PRIORITY REVIEW VOUCHERS TO ENCOURAGE INNOVATION FOR NEGLECTED DISEASES

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Priority Review To Encourage Treatments For Tropical Diseases

Section 1102 of FDA Amendments Act of 2007

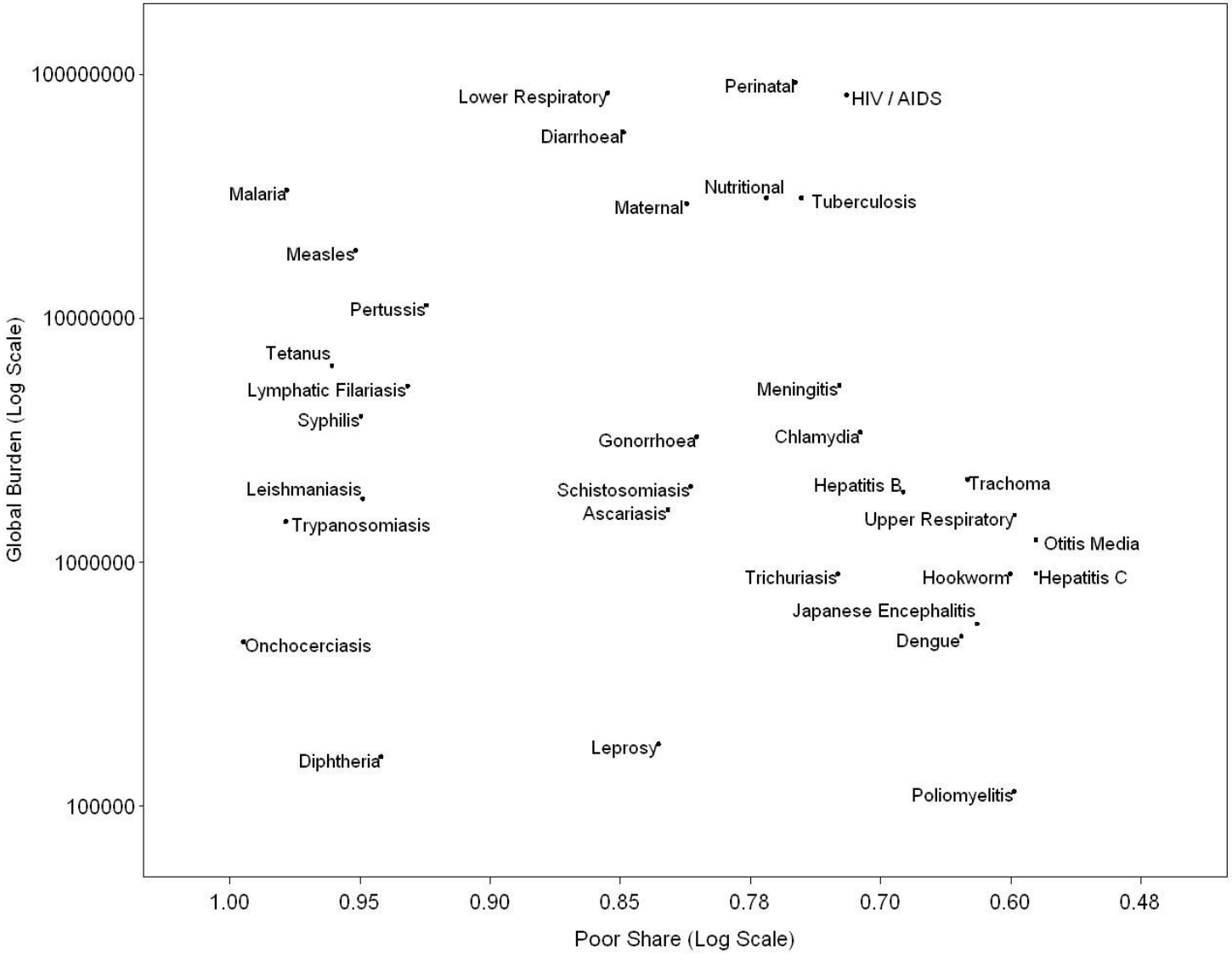
- 16 tropical diseases named in the law
- “Prize” for a new tropical disease drug or vaccine approval is a priority review voucher
- A PRV entitles the bearer to priority review on another drug of its choice

