Does Regulation Hurt Innovation in Animal Pharma? The Case of New Animal Antibiotics

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The views expressed are those of the authors and should not be attributed to the Economic Research Service or USDA.

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Background

- The public health ramifications of antibiotic resistance have increasingly become a source of international policy concern. Antibiotics are widely used both in human health and in livestock production, and any use of antibiotics (in humans or animals) can encourage the development and spread of antibiotic resistance.
- The Food and Drug Administration (FDA), which regulates animal drugs in the US, passed Guidance for Industry #152 (GFI#152) in 2003, requiring new animal drug applications (NADAs) to include studies on the likely impact of the candidate drug on antibiotic resistance. GFI#152 imposed new costs on getting certain drugs approved for sale in the US and may have prevented the approval of others. The policy also reduced the value of some already approved antibiotics by restricting their allowed uses.
- GFI#152 may have led firms to shift research and development (R&D) away from antibiotics for use in animal agriculture. The absence of new drugs might then raise the cost of animal agriculture.
- Like the biotech, seed, and pesticide industries, the animal pharmaceutical industry plays a pivotal role in domestic and international agricultural productivity by developing and marketing antibiotics and other products that impact animal welfare, performance, and disease. This industry's choices of future product sales and development have important ramifications for agriculture, food prices, and public health.
- However, little research in economics covers this industry and the ramifications of regulations on it. We begin to fill this gap by addressing how a piece of legislation making drug approval more difficult impacted innovation.

Research Questions

- Did GFI#152 result in fewer animal antibiotic approvals, compared to non-antibiotic approvals?
- Did GFI#152 result in shifting to greater numbers of approvals for vaccines, largely seen as a potential antibiotic alternative?
- With its focus on reducing antibiotic resistance, did GFI#152 result in a shift to antibiotics being approved under prescription status (versus over-the-counter or under veterinary feed directives)?
- Did GFI#152 reduce innovation for antibiotics containing new chemical entities (called “original” and “pioneer” drugs)?

Data

- In the U.S. veterinary products are vetted and approved by two primary government bodies before they can be marketed. "Drugs" are covered by the FDA's Center for Veterinary Medicine (CVM). "Biologics" (including vaccines) are overseen by the USDA's Animal and Plant Health Inspection Service (APHIS).

- We generated a novel dataset of all animal drug and biologic approvals through a combination of FDA and USDA assistance, and by text-scraping online and archived documents. At the moment, we have information on all 2,165 FDA approved veterinary drugs dating back to 1941, and 7,712 USDA approved biologics, dating back to 1968.

- For approved drugs, we have information on the species the drug has been approved for, the dispensing status (i.e., by prescription only, veterinary feed directive, or over-the-counter), whether the drug is an antibiotic, in addition to other information.

- Using the drug descriptions and ingredients, we define a drug to be "original" if it contains any ingredient that does not appear in any previously approved drug. We define drugs that are subsequently used as the basis for a generic drug as "pioneers".

