Marketing Authorization and Strategic Patenting: Evidence from Pharmaceuticals

Dennis Byrski[1] and Lucy Xiaolu Wang[2,1,3]

[1] Max Planck Institute for Innovation and Competition

[2] University of Massachusetts Amherst

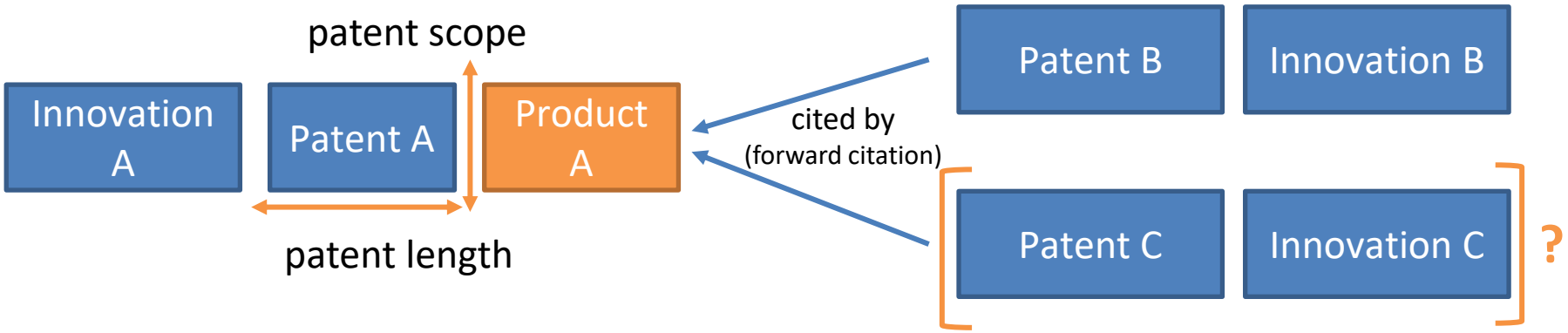
[3] Canadian Centre for Health Economics

ZEW Mannheim, 2024.6.4

Drugs save lives, but too costly with many patents!

- The patent system is designed to promote innovation (more private returns), esp. important for drugs (Mansfield 1986; Lakdawalla 2018)
- But strategic patenting can be welfare-reducing: originators earn supra-competitive profits & limit access to drugs (European Commission 2009)
  - E.g., evergreening (extends length) and fencing (extends breadth)
  - But ex ante incentives are important to long-term R&D (Budish et al 2015)
- The tradeoff between static efficiencies and ex ante R&D incentives has evoked debates on rising patentability standards (not only for drugs)
  - US Supreme Court cases: Mayo 2012, Myriad Genetics 2013
- This paper: EPO “gold standard” examination quality (Chien 2018) + natural experiments in patentability bars due to drug approvals
  - Disclosing trial doc can be prejudicial to patent validity (EP Board of Appeal)

Patents, Products, and Cumulative Innovation



- Longer patent terms spur entry of non-infringing product imitations, broader claims deter them (Gilchrist 2016; Izhak et al 2020)
  - Subsequent entry or imitation after drug approval ≠ subsequent patenting
- There is little systematic evidence on whether the **market approval of a product alter the incentives for cumulative innovation/patenting**
  - For originators, vertically related parties, others
  - For strategic versus innovative follow-on innovation

Research Question:

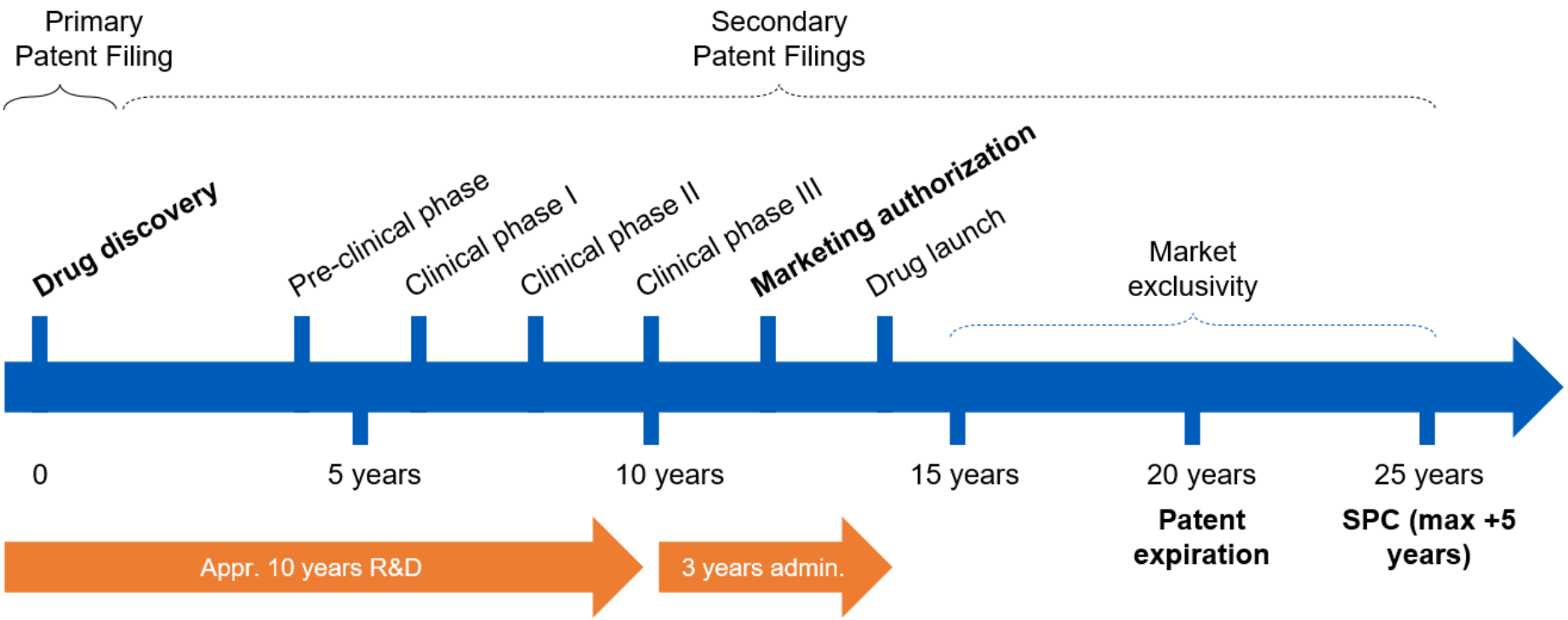
Q: How does marketing authorization of a new drug (new NME) affect follow-on innovation building upon focal drug?

- Intuitively, follow-on patenting can go either way (an empirical Q):
  - More: “Time to explore other new indications and expand the market!”
  - Less: “Time to lay flat and relax, as profit is coming in our way!”
  - Same: “I cannot decide, so maybe just good to patent as usual?”
- Exploit the authorization of new drugs to the (EU/EEA) market
- Show how the focal drug patents with varying approval lags (do *not*) *differ* concerning ex-ante patent and drug characteristics
- Examine how a drug’s approval affects the rate and direction on how firms (selves, related parties, others) conduct follow-on innovations

Literature and Contribution

- **Secondary patents**: examine the relationship btw market authorization and follow-on patenting (of different types & by different parties)
  - (Lemley & Moore 2004; Amin & Kesselheim 2012; Sampat & Shadlen 2017; Hemphill & Sampat 2011; Frakes & Wasserman 2023; Gupta 2023)
- **Intellectual property institutions and follow-on innovation**: leverage novel European institutional details and rich drug-patent dyadic data
  - (European Commission 2009; Hemphill & Sampat 2013; Sternitzke 2013; Galasso & Schankerman 2015; Gaessler et al. 2023; Sampat & Williams 2019)
- **Firm innovation strategies**: how downstream product events intertwine with upstream patenting behaviors in a heavily regulated industry
  - (Acemoglu & Linn 2004; Arcidiacono et al 2013; Budish et al. 2015; Dubois et al 2015; Gaessler & Wagner 2020; Kyle & McGahan 2012; Wang 2022)
- **Policy implication**: ex ante regulation, self-adjustment, & patent quality