Tropical Diseases Specifically Covered by the PRV Amendment

- Tuberculosis, Malaria, blinding trachoma, buruli ulcer, cholera, dengue/dengue haemorragic fever, dracunculiasis (guinea-worm disease), fascioliasis, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchoceciasis, schistosomiasis, soil transmuted helmithiasis, and yaws
- FDA all empowered to add other diseases –

  "Any other infectious disease for which there is no significant market in developed nations and disproportionately affects poor and marginalized populations, designated by regulation of the Secretary"

Annual Global Burden of Disease (DALYs) vs. Share of Burden in Developing Countries, 2005



Background to the Legislation

- 2006 *Health Affairs* article, “Developing Drugs for Developing Countries”
- Senators Brownback and Sherrod Brown add PRVs to FDAA Act of 2007
- Various legislative concerns in the House
- PRV amendment passes in 9/2007

Novelty Criteria to Obtain a PRV

- Drug approved by FDA for a tropical disease must be eligible for priority review
- New indications, formulations or combinations of approved drugs excluded
- But U.S. need not be country of first approval

Some Important Features of Priority Review Vouchers

- Vouchers can be transferred or banked
- Companies must pay a supplemental user fee to utilize a priority voucher
- Companies must give FDA 365 days notice before using the voucher

PRVs Complement Other Initiatives for Neglected Diseases

- PRVs complement other “push” and “pull” initiatives
- Drugs and vaccines for tropical diseases are eligible for a 50% orphan drug R&D tax credit
- Private-public partnerships and company philanthropic activities can benefit from PRVs

Push & Pull Mechanisms

Mechanisms	Pros			Cons	
	Drugs for neglected diseases	Donor pays only if drug	Other pros	Rewards seren-dipity	Other cons
1. Push: $ for R&D	+				-Donor pays in advance -Little incentive for cost control
2. Pull: Guaranteed price	+	+		-	-Time consistency problem
3. Pull: Voucher for extended patent life	+	+		-	-Higher premiums -Some deadweight loss from generic delay
4. Pull: PRV	+	+	+Speeds potential blockbuster	-	-Uncertain value -Drug safety issues?

Global Social Value From PRVs

- Biggest potential benefit involves effective new medicines for tropical diseases
- US consumers could also benefit from early availability of the voucher drugs
- These benefits must be balanced against increased R&D expenditures including government financed tax credits

Necessary Conditions for PRV

1. To create a market for the vouchers:

   Incremental returns from priority review (over standard) $\geq$ voucher price + incremental FDA user fee

1. To induce R&D for drugs for neglected diseases:

   Voucher price + push subsidies + goodwill $\geq$ R&D cost of developing treatment for neglected disease

R&D Costs for Neglected Diseases

- 0rphan drug credit available for 50 % of clinical development costs
- PDPs exploring many existing compounds that would be eligible for the voucher
- Spillovers also available from other public programs (eg Project Bioshield)

The Value to Companies From Priority Review

- The median difference in priority versus standard reviews is 7 months for recent approvals
- Approximately half of the largest selling drug introductions in the 1990s received standard reviews
- A transferable voucher would have optimal value for drugs with high expected sales and standard reviews

