Alternative or Additional Incentives for Drug Development

Do Market Exclusivity Extensions Stimulate Transformative Pharmaceutical Innovation?

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Cautionary tales

- Prescription Drug User Fee Act
- Orphan Drug Act
- Pediatric Exclusivity
Prescription Drug User Fee Act of 1992

- Limited FDA resources, length of FDA review time attacked by:
  - Activists seeking earlier access to HIV/AIDS drugs
  - Mfrs complaining that delays reduce market exclusivity time, increase R&D costs

- PDUFA deadlines: NDAs to be acted on within a year of submission (“standard review”) or 6 months (“priority review”)
  - Decreasing FDA review times extended market exclusivity period by allowing patent-protected new drugs to reach the market sooner
Transient effect of PDUFA on new drug approvals

Munos, NRDD, 2009
Unintended consequences

- Drugs approved closer to the administrative deadline more likely to have safety-based withdrawal

![Odds Ratio for Subsequent Safety-Related Event](image)

Figure 2. Likelihood of Subsequent Safety-Related Problem for Drugs Approved in the Last 2 Months before the Review Deadline as Compared with All Other Drugs, 1993–2004.

The bars indicate odds ratios, and the horizontal lines 95% confidence intervals.

- Drugs receiving faster reviews have higher risk of adverse reactions
Orphan Drug Act of 1983

- For conditions affecting fewer than 200,000 people in the US, provide three primary incentives:
  - 1) federal funding of grants and contracts to perform clinical trials of orphan products;
  - 2) a tax credit of 50% of clinical testing costs; and
  - 3) an exclusive right to market the orphan drug for the approved use for seven years from the date of marketing approval
What role does Orphan Drug exclusivity play?

- 7 year market exclusivity period presumed to contribute to rise in orphan drug approvals

- Data: not so
  - Overall ODE>patent terms for 40% of drugs approved 1985-2005
  - Case studies: only occasional cases where ODE identified to keep competitor off market

Kesselheim and Sampat, 2013
Another perspective: When is Orphan Drug exclusivity granted?

• Sample of 15 orphan cancer drugs approved 2004-10
• Received orphan designation median 2.4 years before approval (IQR 1.2-2.7 years)
  – Delay administrative hassle until determine that end product will be marketable?
  – Identify whether their product will be useful in an orphan disease relatively late in the process?
  – Role of the market exclusivity incentive in driving drug development?
• Most approvals occurred in limited number of cancer subtypes and drug classes
  – 3 renal cell, 3 acute lymphocytic leukemia, 3 myelodysplastic syndrome

Kesselheim et al., JAMA, 2012
Public health concerns

• Complicated access to approved orphan drugs
  – Despite substantial “push” incentives [tax breaks, research funds], orphan drugs expensive

• Gaming system
  – Strategically position drugs as orphans
  – Result: Tested in fewer patients and greater potential for off-label use
Pediatric Exclusivity

• Motivation
  – Few drugs being developed or studied specifically for pediatric patients because of smaller market
    • Children have important physiological differences from adults
    • Drugs frequently used in children without supporting clinical trials
    • Children receive treatments that were ineffective or even dangerous

• FDA Modernization Act of 1997, §111
  – Add 6 mos. market exclusivity to a drug’s patent-protected period if manufacturer conducted study of the drug’s effect in pediatric patients
Success on some measures...

• By 2007, >300 studies, >115 products with labeling changes for pediatric use
  – New dosing
  – Dosing changes
  – Pharmacokinetic information
  – New and/or enhanced safety data
  – Information on lack of efficacy
  – New formulations
  – Dosing instructions extending the age limits in the pediatric populations
... but not on others

- Focus on popular adult drugs not on drugs with pediatric importance
- Subpar quality
- Not published in literature
- Delayed until near end of ME period
- Studies in “easier” pediatric populations (older children) vs. test in variety of subjects
Over-incentivize

- Ratio of over 10 to 1 net economic benefit as compared to cost of trials (Li et al., *JAMA*, 2007)
  - In some drug classes, as high as 17 to 1
- Was goal to obtain the pediatric exclusivity incentive, rather than to conduct clinically meaningful tests in reasonable time frame?
Pressing public health need: Antibiotic innovation

- Offer longer exclusivity periods?
  - US GAO: 25-30 yr patents for antibiotics for MDR bacteria
  - 2012 FDASIA: extend data exclusivity period for new antibiotics and antifungals by 5 yrs
Systemic antibacterials approved by FDA (1980-2009)

- Orphan Drug Act
- Hatch-Waxman
- PDUFA
- GATT
- Orange Book listing
- Pediatric Exclusivity
- PRVs

Outterson et al. JLME 2013
Alternative solutions

• Better funding for basic science
  – Open innovation model
  – Prizes

• Directly link incentives to desired health outcomes
  – Reimbursement linked to public health impact

• Variable, transparent market exclusivity periods linked to actual investment