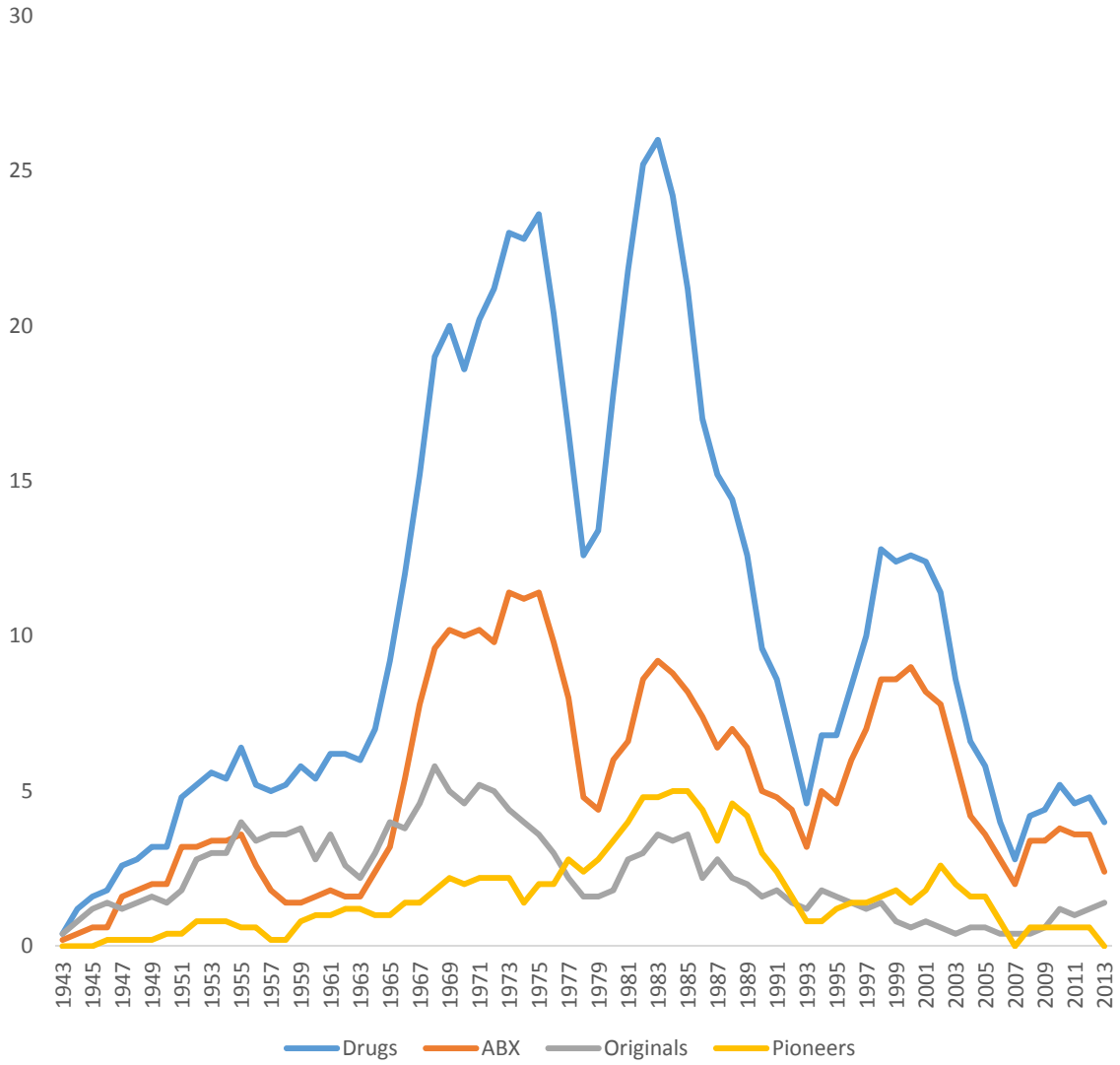
- We control for market size using USDA market-level data.

Table 1. Number of Non-generic Health Products Approved for Major Food Producing Species

	Drugs approved by FDA Center for Veterinary Medicine, 1943-2017					Biologics approved by USDA's Animal and Plant Health Inspection Service, 1985-2017	
Major food animal species	**All**	**Antibiotics**	**Over-the-counter**	**Originals**	**Pioneers**	**Biologics**	**Vaccines**
Cattle	359	202	260	93	56	146	82
Chickens	285	148	278	57	57	128	91
Swine	260	120	215	50	39	114	71
Turkeys	109	73	103	25	20	45	24
Total	**748**	**371**	**631**	**165**	**121**	**396**	**256**

Source: Economic Research Service, USDA.