Approval Times (Months) for Priority and Standard NMEs and New BLAs since 2000

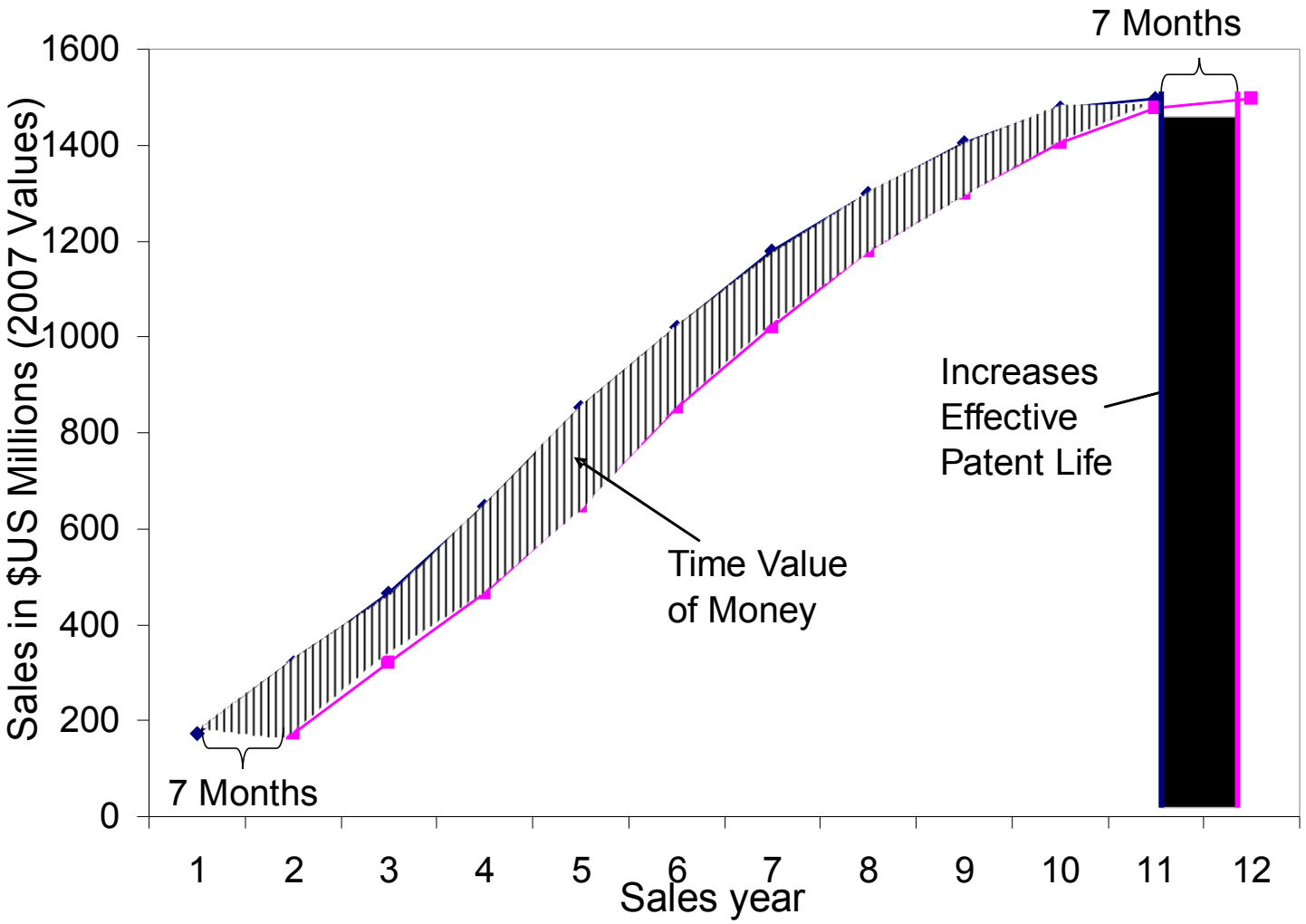
Calendar Year	Standard Review Median Total Approval Time	Priority Review Median Total Approval Time	Differences for Median Total Approval Time	Standard Review Median FDA Review Time	Priority Review Median FDA Review Time	Difference for Median FDA Review Time
2000	19.9	6	13.9	15.4	6	9.4
2001	19	6	13	15.7	6	9.8
2002	15.9	16.3	-0.4	12.5	13.8	-1.3
2003	23.3	6.7	16.4	13.8	6.7	7.1
2004	24.7	6	18.8	16	6	10
2005	23	6	17	15.8	6	9.8
2006	13.7	6	7.7	12.5	6	6.5
Mean	20	8	12	15	7	7

Beginning in 2004, these figures include new BLAs for therapeutic biologic products. Source: http://www.fda.gov/cder/rdmt/NMEapps93-06.htm