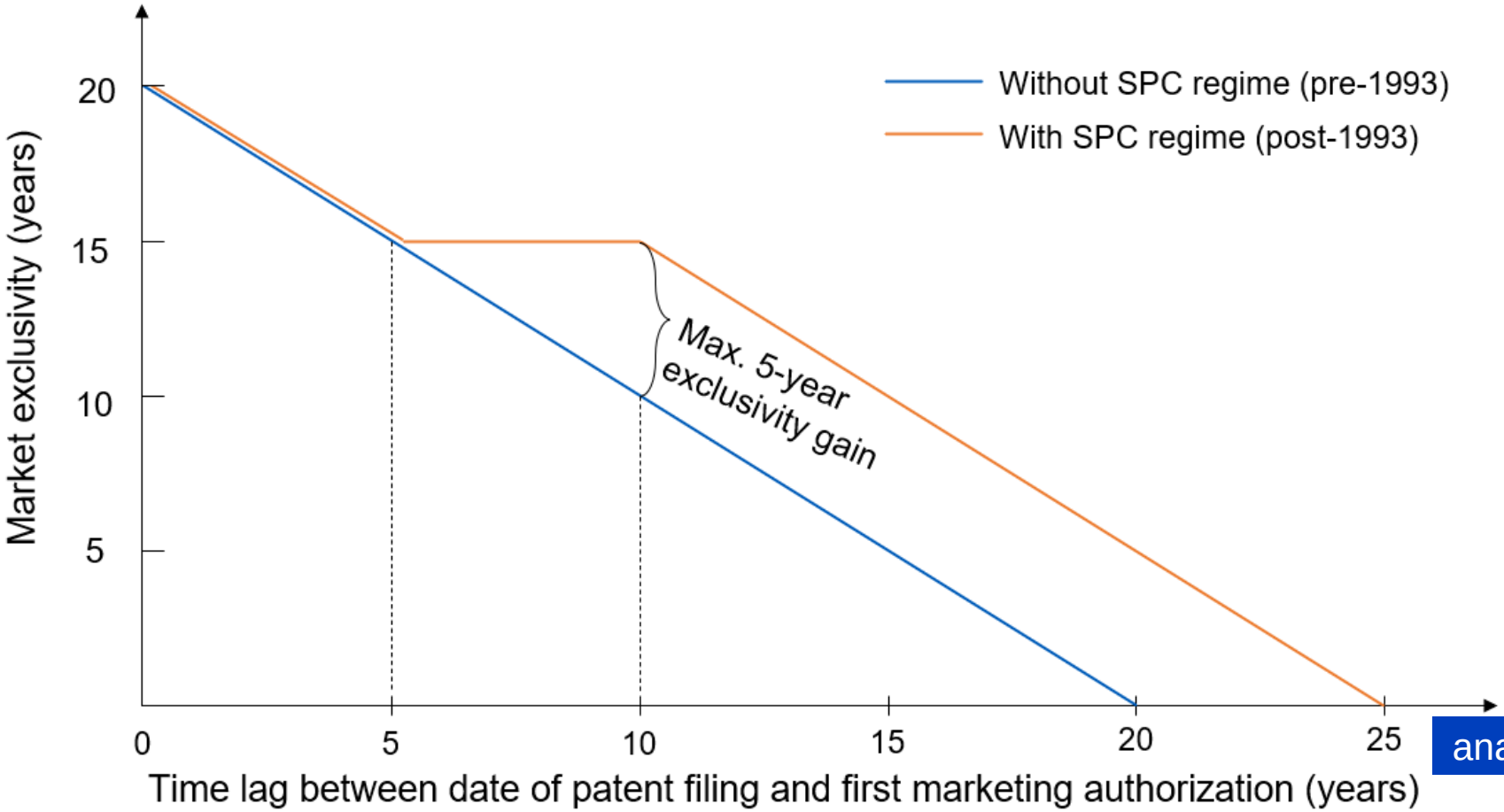
The Drug Development Process in EU (EEA)



- In European Economic Area (EU+Iceland, Liechtenstein, Norway), originators submit applications for market authorization to European Medicines Agency (/national)
  - verifies safety, efficacy, quality; drugs can then be sold for approved indications
- Market exclusivity: firms hold exclusive right to market/sell a patented drug

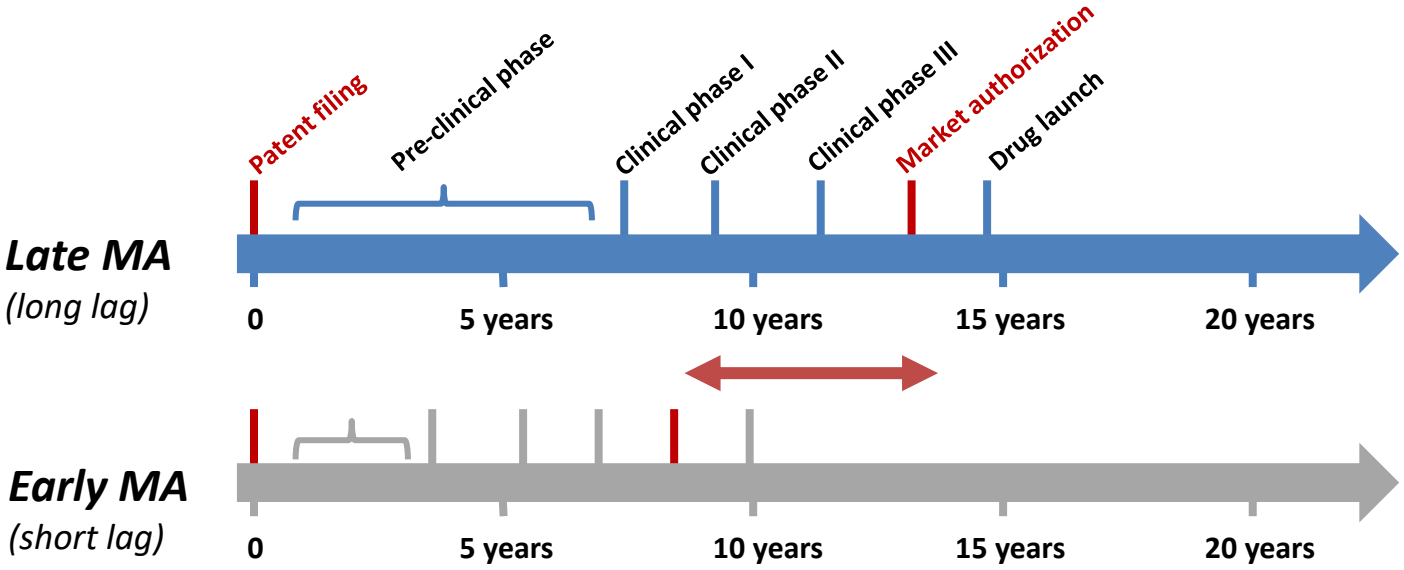
EU Patent Term Extension (SPC Regime)

- Supplementary Protection Certificates (SPC) regime, 1993- (our sample): patent term extension is capped at 5 years, so market exclusivity can be seen as constant for patents w/ 5-10 years' approval lag
- SPC term (≤5 years)= date of 1st MA in EEA – filing date of basic patent – 5



analysis

It takes a long & uncertain time to develop a drug…



- Approval lag *cannot* be predicted perfectly at the time of the patent filing: whether/when the drug will be on the market (à la Gilchrist 2016)
  - Scientific uncertainty: drug R&D process is highly uncertain & non-linear
    - e.g., mRNA technology was viewed as non-promising for decades until Covid
    - e.g. (small molecule drugs w long lags): Prozac, Lipitor, Plavix, Gleevec, …
  - Organizational factors: mergers & acquisitions, $, licensing, transfer, …
- Meanwhile, the patent system rewards "first-to-file" as the patent owner
  - Firms often file patents once a molecule of $-interest is *vaguely* identified
  - Strategic delay of MA is costly: later product entry (lost 1st-mover advantage)

Data Construction: primary patent-drug dyadic data

- **Patent-drug linkage**: data on primary patent covering an NME (new molecular entity) and the approved drug from public registers.
  - SPC data from the German Patent Office – i.e., Deutsches Patent- und Markenamt (DPMA): originator specifies the core (basic) patent for a drug
  - Restrictions: 1) exclude patents filed 20+ years before data collection (1997+); 2) only keep SPCs on the 1st drug rel. to primary patents (unique patent family-drug links)
  - **Approval lag**: lag btw original filing date of focal drug's primary patent (priority date) and the 1st EU market authorization (allow 5+ years post approval periods)
- **Patent data**: patent info on the primary patents from EPO PATSTAT
  - Link via appl_no w patent info at patent family level; EPO search report
- **Drug data**: Cortellis, link by patent family id, tag pharma cites; categorize product, process, 2ndary patents; crosswalk conditions w WHO ICD-9 code

