Division of
Pharmacoepidemiology & Pharmacoeconomics
Department of Medicine, Brigham & Women's Hospital, Harvard Medical School

Improving the Evidence Base for Treatment Decision-Making in Older Adults

Incentives for Drug Development: Learning from the Experience of Pediatric Exclusivity

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Proposal

- How to increase rigorous , informative testing of anticancer treatments in older adults so that can be sure that these patients get the benefits of these innovations and minimize risk?

- Follow the lead of pediatric drug development by providing additional **market exclusivity** as an incentive for drug manufacturers

Drugs and Market Exclusivity: Basic Principles

- After FDA approval, period of market exclusivity protects new drugs from direct competition
- During this time, U.S. allows pharmaceutical companies to charge whatever they want
  - **Floor**: Hatch-Waxman Act: all new drugs guaranteed ~6-7 years of no generics
    - BPCIA 2010: Biologics get 12 years
  - **Ceiling**: Drugs protected by patents lasting 20 years
    - "Primary patent" on underlying active ingredient sought around time of discovery/synthesis
- Average market exclusivity period of ~14-15 years

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Kesselheim et al, JAMA IM, 2017

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

Carrot vs Stick: BPCA vs PREA

- Best Pharmaceuticals for Children Act (2002)
  - **6 mos additional exclusivity** if trials in response to Written Request
  - Office of Pediatric Therapeutics, Pediatric Trials Network
- Pediatric Research Equity Act (2003)
  - Companies must conduct studies "(i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each relevant pediatric subpopulation"
  - Waiver for rare disease drugs, "impossible or highly impractical", can defer
  - Can petition to have PREA study count for BPCA

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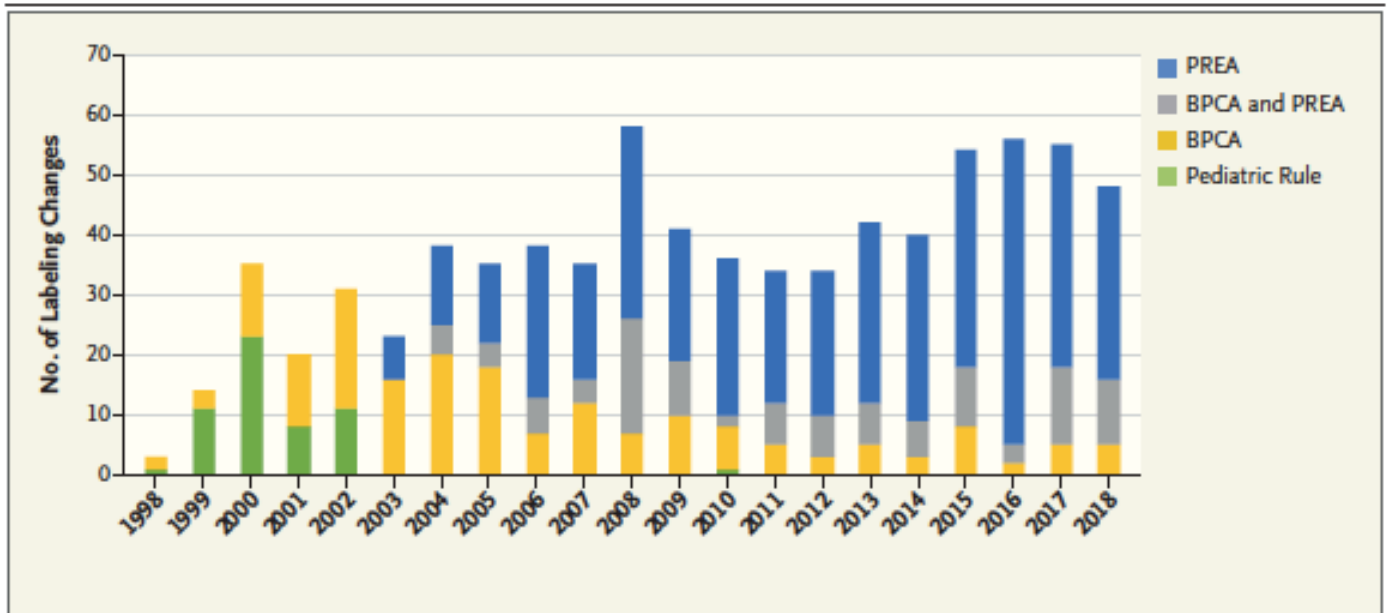
Bourgeois and Kesselheim, NEJM, 2018

Impact

- BPCA: through 2018, 453 WRs issued for 242 drugs leading to 295 products with labeling changes for pediatric use
  - New dosing, dosing changes, pharmacokinetic info, new and/or enhanced safety data, info on lack of efficacy, new formulations, dosing instructions extending age limits in pediatric populations
- PREA: through 2018, 532 labeling changes, usually through indication expansion from adults to children/adolescents



Bourgeois and Kesselheim, NEJM, 2018

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Concerns about implementation: BPCA

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

Over-incentivize

- Ratio of ~7:1 cost to consumers as compared to cost of trials

Table 3. Cost of Investment, Net Return (Cost to Consumers), and Ratio of Net Return (Cost to Consumers) to Cost of Investment by Drug Category