Components of Value from Priority Review

- Time value of money
- Increases in effective patent life
- First or early mover advantages

U.S. Sales Profile with Voucher



Stylized Example

- PRV shifts introduction date forward by 7 months and leaves patent expiration unchanged
- Expected patent life is 11 years
- Sales at peak are $1.5 billion
- Cost of capital is 11%

Implications

- Expected value of increased sales (before deductions for expenses and taxes)

– Time value of money component	$322.00 million
– Increased patent life	$277.00 million
Total	$599.00 million

- Expected value of after tax income →

  $150 to $200 million

Will PRVs Increase Effective Patent Life?

Hatch-Waxman formula for patent life extension on a new molecular entity

Patent term extension =
½ (development time) + review time

Patent Term Restoration is Subject to Important Constraints

- Maximum patent life restoration is 5 years
- No restoration beyond 14 years of effective patent life from date of approval
- But firms also may obtain an additional 6 months of “pediatric exclusivity”

Standard Review Drugs With More Than $1 Billion in Sales in the Year Before Generic Entry

BRAND (CHEMICAL NAME)		GENERIC ENTRY	FDA APPROVAL	MARKET EXCLUSIVITY[A]	GENERIC TRIGGER EVENT
1	Zestril/Prinivil (lisinopril)	June 2002	December 1987	14 years 6 months	14 year Hatch-Waxman EPL
2	Paxil (paroxetine)	September 2003	December 1992	10 years 8 months	Litigation
3	Celexa (citalopram)	October 2004	July 1998	6 years 3 months	Litigation
4	Allegra (fexofenadine)	September 2005	July 1996	9 years 2 months	Litigation
5	Pravachol (pravastatin)	April 2006	October 1991	14 years 6 months	14 year Hatch-Waxman EPL
6	Zocor (simvastatin)	June 2006	December 1991	14 years 6 months	14 year Hatch-Waxman EPL
7	Zoloft (sertaline)	August 2006	December 1991	14 years 6 months	14 year Hatch-Waxman EPL
8	Norvasc (amlodipine)	March 2007	July 1992	14 years 8 months	Litigation
9	Ambien (zolpidem)	April 2007	December 1992	14 years 4 months	5 year Hatch-Waxman Extension
10	Coreg (carvedilol)	September 2007	September 1995	12 years	5 year Hatch-Waxman Extension
11	Protonix (pantoprazole)	December 2007	February 2000	7 years 11 months	Litigation

Note: A A 6 month pediatric exclusivity period was added to the listed patents for all these products except Protonix