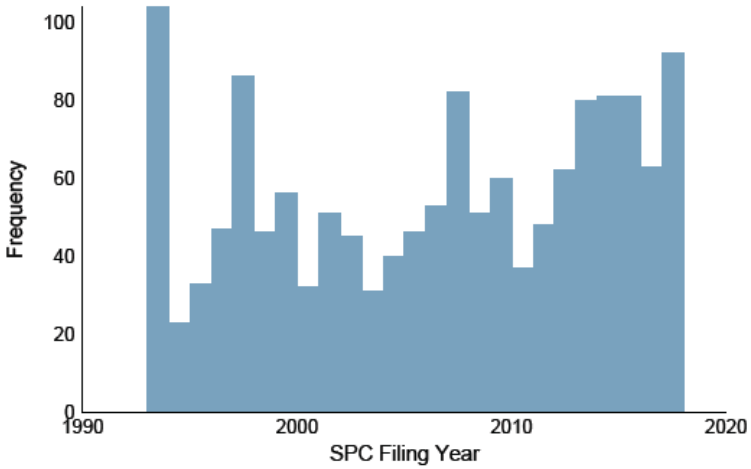
Deutsches Patent- und Markenamt

Europäisches Patentamt
European Patent Office
Office européen des brevets

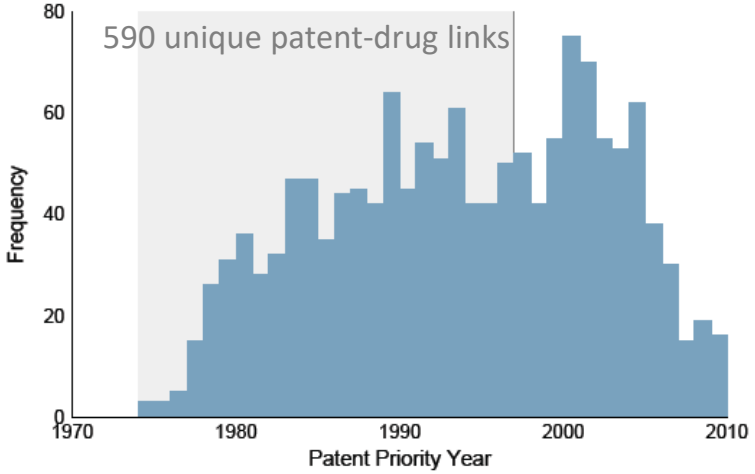
Clarivate Cortellis™

Samples: full/restricted, early/late MA sample split

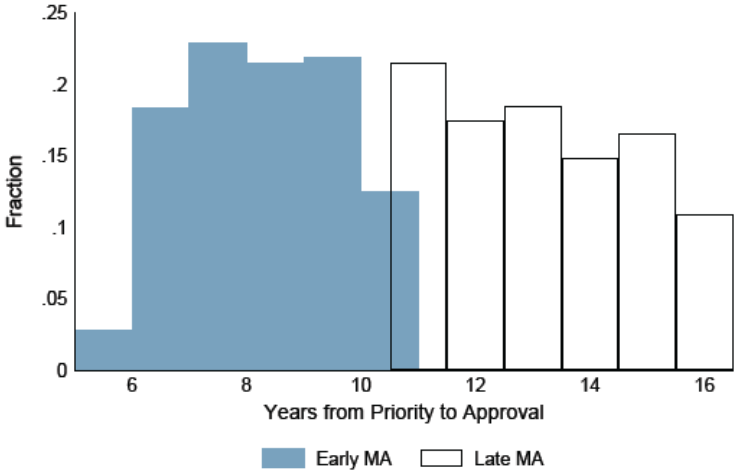
(a) SPC filings - full sample



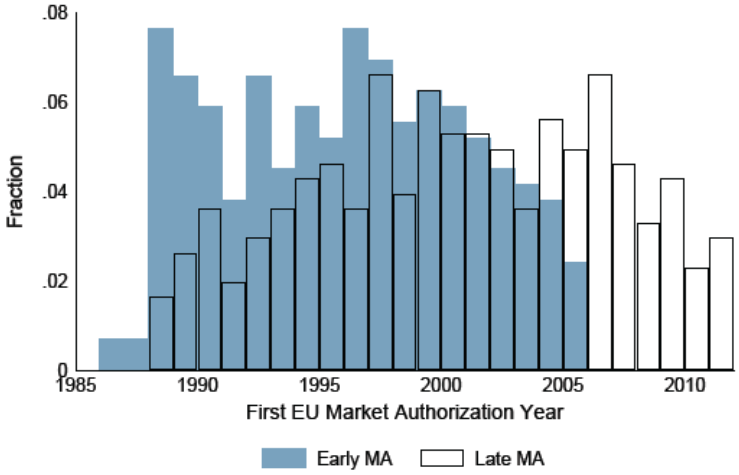
(b) Primary patent priory filings - full sample



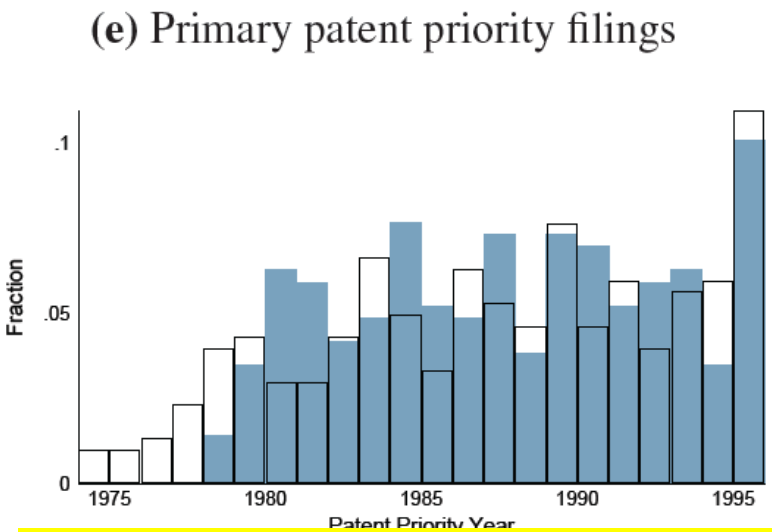
(c) Time to approval

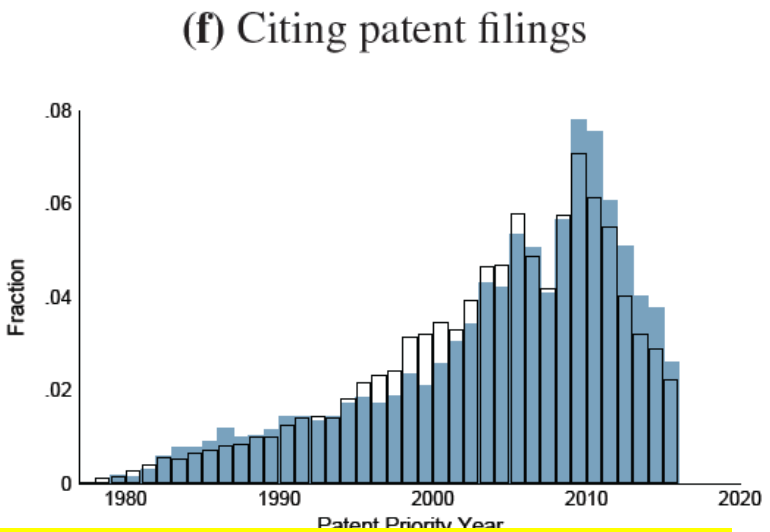


(d) First EU marketing authorization

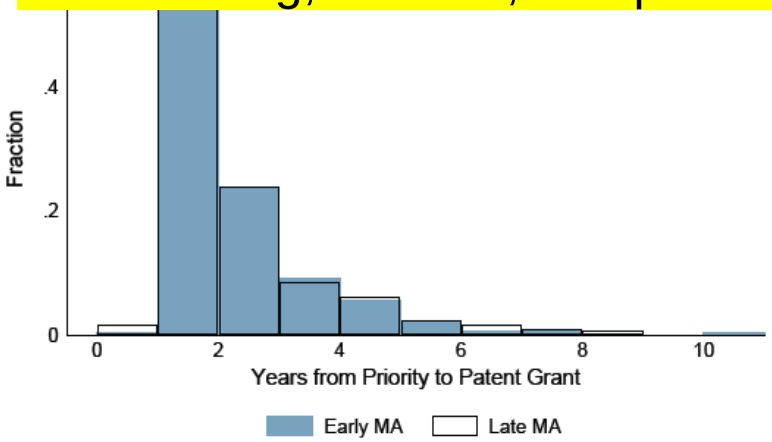


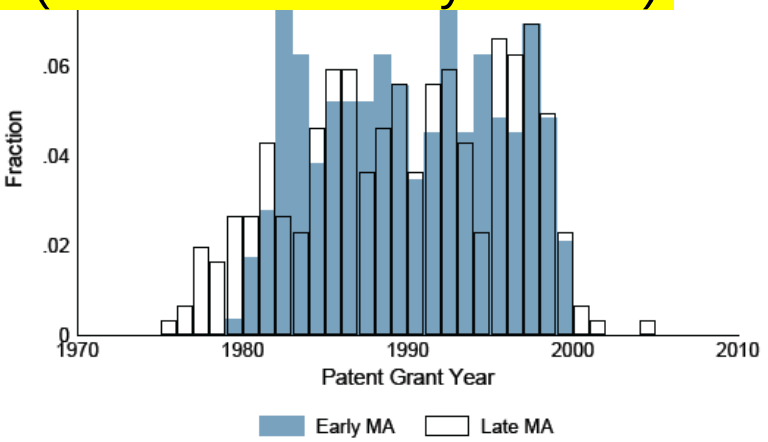
Distribution of timing-related variables





Patents with early vs. late MA (split approval lag at median: 10 years) are similar regarding priority time, time span at the patent offices (time to patent grant), similar technological nature (e.g., ICD-9, complexity, resubmissions), and similar ex-ante drug, disease, and patent characteristics (t-test across many metrics).