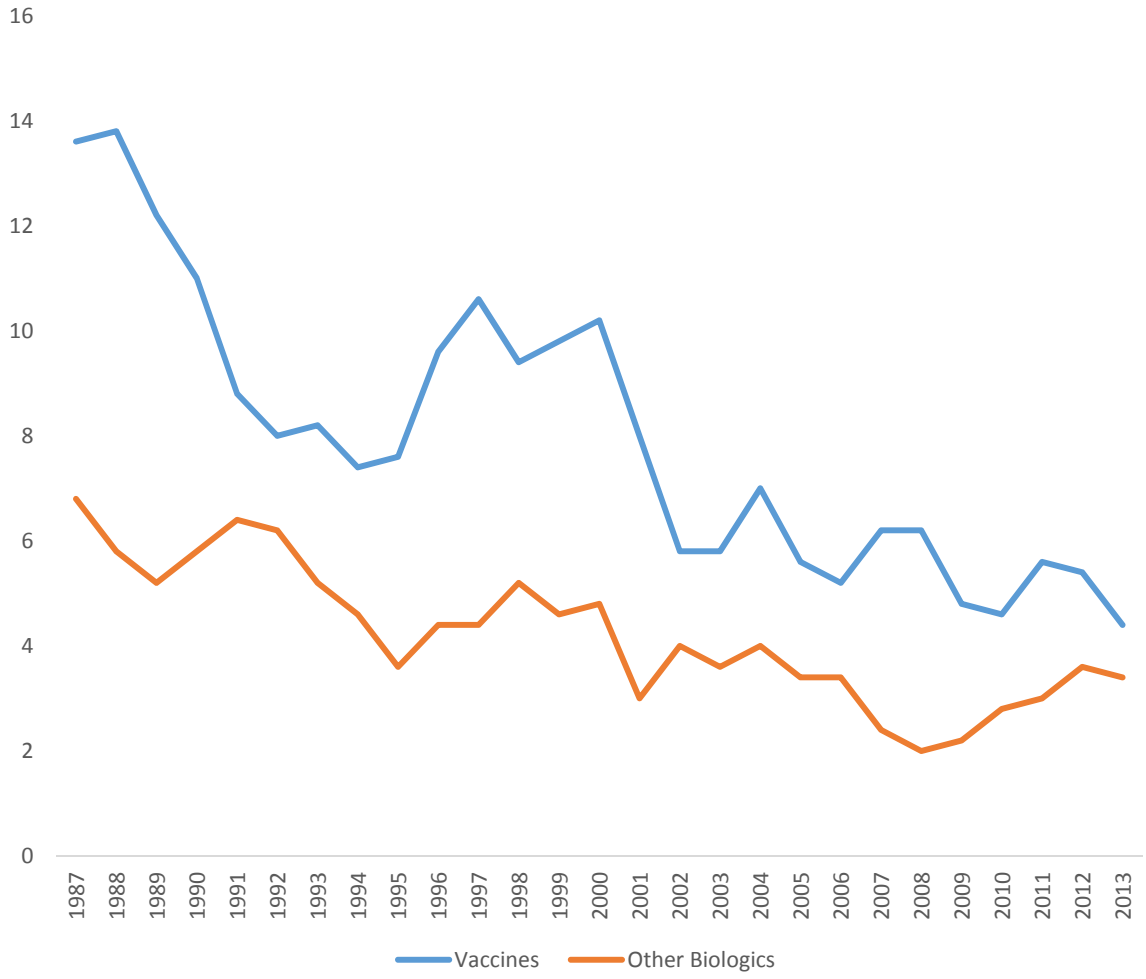
Figure 1. Non-Generic Drug Approvals for Food Production Animals, 1943-2013 (centered 5 year moving average)



Source: Economic Research Service, USDA.

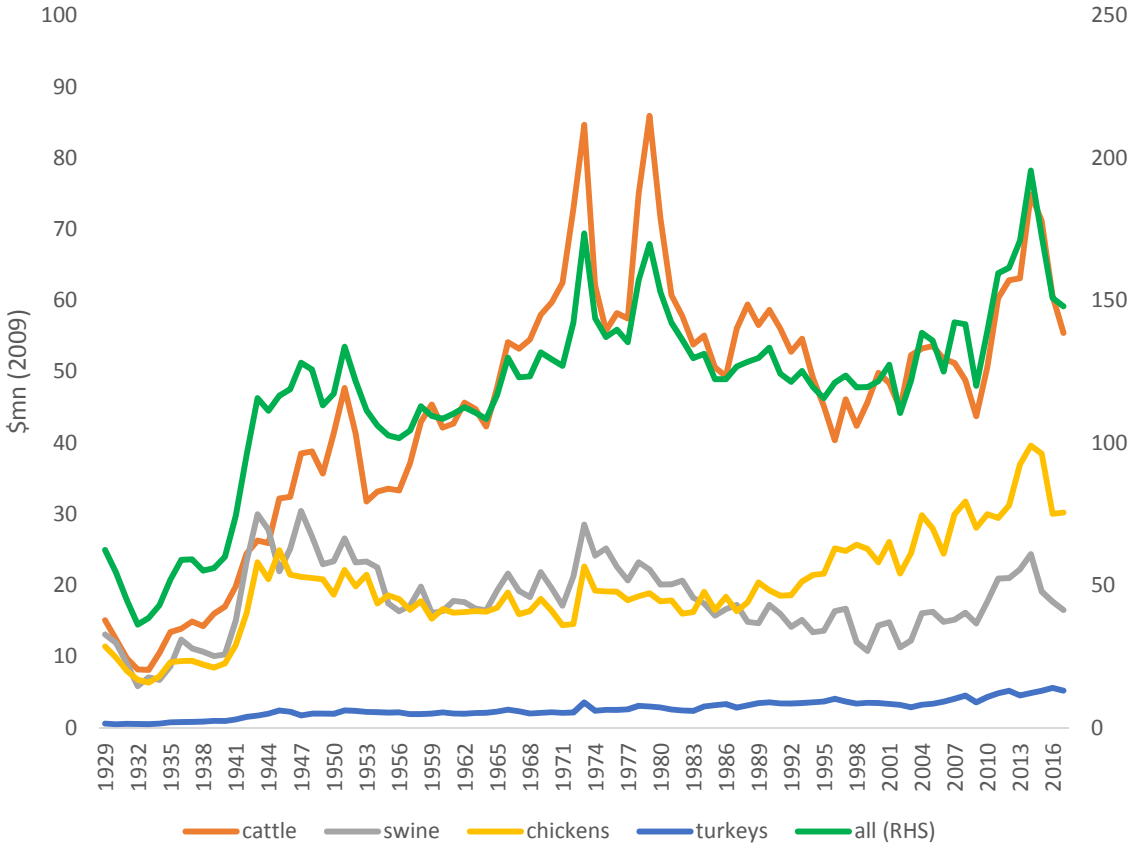
Notes: "Drugs" are all non-generic products approved by FDA's CVM. "ABX" refers to non-generic antibiotics. "Originals" are new chemical entities; non-originals are those products that are new compounds of previously approved chemical entities or new label uses of previously approved chemical entities. "Pioneers" are products that form the basis for generics.