Characteristic	No. (N = 48)	Cost, Median (IQR), $ Millions[a]		Ratio of Net Return (Cost to Consumers) to Cost of Investment, Median (IQR), %[b]
		Cost of Investment	Net Return (Cost to Consumers)	
Therapeutic class				
Cardiovascular/circulatory	4	71.2 (56.9 to 99.3)	126.1 (−32.0 to 288.2)	200 (−30 to 560)
Central and peripheral nervous systems	10	141.9 (87.8 to 286.8)	266.1 (57.5 to 694.7)	250 (30 to 590)
Diabetes/metabolic/nutrition	5	23.3 (16.8 to 27.2)	208.8 (155.2 to 496.4)	1120 (730 to 1250)
Hematology	2	83.1 (NA)	1200.1 (NA)	1180 (NA)
Infectious diseases	9	10.0 (6.9 to 13.7)	132.0 (47.7 to 368.9)	1320 (690 to 2770)
Oncology	6	41.2 (20.1 to 53.5)	297.6 (190.5 to 323.7)	750 (440 to 2710)
Respiratory	2	584.4 (NA)	−405.7 (NA)	−30 (NA)
Other	10	32.1 (25.8 to 70.6)	122.4 (46.2 to 490.1)	450 (80 to 1520)
Blockbuster drug				
Yes	20	40.5 (26.5 to 82.2)	493.7 (350.7 to 804.7)	1050 (590 to 2910)
No	28	30.2 (16.5 to 112.7)	58.8 (9.8 to 156.2)	190 (20 to 720)

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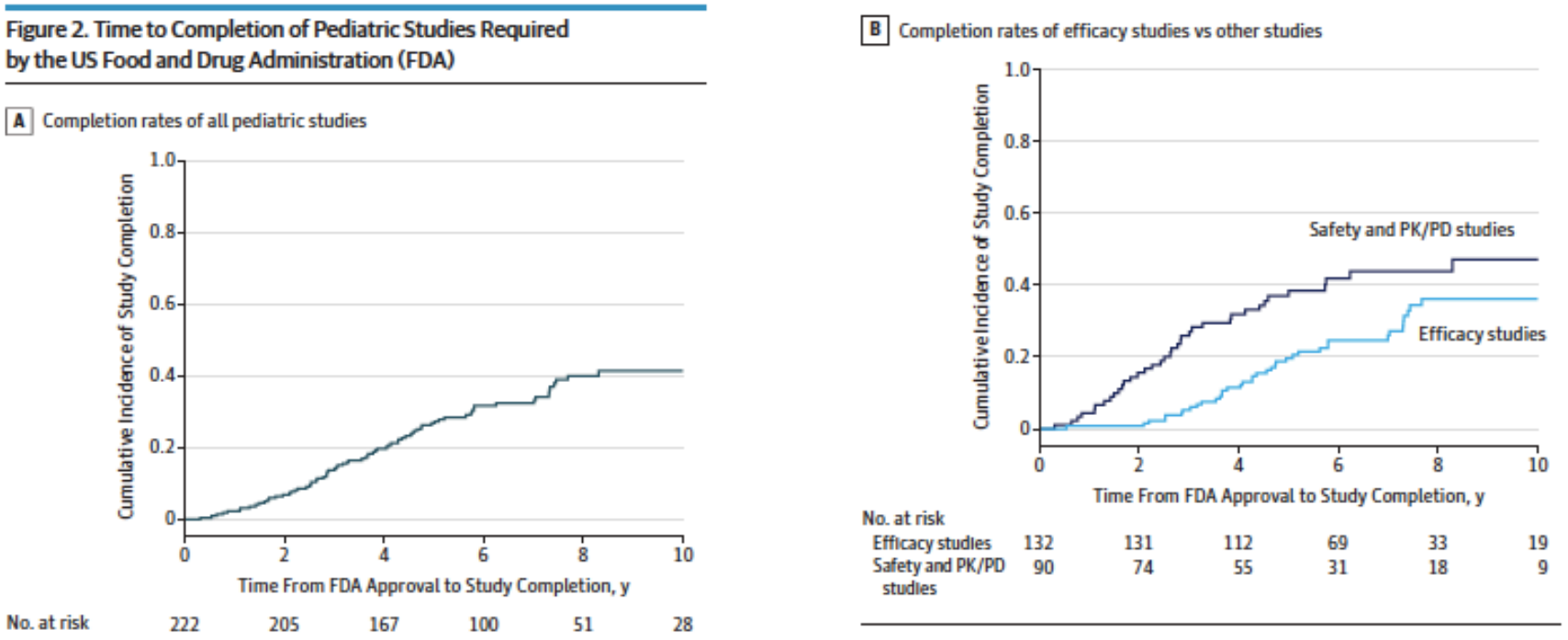
Sinha et al. Kesselheim, JAMA IM, 2018

Concerns about implementation: PREA

- Waivers/deferrals are common (78% of drugs approved 2003-2012)
  - Drugs approved 2007-2014: After a median of 7 years, only 34% had been completed (28% of efficacy studies)
  - 16% had pediatric information in labeling at time of approval



Hwang, Orenstein, Kesselheim, Bourgeois, JAMA Pediatrics, 2019

Conclusions and Policy Options

- Need to test cancer drugs in older patients, but additional market exclusivity incentives are problematic
  - Not the same underlying logic, inefficient experience
- Require new drug applications for cancer drugs incorporate trials that include a representative sample of older adults
  - When scientifically appropriate, require post-approval observational evaluations to extend labeling
  - Include a formal re-review of the product after a short period
- Direct funding of trials through the National Institutes of Health
- Set predetermined award amount for each requested study

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Luo and Kesselheim, JAMA, 2015