Similar Ex-Ante Drug & Patent Characteristics

Early MA vs Late MA	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Early MA (N = 288)			Late MA (N = 302)				
	Mean	Median	Std. Err	Mean	Median	Std. Err	Diff	p-value
Time to approval	8.26	8	1.3	13.21	13	1.7	4.94	0.000***
Time to patent grant	2.33	2	1.2	2.44	2	1.4	0.11	0.322
Patent priority year	1987.38	1987	5.1	1987.00	1987	5.8	-0.39	0.394
First patent grant year	1989.66	1990	5.4	1989.36	1990	6.3	-0.30	0.533
First MA year	1995.64	1996	5.0	2000.17	2000	6.1	4.53	0.000***
Market exclusivity	15.00	15	0.0	12.88	13	1.7	-2.12	0.000***
Initial forward cit.	0.66	0	1.1	0.64	0	1.1	-0.02	0.812
Initial self cit.	0.27	0	0.5	0.28	0	0.5	0.02	0.684
Initial other cit.	0.40	0	0.9	0.36	0	0.8	-0.04	0.586
Initial same ICD9 cit.	0.25	0	0.5	0.25	0	0.5	0.00	0.967
Initial other ICD9 cit.	0.03	0	0.2	0.04	0	0.2	0.00	0.915
Initial biotech patent cit.	0.00	0	0.0	0.00	0	0.1	0.00	0.329
Initial secondary patent cit.	0.13	0	0.4	0.10	0	0.3	-0.03	0.334
Initial process patent cit.	0.02	0	0.2	0.03	0	0.2	0.00	0.875
Initial product patent cit.	0.19	0	0.4	0.21	0	0.5	0.02	0.544
Size of patent family	26.83	24	16.7	24.77	24	14.6	-2.06	0.112
Number of applicants	1.09	1	0.3	1.10	1	0.3	0.01	0.827
Transn. patent family	0.87	1	0.3	0.85	1	0.4	-0.01	0.630
Triadic patent family	0.52	1	0.5	0.56	1	0.5	0.05	0.268
Tech area organic chem.	0.44	0	0.5	0.50	1	0.5	0.07	0.110
Tech area pharma.	0.47	0	0.5	0.36	0	0.5	-0.10	0.010***
Tech area biotech.	0.06	0	0.2	0.10	0	0.3	0.05	0.035**
Tech area material chem.	0.01	0	0.1	0.01	0	0.1	-0.00	0.616
Applicant country US	0.36	0	0.5	0.33	0	0.5	-0.03	0.497
Applicant country Europe	0.47	0	0.5	0.43	0	0.5	-0.04	0.311

Mean comparison – similar disease characteristics

- Similar early/late MA mean by ICD-9 categories (& leave-one-out analyses)
  - Small size diff in 1) early: endocrine/immun. & mental disorders; 2) *late: skin diseases

Early MA vs Late MA	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Early MA (N = 288)			Late MA (N = 302)				
	Mean	Median	Std. Err	Mean	Median	Std. Err	Diff	p-value
Number of ICD9	2.32	2	2.4	2.26	2	2.4	-0.06	0.790
Infectious/parasitic diseases	0.23	0	0.4	0.26	0	0.4	0.03	0.470
Neoplasms	0.14	0	0.4	0.15	0	0.4	0.00	0.905
Endocrine/immun. disorders	0.12	0	0.3	0.18	0	0.4	0.06	0.066*
Blood diseases	0.03	0	0.2	0.02	0	0.2	-0.01	0.482
Mental disorders	0.05	0	0.2	0.09	0	0.3	0.04	0.061*
Nervous system diseases	0.12	0	0.3	0.11	0	0.3	-0.01	0.633
Circulatory system diseases	0.17	0	0.4	0.15	0	0.4	-0.03	0.435
Respiratory system diseases	0.07	0	0.3	0.05	0	0.2	-0.02	0.321
Digestive system diseases	0.06	0	0.2	0.04	0	0.2	-0.02	0.405
Genitourinary diseases	0.08	0	0.3	0.12	0	0.3	0.04	0.192
Pregnancy/childbirth	0.00	0	0.1	0.00	0	0.1	-0.00	0.952
Skin diseases	0.07	0	0.3	0.02	0	0.2	-0.04	0.017**
Musculoskeletal diseases	0.07	0	0.3	0.09	0	0.3	0.01	0.578
Conditions perinatal period	0.04	0	0.2	0.02	0	0.1	-0.02	0.213
Ill-defined conditions	0.09	0	0.3	0.08	0	0.3	-0.02	0.542
Ijury/poisoning	0.08	0	0.3	0.07	0	0.2	-0.01	0.541

Empirical Strategy: Event Studies (à la S&S 2023)

- Drugs that never been approved should not be valid counterfactuals; rather, drugs approved but with early/later MAs (within drug comparison)
- Event study design exploits the variation in the timing of the treatment (early/late MA) across units & end-binning (Schmidheiny & Siegloch, 2023)
- Baseline: $$\mathbf{E}[y_{it}|\, X_{it}] = \exp[\alpha + \sum_{j=\underline{j}}^{\bar{j}} \beta_j\, MA_{it}^{j} + \delta_t + \theta_i]$$
  - y_{it} : # of forward citations (other DVs: examiner citations, self, other, etc)
  - MA_{it}^{j}: drug approval happening j periods away from t
  - δ_t & θ_i: citation year and patent fixed effects (drug-patent 1-1 level)
- Preferred specification: w demanding patent grant & SPC grant controls

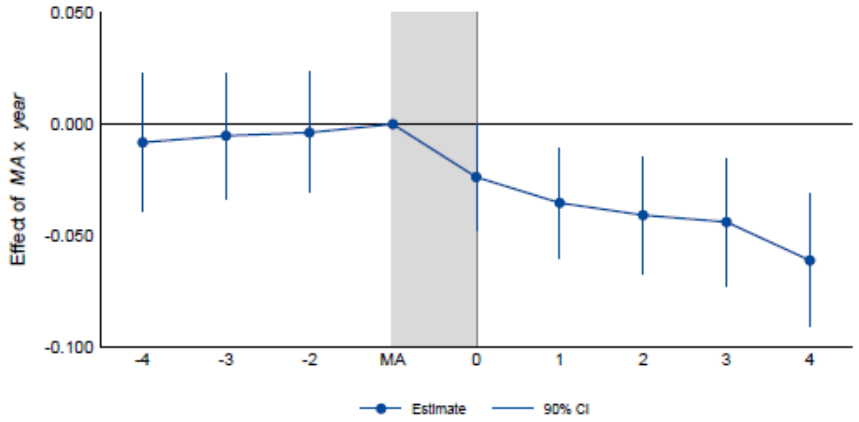
$$\mathbf{E}[y_{it}|\, X_{it}] = \exp[\alpha + \sum_{j=\underline{j}}^{\bar{j}} \beta_j\, MA_{it}^{j} + \sum_{j=\underline{j}}^{\bar{j}} \gamma_j\, patent_{it}^{j} + \sum_{j=\underline{j}}^{\bar{j}} \eta_j\, SPC_{it}^{j} + \delta_t + \theta_i]$$

  - Lit.: patent grants (Gans et al., 2008), SPC grants (Mejer, 2017) are important
  - Estimates w a “partial effects” interpretation (Sandler & Sandler, 2014; Miller, 2023)