Figure 2. Biologic Approvals for Food Production Animals, 1987-2013 (centered 5 year moving average)



Source: Economic Research Service, USDA.

Figure 3. Cash Receipts (Real 2009 Dollars) by Commodity



Source: USDA ERS. The 2016 and 2017 figures are forecasts. We USDA ERS: For everything but Turkeys, download real 2009 dollars as well as nominal dollars from "Annual cash receipts by commodity (condensed), U.S. and States, 1910-2017F" series on https://www.ers.usda.gov/data-products/farm-income-and-wealth-statistics/data-files-us-and-state-level-farm-income-and-wealth-statistics/. For Turkeys, we download the "Turkeys Production," measured in nominal dollars, from NASS Quickstats. We generate a deflator for the turkey series by comparing the nominal and 2009-chained values for cattle, swine, and chickens. We use this deflator to convert the turkey series from nominal to real dollars.

Empirical Methods

Our goal is to estimate whether the adoption of GFI#152 led to changes in the types of products approved. Ergo, we would like to examine the impact on, for example, the development of new antibiotics before and after 2003, compared to development of non-antibiotics. This suggests a difference-in-difference approach, but with variations.

We first divide approvals into categories according to health product type in order to calculate the number of products of that type approved per year. These groupings are more or less narrow, depending on the question of interest.

Let y_{jt} be a count of health products approved in year *t* in category *j*. Our regression takes the form:

$$y_{jt} = f\left(\sum_j \alpha_j \cdot Cat_j + \sigma \cdot Post2003 + \sum_j \delta_j \cdot Cat_j \cdot Post2003 + X'\beta\right) \quad (0.1)$$

Where the function $f(\bullet)$ is an appropriate model for count data, typically a poisson process. The explanatory variable Cat_j is a dummy variable equal to 1 if the observation belongs to category j and *Post2003* is a dummy variable equal to 1 if the year is greater than 2003. The coefficients δ_j on the interaction terms between Cat_j and *Post2003* track how each drug category has fared since 2003, relative to a baseline category. We interpret this as the impact of GFI #152, which took effect in this year, on this category of health product. Naturally, this interpretation requires our assumption that there were no other category specific factors that occurred after this year.

Additional explanatory variables *X* include time trends and estimates of the (domestic) market size for drugs.

Results

- 5 categories of health products: over-the-counter (OTC) non-antibiotic drugs, prescription (RX) non-antibiotic drugs, OTC antibiotic drugs, RX antibiotic drugs, and biologics.
- Annual approvals for each drug category for 1944-2015.
- Annual biologics approvals for 1985-2015.
- In some regressions, we further divide each of these categories into approvals by the four major food animal species: cattle, poultry, swine, and turkeys. This gives us 20 species-health categories, for example, OTC non-antibiotics for cattle. In each case we include as a control variable total US cash receipts (in real 2009 dollars) for animals and animal products, and cash receipts for each of these major species when we divide health products up by species.
- In each regression, we also include category specific fixed effects, and various time trends.