Strategic Uses of Hatch-Waxman Act by Generics

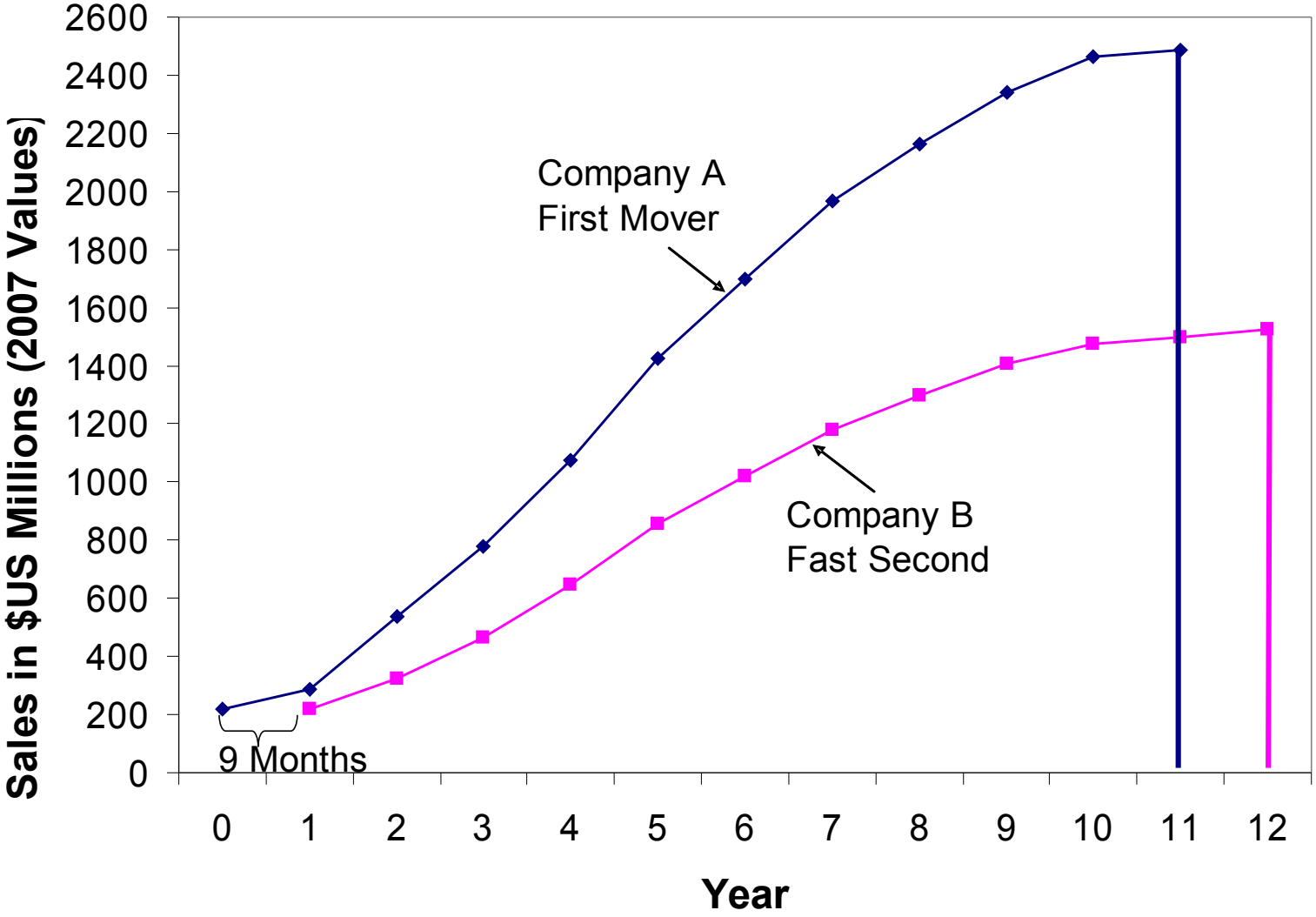
- Generics compete to be the first firm to challenge patents for 180 day exclusivity
- Generic firms have developed a business model involving prospecting in patent suits
- Major branded products are subject to patent challenges four years after launch