Marketing authorization & self-citations: by source/type

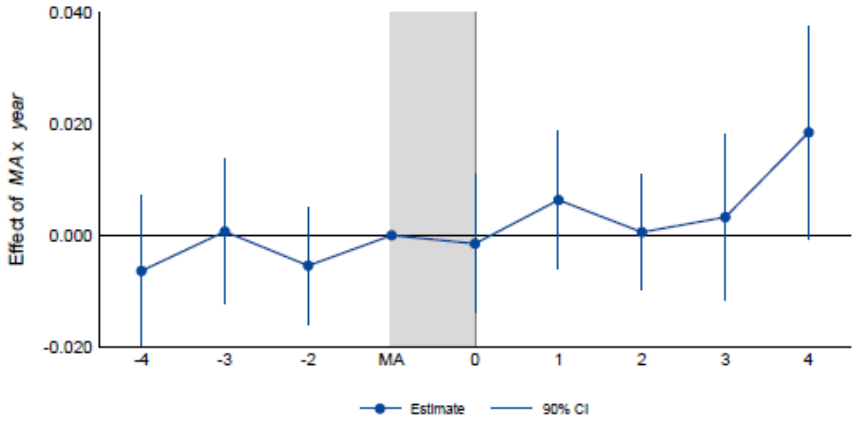
(c) Examiner citations

Self-citations added by examiners (high quality)



(d) Applicant citations

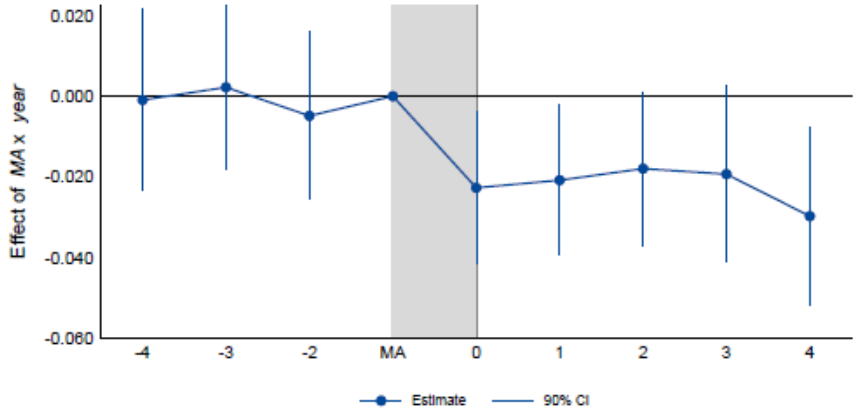
Self-citations added by applicants



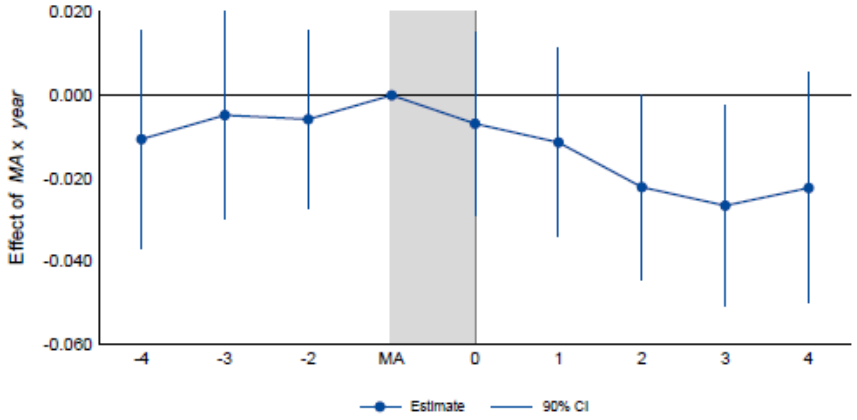
XY-ref.: suggest legally "weak" patents as they increase the likelihood of a post-grant validity challenge (Wagner & Wakeman, 2016)

(e) XY-citations

(X: a single prior patent doc can undermine the novelty/inventiveness of claimed invention; Y: do so in combination w/ other docs)



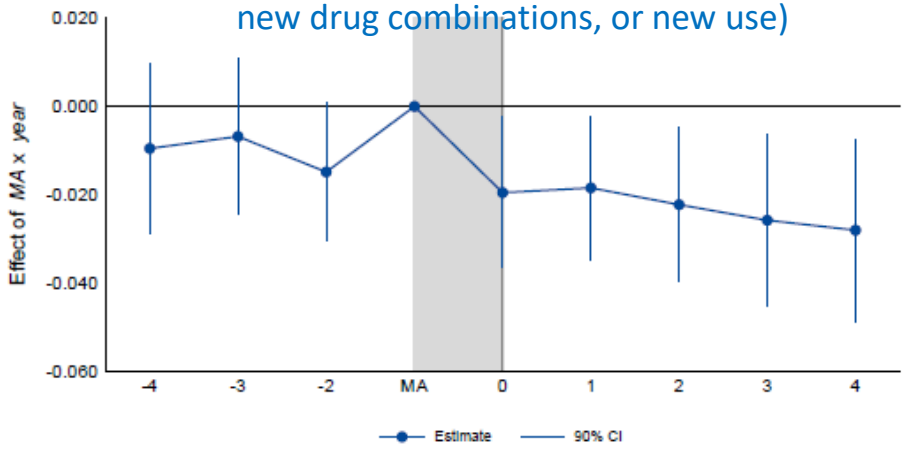
(f) No XY-citations



Market Authorization & self-citations: by type of patent

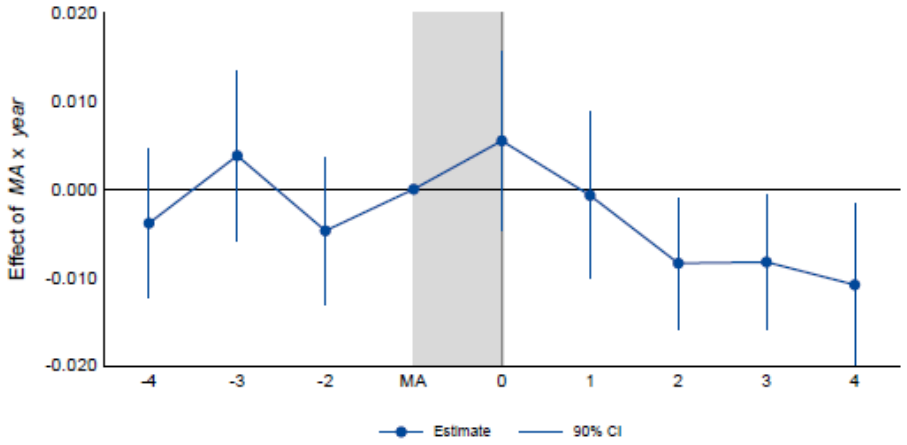
(a) Self-citations - secondary patents

(e.g., new formulations, new dosage forms, new drug combinations, or new use)



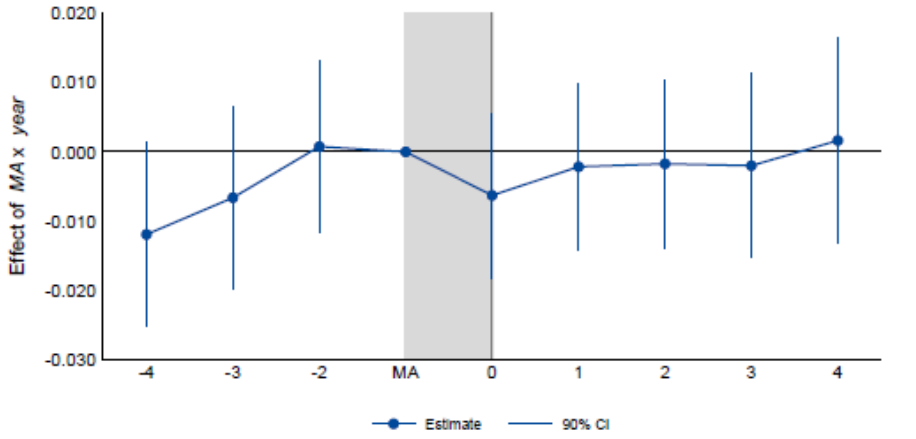
(b) Self-citations - process patents

(e.g., new manufacturing process)