Table 2. Regression Results – Policy Impact

Dependent variable: Annual Product Approvals by Category

	(1)	(2)	(3)	(4)	(5)	(6)
log(total market)	2.035***	2.609***	2.078***	1.914***	2.348***	1.968***
	(0.278)	(0.295)	(0.280)	(0.291)	(0.300)	(0.318)
log(own species market)				0.036	0.045	-0.005
				(0.162)	(0.161)	(0.207)
Year > 2003	-2.677***		-2.793***	-2.600***		-2.758***
	(0.349)		(0.360)	(0.329)		(0.340)
(Year > 2003) x RX Non-Antibiotics	1.422**		2.585***	1.246*		2.011**
	(0.549)		(0.660)	(0.534)		(0.666)
(Year > 2003) x OTC Antibiotics	0.924*		0.776	0.757*		0.751
	(0.407)		(0.438)	(0.383)		(0.409)
(Year > 2003) x RX Antibiotics	2.508***		2.429***	2.621***		2.625***
	(0.446)		(0.548)	(0.406)		(0.495)
(Year > 2003) x Biologics	1.468***		2.512***	1.483***		2.538***
	(0.360)		(0.416)	(0.342)		(0.395)
Max[Year – 2003,0]		-0.415***			-0.378***	
		(0.065)			(0.057)	
Max[Year – 2003,0] x RX Non-Antibiotics		0.298***			0.252***	
		(0.081)			(0.075)	
Max[Year – 2003,0] x OTC Antibiotics		0.170*			0.136*	
		(0.073)			(0.064)	
Max[Year – 2003,0] x RX Antibiotics		0.370***			0.357***	
		(0.074)			(0.064)	
Max[Year – 2003,0] x Biologics		0.238***			0.216***	
		(0.067)			(0.059)	
Observations	319	319	319	1,276	1,276	1,276
Product Categories	Health	Health	Health	Health x Species	Health x Species	Health x Species
Category Fixed Effects?	Y	Y	Y	Y	Y	Y
Time Trends	Linear	Linear	Linear	Linear	Linear	Linear
Category Trends	N	N	Y	N	N	Y
Log Likelihood	-672	-672	-649	-1,524	-1,533	-1,486
Akaike Inf. Crit.	1,369	1,369	1,330	3,104	3,123	3,066

Note: *p<0.05; **p<0.01; ***p<0.001

Health categories include [OTC Non-Antibiotics, RX Non-Antibiotics, OTC Antibiotics, RX Antibiotics, Biologics]
Species categories include [Cattle, Poultry, Swine, Turkeys]

Explanation of Table 2:

- Columns 1, 3, 4, and 6 assess the impact of GFI #152 by looking for a discrete shift in the annual number of product approvals by category, after 2003. Column 1 is a baseline. Not included in the table are fixed effects for each product category and a time trend.
- Annual product approvals dropped after 2003 for all categories.
- Relative to the baseline of over-the-counter (OTC) non-antibiotic drugs, OTC antibiotics decreased by less. Prescription or VFD (RX) antibiotics also decreased by less than the baseline, and by less than RX non-antibiotics. Indeed, RX antibiotics barely dropped at all after the policy took effect. Annual approvals of biologics also dropped by less than the baseline.
- Column 1 models the impact of GFI #152 as a discrete shift in the annual number of health products after 2003. However, it may also be that the impact of the policy was gradual, only taking full effect after all products whose development was initiated prior to 2003 are approved. Column 2 investigates this possibility by modeling the impact of GFI#152 as a change in trend. This does not substantively alter our conclusions. The trend for all health products is reduced after 2003, but relative to baseline (OTC non-antibiotics) the trend for RX antibiotics is highest, followed by RX non-antibiotics and biologics, followed by OTC antibiotics.
- In column 3, we allow each drug category to follow its own (linear) time trend, but otherwise continue to model the impact of GFI #152 as a discrete shift. We continue to find that biologics, and antibiotics (both OTC and RX) had smaller negative shifts compared to our baseline of OTC non-antibiotics. Notably, however, we find some evidence that RX antibiotics were more negatively impacted than RX non-antibiotics.
- Whereas columns 1-3 measure the impact of GFI #152 on the number of products approved, columns 4-6 measure the number of approvals by species. The two concepts are correlated, but distinct. Obtaining approval for a drug (which is what we measure in columns 1-3) implicitly requires the drug sponsor to conduct both initial research designed to discover/understand the drug and clinical trials to prove the drug's efficacy/safety for a target species. Obtaining approval for a specific species only requires the second step, clinical trials. Thus, the cost of getting approval for an additional species is less than the cost of developing a new drug.
- In columns 4-6, we add species-product fixed effects, as well as cash receipts for the species. Column 4 measures the impact of GFI #152 as a discrete shift in approvals per year. Column 5 models the impact of GFI #152 as a change in trend. Column 6 allows each species-product category to have its own time trend.
- Across all specifications, approvals of OTC non-antibiotics and antibiotics decreased the most after 2003.
- OTC non-antibiotics decreased by more than OTC antibiotics, but this relationship is not statistically significant in columns 3 and 6.
- Approvals of RX non-antibiotics, RX antibiotics, and biologics decreased the least after 2003. The coefficient on RX antibiotics and biologics is always statistically significant.