Priority Review Vouchers and First Mover Advantages

Scenario Assumptions –

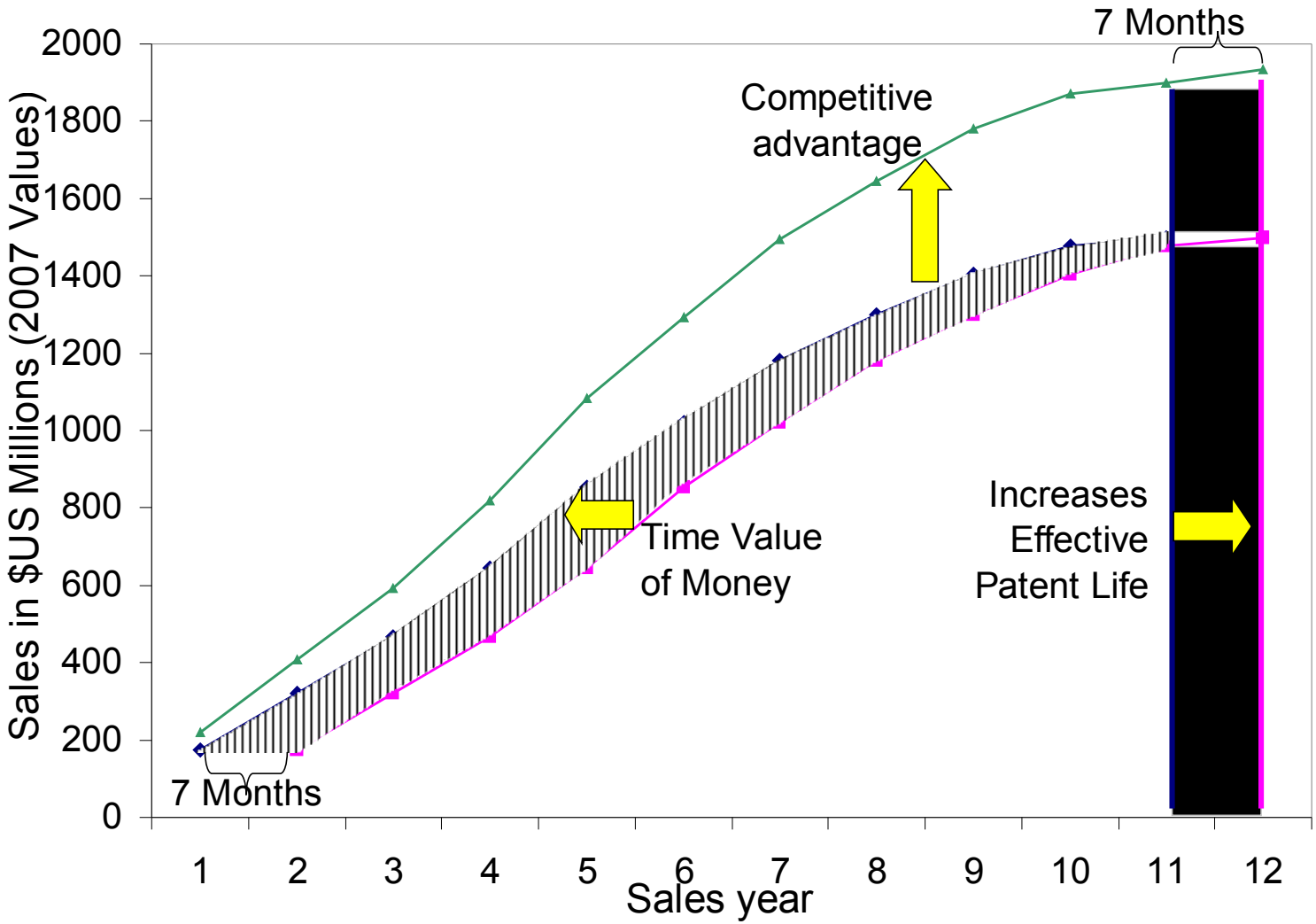
- Assume two companies in a race to introduce a new class of therapies for large expected market
- Company A is 2 months ahead in expected NDA filings and will receive priority review
- Company B expects standard review as second entrant to market with launch lag of 9 months

First Mover Advantage



2 Has Priority Review Voucher

Reduces delay from 9 to 2 months



FDA Will Play A Critical Role in the Evolution of Markets for Vouchers

- Companies doing research on neglected diseases need signals on what projects will be eligible for priority review
- FDA has expressed some willingness to give evaluations early in development process for new tropical medicines
- Some drugs may be eligible for fast-track or accelerated approval program

FDA Will Play A Critical Role in Market Value for Vouchers

- Companies must have expectation FDA will act in accordance with the law's objective on PRVs
- Otherwise time inconsistency or credibility issues will dampen incentives
- Markets may be slow to develop until some approvals of voucher drugs occur

Some Important Issues

- Will vouchers slow the approval of other drugs?
- Will faster reviews of voucher drugs in US create greater safety risks?
- Will approved medicines for tropical diseases be distributed to developing countries?