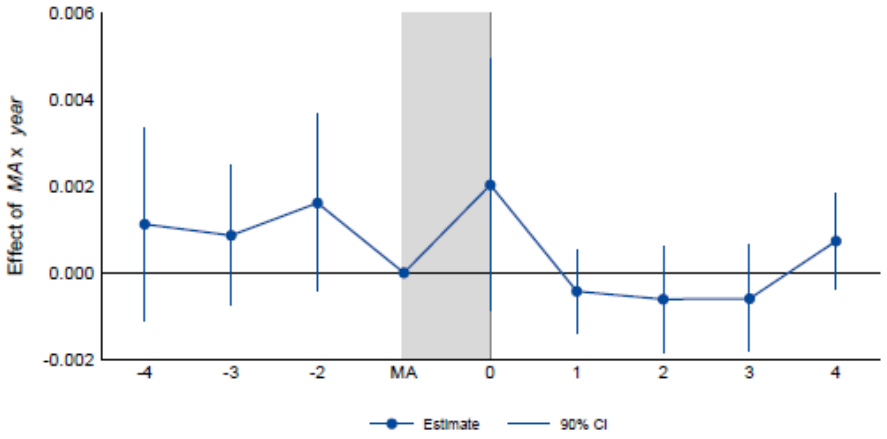
(c) Self-citations - product patents

(e.g., new products (derivatives), new macromolecule)



(d) Self-citations - biotech patents

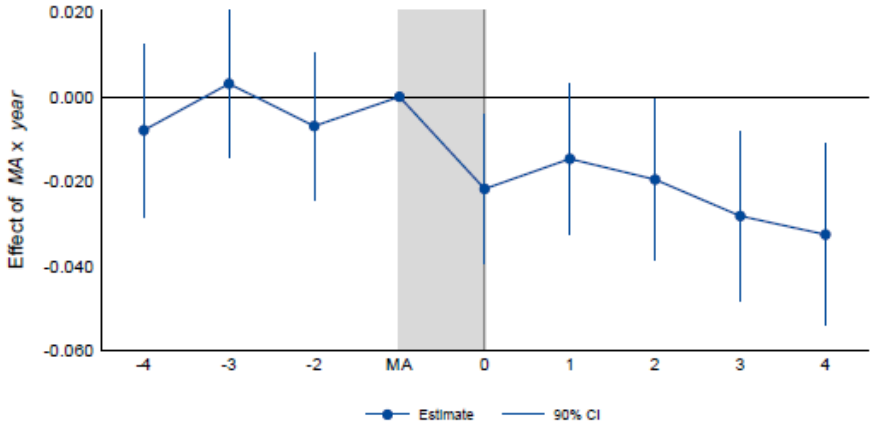
(e.g., biological product/process patents)



MA & self-citations: by disease; & placebo events

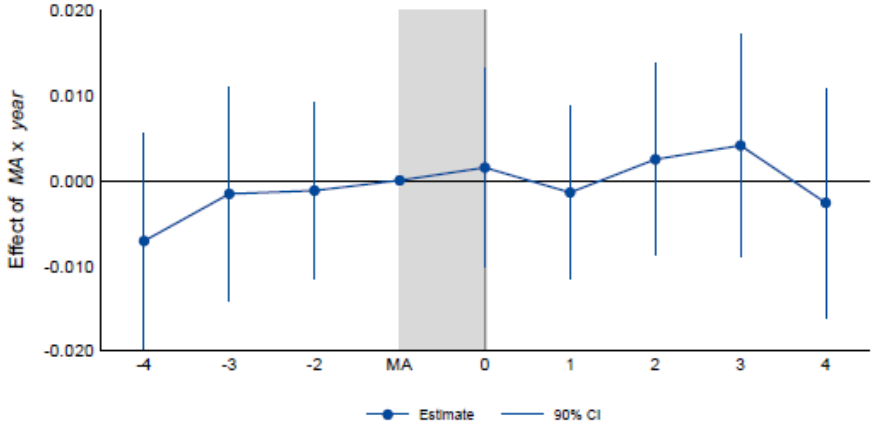
(e) Self-citations - same ICD-9

Same disease area/indication as approved drug



(f) Self-citations - different ICD-9

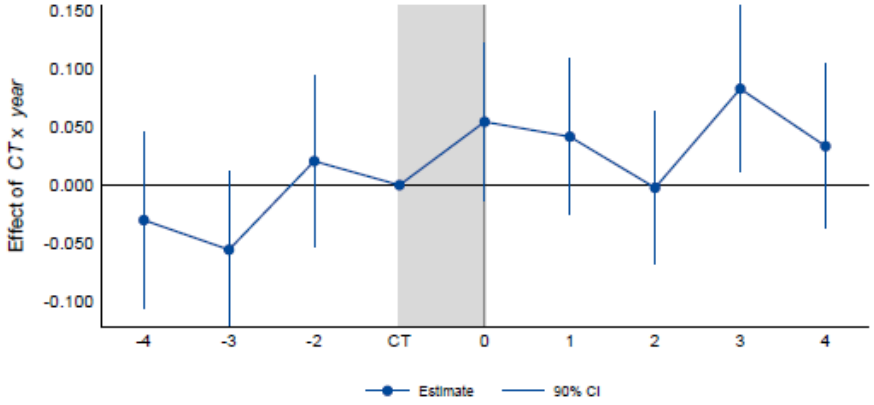
Explore new treatment options for a focal drug

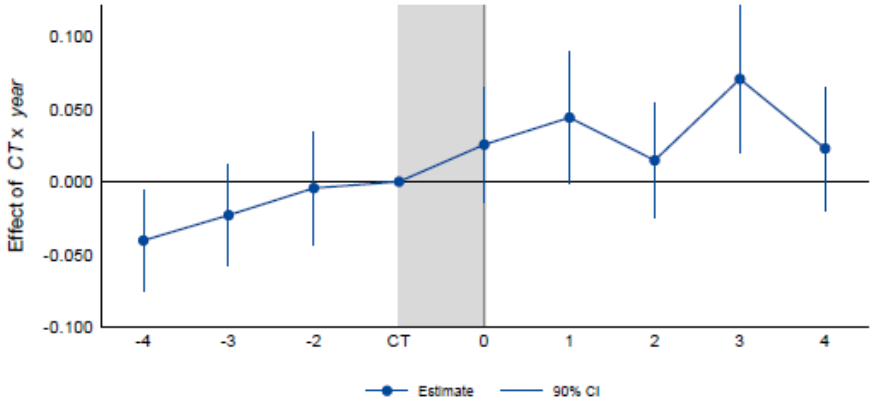


(g) Phase II/III: self-citations - all patents

(h) Phase II/III: self-citations - secondary patents

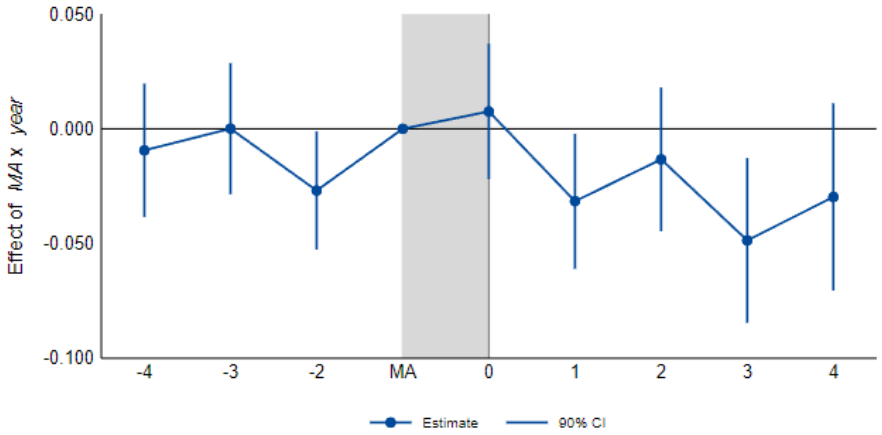
Use end of phase II/start of phase III as a major milestone event to test the mechanism (disclosure/enforceability)



