly already existed—prior the BPCIA. Did this threat of new competitors to the existing drugs induce firms to build patent portfolios to protect their market shares?

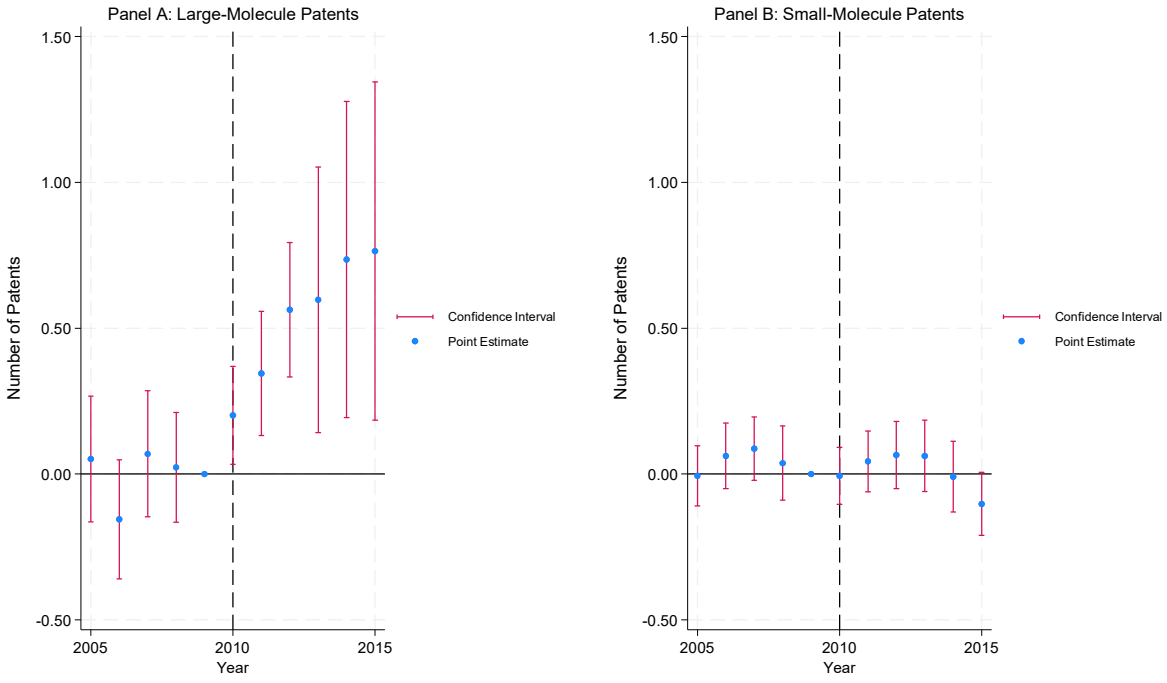
C. Findings

With the above-stated sample restriction in place—i.e., limiting to patents associated with drugs in existence prior to the BPCIA—we begin to explore the biologics patenting response to the BPCIA by showing in Panel A of Figure 9 how biologics patenting frequency evolves year-by-year leading up to and following the BPCIA. Specifically, we focus on the year in which the relevant biologics patent was filed with the Patent Office and estimate the following specification over the 2005-2015 period, where the unit of observation is a given drug-by-year cell:

(1)
$$Patent_Count_{it} = \alpha + \boldsymbol{\delta_i} + \sum_{t=2005}^{2015} \boldsymbol{\beta_1 YEAR_t} + \varepsilon_{it}$$

where i denotes the individual drug and t the calendar year or filing and where $\boldsymbol{\delta_i}$ captures drug fixed effects. As above, Patent_Count$_{it}$ captures the number of patents associated with drug i in our database with an initial filing date of year t.[18]

Figure 9



As demonstrated by Panel A, biologics patenting counts among those drugs already approved by the time of the BPCIA fluctuate a little year-by-year prior to the BPCIA's adoption but generally remain flat. In the year in which the BPCIA is passed and thereafter, biologics

[18] To facilitate a comparison of how trends in the level of patenting over time between large and small molecule patents, we estimate Ordinary Least Squares specification to produce Figure 9, allowing us to interpret the coefficients as the number of patents per drug falling into the different time bins. In the Online Appendix, we show a corresponding figure that draws from Poisson specifications, where the coefficients in each panel of the figure are interpreted in log changes in patent counts. Nonetheless, these interpretation points aside, the pattern in the figures is virtually identical between the OLS and Poisson approaches.

patenting volume begins to increase notably. By 2012, the patenting volume has roughly doubled the 2009 level.

Consistent with a causal effect of the introduction of the biosimilar threat from the BPCIA, this sharp acceleration in patenting following 2010 is unique to biologics, as we observe no such increase in small-molecule patenting as demonstrated by Panel B (where we estimate a similar specification on small-molecule drugs likewise approved prior to 2010). In Figure ___ of the Online Appendix, we formalize the comparison of the large- and small-molecule response to the BPCIA and estimate a corresponding difference-in-difference specification. The findings confirm the statistical significance of the larger large-molecule response.

In Figure ___ of the Online Appendix, we further show responses to the BPCIA by patent type. Consistent with the above findings of stronger evergreening practices in the case of device patents—and thus potentially stronger strategic practices—we find the strongest response to the enactment of the BPCIA in the case of device patents. And, likewise consistent with the weakest evidence of evergreening in the case of main-compound patents, we find the weakest impact of the BPCIA on the rate of main-compound patenting—in fact, we seem to find no change in the rate of such patenting. As above, this heterogeneity in our results lends confidence to a strategic interpretation of our findings, whereby firms may be increasing their patenting in response to the biosimilar threat to forestall biosimilar competition in ways that go beyond using patents in the paradigmatic fashion to justify the development of the innovation underlying the specific patent.

[ADD SIMULATIONS OF EFFECTS OF CONGRESSIONAL BILLS AIMED AT CURBING THICKETING AND EVERGREENING
AND FURTHER DISCUSS WELFARE IMPLICATIONS]