FDA Review Times Under PDUFA

- FDA review times have declined from 24.2 months in 1992 to 14.2 months in 2005
- Critics want to fund FDA from general revenues and remove review time targets

“Do Faster FDA Reviews Adversely Affect Patent Safety?” H Grabowski & R. Wang*

- Dependent variable is adverse drug reactions
- Some evidence of knowledge spillovers for drugs that are first available abroad
- After controlling for utilization, novelty, category and other factors, no evidence that faster reviews have led to more adverse events

* Publication in press, *Journal of Law and Economics*, May 2008

Model Specification

The basic specification for the negative binomial regression model in the current analysis is

$$E\left(ADR_{it}\right) = \exp\left(\alpha R_{it} + \beta N_{it} + \gamma P_{it} + \in_{it}\right)$$

Where $E(ADR_{it})$ is the expected value of the counts of adverse drug reactions

R_{it} are the regulatory related variables

N_{it} are the NME characteristic variables

P_{it} are the patient specific variables

Negative Binomial Model Results on the Determinants of Adverse Drug Reactions (ADRs) (n=823)

ADR Type	Serious				Hospitalization				Deaths			
Specifications	Basic		Alternative		Basic		Alternative		Basic		Alternative	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	-0.44	0.49	-0.54	0.46	-0.84^{+}	0.46	-0.97*	0.43	-1.53^{+}	0.82	-1.63*	0.82
Priority review	0.96**	0.20	0.95**	0.19	0.98**	0.21	0.98**	0.19	1.20**	0.34	1.18**	0.31
Accelerated approval	0.59*	0.30	0.61*	0.29	0.59*	0.30	0.62*	0.29	0.67	0.51	0.67	0.50
Biological product	1.25**	0.22	1.24**	0.22	1.30**	0.21	1.28**	0.21	1.02**	0.37	1.00**	0.36
Orphan product	0.16	0.21	0.14	0.21	0.20	0.23	0.18	0.23	0.23	0.33	0.23	0.33
Log (FDA review)	-0.08	0.09			-0.10	0.09			-0.12	0.13		
FDA review			-0.006	0.004			-0.006	0.004			-0.01*	0.005
BB warning	0.66*	0.27	0.65*	0.27	0.58*	0.27	0.57*	0.27	0.58	0.43	0.56	0.43
BB/Pregnancies	-1.29**	0.44	1.32**	0.44	-1.13*	0.45	-1.16*	0.45	-1.44*	0.59	1.49*	0.59
Percent<20 years	0.37	0.40	0.38	0.39	0.57	0.40	0.57	0.41	0.58	0.57	0.58	0.57
Percent>=65 years	0.96**	0.27	0.93**	0.27	0.82**	0.27	0.79**	0.27	1.83**	0.41	1.75**	0.41
Percent female	0.62^{+}	0.35	0.62^{+}	0.34	0.87**	0.34	0.86*	0.33	0.23	0.53	0.20	0.52
Log (US launch lag)	-0.13**	0.03	-0.13**	0.03	-0.10**	0.04	-0.10**	0.04	-0.12**	0.05	-0.12*	0.05
Log (oral sales)	0.34**	0.02	0.34**	0.02	0.36**	0.02	0.36**	0.02	0.26**	0.03	0.26**	0.03
Log (Injectable sales)	0.50**	0.03	0.50**	0.03	0.51**	0.04	0.51**	0.04	0.41**	0.04	0.42**	0.04
Log (Other sales)	0.22**	0.03	0.22**	0.03	0.22**	0.04	0.22**	0.04	0.18**	0.05	0.18**	0.05
Product age	-0.15**	0.05	-0.15**	0.05	-0.17**	0.05	-0.17**	0.05	-0.06	0.08	-0.06	0.08
Event year indicators	Yes		Yes		Yes		Yes		Yes		Yes	
Therapeutic area indictors	Yes		Yes		Yes		Yes		Yes		Yes	
Dispersion	1.09		1.09		1.07		1.06		1.71		1.67	

Notes: $^{+}$ significant at the 0.1 level
* significant at the 0.05 level
** significant at the 0.01 level

Source: Authors

Summary of Our Findings

- Higher risks associated with priority review, accelerated approval, black box warnings, biological entities, and shorter US launch lags
- After controlling for these factors, FDA review time is not statistically significant
- PRVs unlikely to have much effect on order of launch among major markets

Criteria for Evaluating Incentive Mechanisms for Neglected Diseases (Towse & Danzon, 2005)

1. Incentivize new research without wasting resources
1. Specify which treatments are eligible
1. Be credible in eyes of developers
1. Specify treatment of follow-on drugs
1. Create product used by consumers