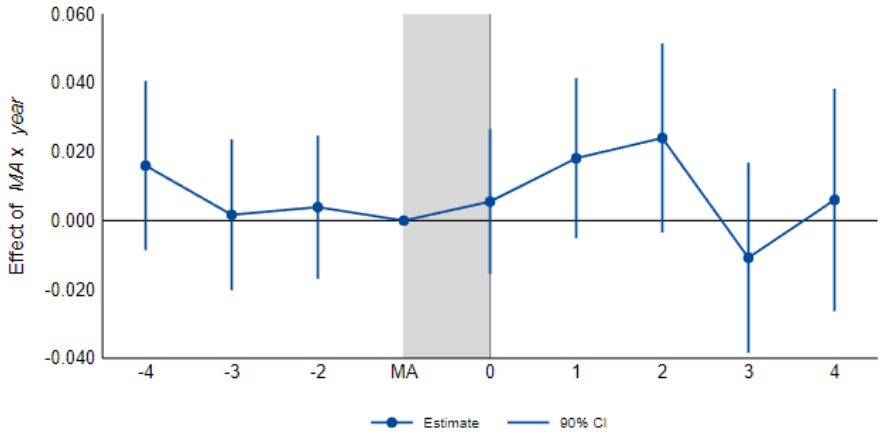


MA & **other** parties' forward citations: big picture

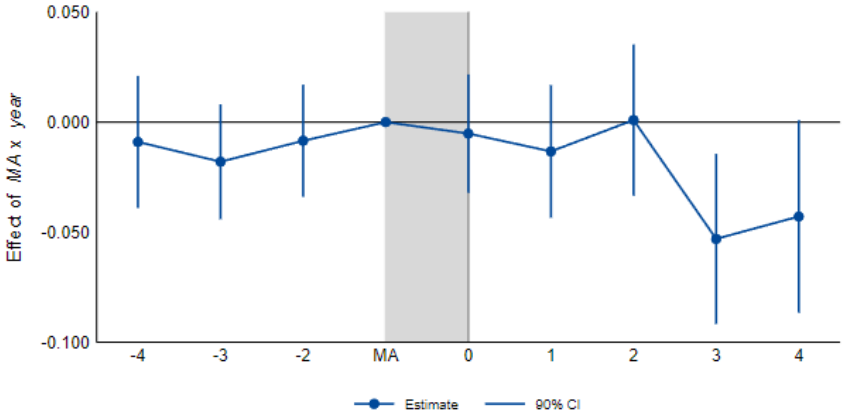
(a) Other citations - secondary patents



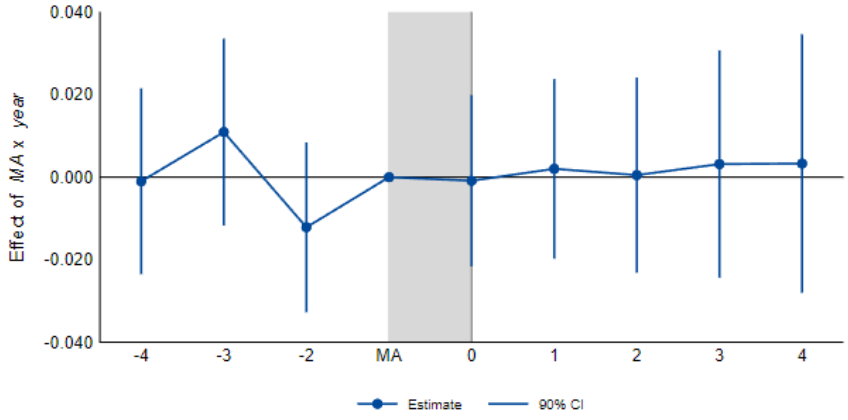
(b) Other citations - product patents



(c) Other citations - same ICD-9



(d) Other citations - different ICD-9

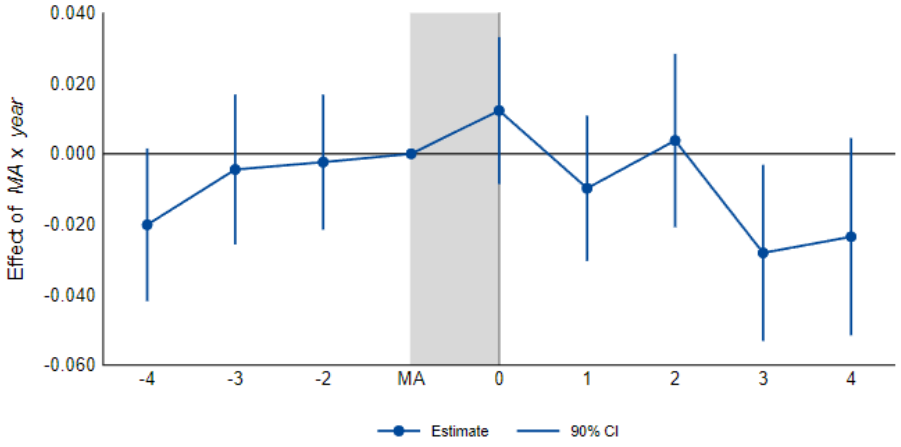


MA & other citations: by vertical relationship

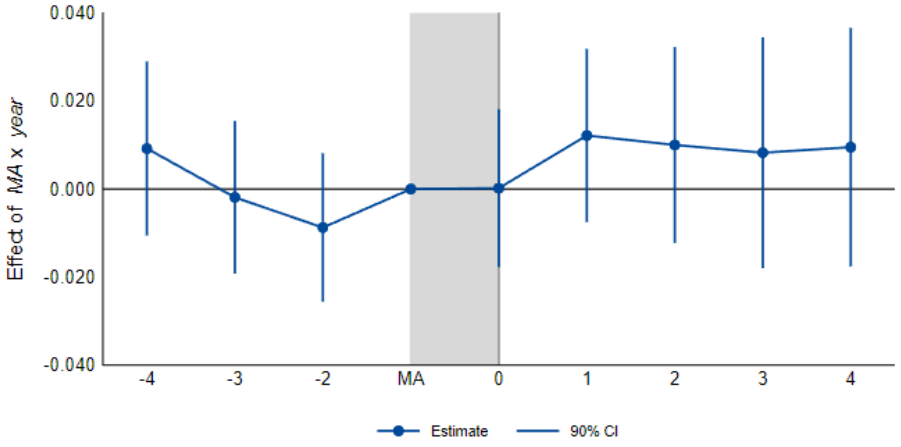
- The originator is likely to have several collaborators when developing an NME and executing clinical trials.
- Follow-on patenting and innovation activities surrounding the focal drug are often conducted by different parties.
- Generic firms file for a substantial number of secondary patents to protect their own exclusivity when generic entry happens (Howard, 2007)

(e) Citations - vertically related

(presumably vertically related via observed clinical collaboration)



(f) Citations - not vertically related



MA and forward citations: results summary

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	DV: Log Forward Citations							
	All	Self	Other	Secondary	Process	Product	= ICD9	≠ ICD9
n years before MA	-0.006	0.006	-0.012	-0.024	-0.018	0.014	-0.026	0.017
	(0.038)	(0.021)	(0.037)	(0.026)	(0.013)	(0.020)	(0.025)	(0.022)
4 years before MA	-0.023	-0.015	-0.010	-0.019	-0.022*	0.003	-0.016	-0.011
	(0.031)	(0.020)	(0.028)	(0.020)	(0.011)	(0.017)	(0.021)	(0.015)
3 years before MA	-0.034	-0.005	-0.035	-0.009	-0.008	-0.005	-0.014	0.008
	(0.028)	(0.018)	(0.027)	(0.020)	(0.011)	(0.015)	(0.018)	(0.015)
2 years before MA	0.003	-0.009	0.009	-0.040**	-0.018*	0.006	-0.010	-0.013
	(0.026)	(0.017)	(0.024)	(0.018)	(0.009)	(0.014)	(0.018)	(0.014)
Year of MA	-0.023	-0.027*	-0.001	-0.015	0.002	0.003	-0.022	-0.001
	(0.026)	(0.016)	(0.025)	(0.019)	(0.012)	(0.014)	(0.017)	(0.014)
1 year after MA	-0.017	-0.029*	0.006	-0.049***	0.012	0.017	-0.024	0.001
	(0.028)	(0.016)	(0.026)	(0.019)	(0.013)	(0.015)	(0.019)	(0.014)
2 years after MA	-0.024	-0.036**	0.001	-0.036*	-0.010	0.022	-0.014	0.002
	(0.032)	(0.017)	(0.030)	(0.020)	(0.014)	(0.018)	(0.022)	(0.016)
3 years after MA	-0.084**	-0.040**	-0.050	-0.075***	-0.015	-0.011	-0.073***	0.003
	(0.037)	(0.019)	(0.035)	(0.022)	(0.016)	(0.018)	(0.024)	(0.018)
4 years after MA	-0.074*	-0.046**	-0.037	-0.058**	-0.015	0.006	-0.068**	-0.002
	(0.040)	(0.021)	(0.039)	(0.025)	(0.017)	(0.020)	(0.027)	(0.020)
n years after MA	-0.120**	-0.053**	-0.076	-0.090***	-0.019	-0.009	-0.083**	-0.027
	(0.049)	(0.025)	(0.047)	(0.028)	(0.019)	(0.024)	(0.032)	(0.023)
Patent Grant	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
SPC Grant	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patent-Drug FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Citation Year FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	12390	12390	12390	12390	12390	12390	12390	12390
Cluster	590	590	590	590	590	590	590	590

Additional Analysis and Robustness Checks

- To rule out alternative factors that might explain the decrease in forward citations due to drug approvals, such as

- **Market exclusivity & incentives for competitive entry**:
  - Given the fixed primary patent term (20 years from filing), earlier MA -> longer market exclusivity, can + competitive entry & certain innovation
  - If early MA -> more competition -> incentive to file 2ndary patent, then we underestimate the magnitude of the net post-MA reduction in patenting
  - Strategy: Zoom in a subset with constant ME due to a kink in SPC regime