Table 3. Regression Results – High Quality Drugs

	Dependent variable:					
	all	pioneer	original	all	pioneer	original
	(1)	(2)	(3)	(4)	(5)	(6)
log(total market)	2.572***	2.820***	1.224	2.403***	3.409***	1.244
	(0.302)	(0.776)	(0.686)	(0.304)	(0.759)	(0.702)
log(own species market)				-0.056	-1.303**	-0.617
				(0.167)	(0.422)	(0.347)
Year > 2003	-2.864***	-19.086	-1.768*	-2.732***	-18.187	-1.664*
	(0.351)	(1,594.151)	(0.744)	(0.330)	(1,246.347)	(0.736)
(Year > 2003) x RX Non-Antibiotics	1.422**	1.414	1.085	1.240*	1.340	1.012
	(0.549)	(2,254.470)	(1.027)	(0.533)	(1,762.601)	(1.021)
(Year > 2003) x OTC Antibiotics	0.924*	17.298	-15.068	0.758*	16.451	-13.767
	(0.407)	(1,594.151)	(996.696)	(0.383)	(1,246.347)	(459.647)
(Year > 2003) x RX Antibiotics	2.508***	1.531	2.471**	2.617***	0.904	2.485**
	(0.446)	(2,254.470)	(0.884)	(0.405)	(1,762.601)	(0.851)
Observations	288	288	288	1,152	1,152	1,152
Product Categories	Health	Health	Health	Health x Species	Health x Species	Health x Species
Time Trend	Linear	Linear	Linear	Linear	Linear	Linear
Species Fixed Effects	NA	NA	NA	Yes	Yes	Yes
Log Likelihood	-559	-200	-268	-1,303	-421	-550
Akaike Inf. Crit.	1,139	420	557	2,633	869	1,127

Note: *p<0.05; **p<0.01; ***p<0.001

Explanation of Table 3

- Columns 1-3 from Table 4 look at the determinants of drug development across 4 health categories, while columns 4-6 look at the determinants of drug approvals across 16 species-categories.
- Given how few drugs satisfy the criteria of being originals or pioneers, (see Table 1), there is not enough variation within category classes to completely identify all coefficients when species-health category fixed effects are included in columns 4-6. Instead, these models include species fixed effects and health category fixed effects, but not their interaction. Furthermore, because our definitions of original and pioneer drugs are inapplicable to veterinary biologics, these are excluded from the regressions presented.
- Columns 1 and 4 replicate the regressions from columns 1 and 4 of Table 2 without biologics and species-health fixed effects. The results about the impact of GFI #152 are largely unchanged.
- We find no significant impact of GFI #152 on the approval of pioneer drugs. Note that very few pioneers are identified after 1990. This may be due to the fact that we can only identify a pioneer drug after a generic competitor has been introduced, and there is generally a considerable lag between a pioneer drug's approval and the approval of its generic competitor. The median gap between the approval date of generics and pioneers is 21 years, implying only half of pioneers from 1990 will have been identified by 2011.
- Approvals of new prescription antibiotics increased after 2003, both in absolute terms and relative to all other drug categories**.**
- These conclusions are not significantly changed when we turn to approvals by species-health category.

Preliminary Conclusions

- Across all specifications, approvals of OTC non-antibiotics and antibiotics decreased the most after 2003.
- We typically find OTC non-antibiotics decreased by more than OTC antibiotics, but this relationship is not statistically significant.
- Approvals of RX non-antibiotics, RX antibiotics, and biologics decreased the least after 2003.
- GFI#152 did not appear to impact the development of high-quality new innovations.
- Our results suggest GFI #152 did not reduce the production of new antibiotics. It did, however, shift antibiotic approvals towards those requiring prescriptions and raise the production of veterinary biologics, which can substitute for the use of antibiotics in many settings.