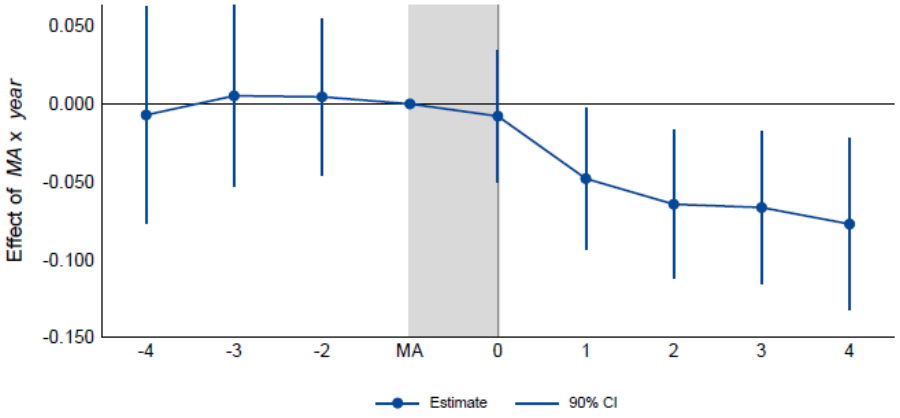
- **Unpredictable delays in approval**: If more valuable drugs were approved earlier, this would introduce upward bias into our event study estimates
  - Strategy: instrumental variable approach (IV: time-to-phase I)

- **Field of application**: whether effects are driven by unobserved differences in disease categories, as secondary patents are more relevant for some therapeutic areas, e.g., depressants (Abd et al., 2015)
  - Strategy: leave-one-out ICD-9 disease area specific analyses

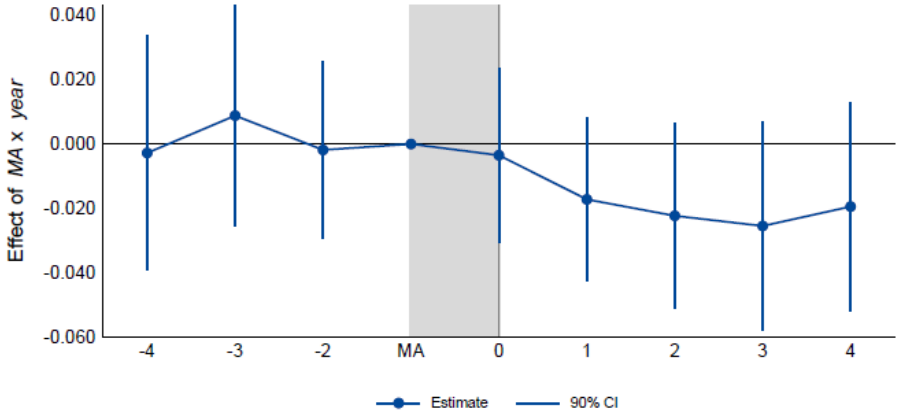
Market Exclusivity & Incentives for Competitive Entry

- **Strategy**: exploit the discontinuity (kink) in market exclusivity *extensions* provided by the SPC system: uniform total ME (15 years) for focal inventions authorized 5-10 years from priority dates SPC fig
  - Here ME is indept of the approval lag (constant incentives for competitive entry)
- **Results**: robust to this restriction and some point estimates become slightly larger, supporting the notion that the true effects are larger
  - Some estimates are less precise given the drop of sample size

(a) Self-citations - all patents



(b) Self-citations - secondary patents



Unpredictable Delays in Approval: IV estimation

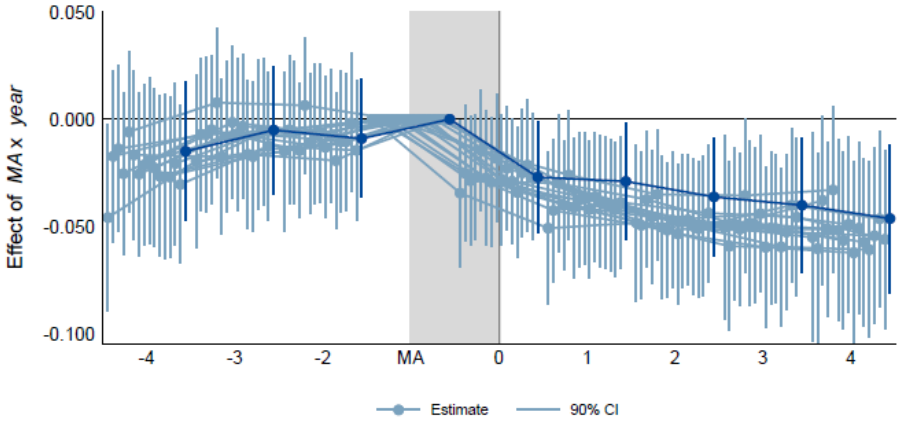
- IV approach: time from patent filing to the beginning of phase 1 trial (IV) is the most random part able to predict the whole lag (à la Gilchrist 2016)
  - cross-sectional data using the total # of self-cites as Y, IV (file to 1st trial) for the time to approval; IV estimates > OLS (oppos. to the worry of upward bias)
  - Results suggest our event study estimates are conservative (likely l.b.)

Log/Linear	(1)	(2)	(3)	(4)	(5)	(6)
DV: Log Self Citations	IV: Time to Phase I Trials			IV: Time to Phase III Trials		
	OLS	Reduced Form	IV	OLS	Reduced Form	IV
Time to Approval (Priority)	0.049		0.290*	0.045		0.060
	(0.051)		(0.169)	(0.040)		(0.055)
IV: Time Phase I		0.082*				
		(0.044)				
IV: Time Phase III					0.047	
					(0.044)	
Priority Year FE	Yes	Yes	Yes	Yes	Yes	Yes
Patent Grant Year FE	Yes	Yes	Yes	Yes	Yes	Yes
Patent Controls	Yes	Yes	Yes	Yes	Yes	Yes
Underidentification test			9.18			36.99
Weak identification test			9.34			82.33
Observations	77	77	77	125	125	125

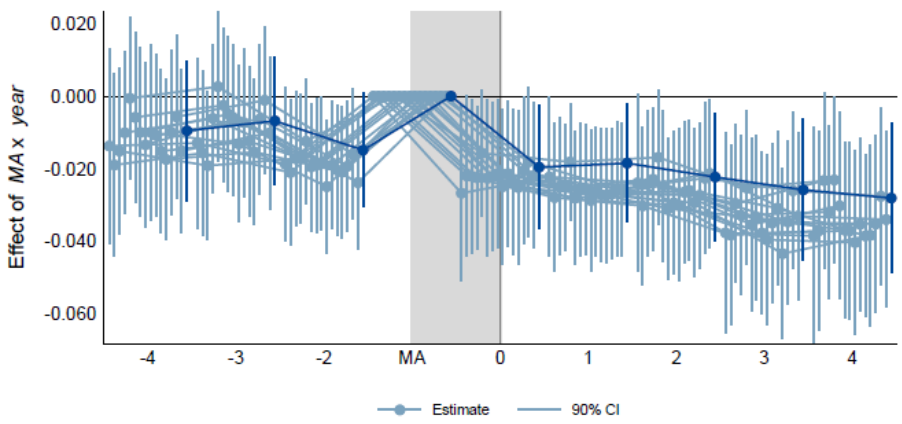
Field of Application: leave-one-out ICD-9 analysis

- Concern: differences in unobservables can yield other dynamics not captured by patent-drug fixed effects
- Strategy: estimate leave-one-out event studies separately for each of the 16 ICD-9 disease categories
- Results & conclusion: similar patterns; strategic patenting behaviors are not driven by various incentives across drug types

(c) Self-citations - all patents



(d) Self-citations - secondary patents



Conclusion & Discussion

- We find that strategic follow-on patenting **decreases** after a drug's market authorization, when the patentability standards are higher
  - More reductions for less novel patents: secondary/process patents, patents target the same disease areas, by firms themselves & related parties
  - Not much change in meaningful follow-on patenting: product patents, patents target different disease areas, and biotech patents
  - Self-citation drops are most pronounced in high-quality citations: novelty-threating citations (XY citations) and examiner-added citations
  - Empirical test indicates enforcement channel (w higher patentability bars)
- Suggest increasing patentability standard within the current system, e.g., through product market related info (prior art) disclosure, can reduce marginal patents and direct to more meaningful patents
- Complementing "ex ante regulation" suggestions to give examiners more time (Frakes & Wasserman, 2023), regulatory data disclosure in the drug approval process can spur more valuable, enforceable patents