Pre-market development times for biologic versus small-molecule drugs

Reed F. Beall, Ph.D.

UNIVERSITY OF CALGARY

Assistant Professor
Department of Community Health Sciences
Cumming School of Medicine
O'Brien Institute of Public Health
University of Calgary
Alberta, Canada

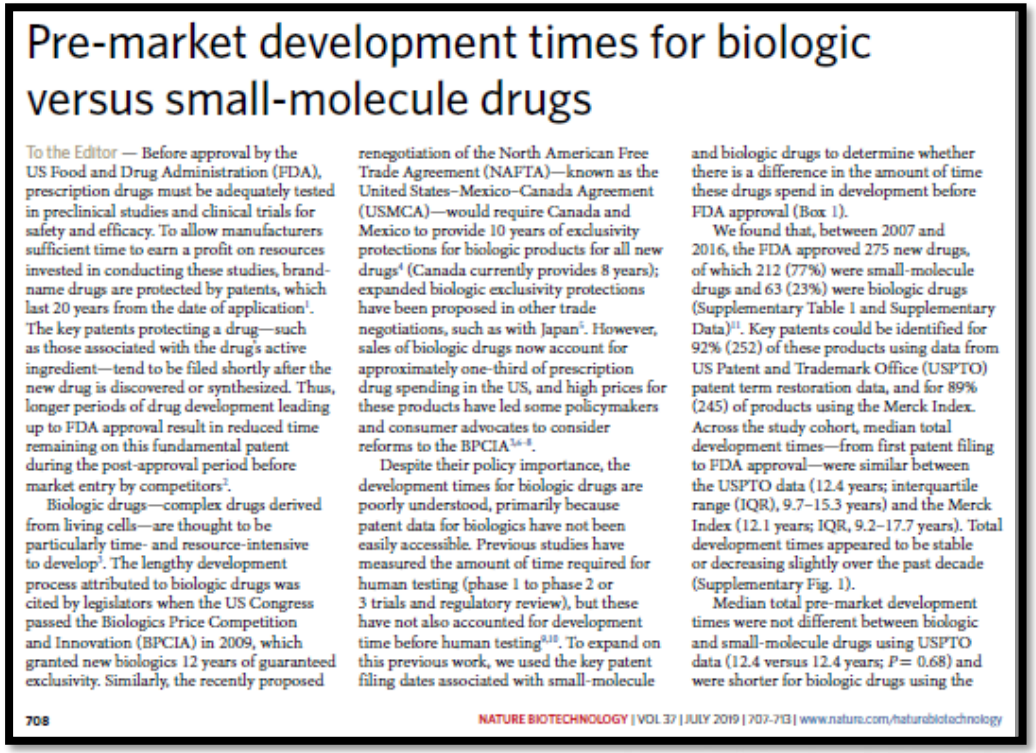
Affiliated faculty
Program on Regulation Therapeutics & the Law (PORTAL)
Division of Pharmacoepidemiology & Pharmacoeconomics
Brigham & Women's Hospital / Harvard Medical School
Boston, United States

Overview

Beall R, Hwang T, Kesselheim A (2019). Pre-market development times for biologics versus small-molecule drugs. Nature Biotechnology.

https://rdcu.be/bHble

- Introduction
- Methods
- Results
- Discussion



Pre-market development times for biologic versus small-molecule drugs

To the Editor — Before approval by the US Food and Drug Administration (FDA), prescription drugs must be adequately tested in preclinical studies and clinical trials for safety and efficacy. To allow manufacturers sufficient time to earn a profit on resources invested in conducting these studies, brand-name drugs are protected by patents, which last 20 years from the date of application[1]. The key patents protecting a drug—such as those associated with the drug's active ingredient—tend to be filed shortly after the new drug is discovered or synthesized. Thus, longer periods of drug development leading up to FDA approval result in reduced time remaining on this fundamental patent during the post-approval period before market entry by competitors[2].

Biologic drugs—complex drugs derived from living cells—are thought to be particularly time- and resource-intensive to develop[3]. The lengthy development process attributed to biologic drugs was cited by legislators when the US Congress passed the Biologics Price Competition and Innovation (BPCIA) in 2009, which granted new biologics 12 years of guaranteed exclusivity. Similarly, the recently proposed renegotiation of the North American Free Trade Agreement (NAFTA)—known as the United States–Mexico–Canada Agreement (USMCA)—would require Canada and Mexico to provide 10 years of exclusivity protections for biologic products for all new drugs[4] (Canada currently provides 8 years); expanded biologic exclusivity protections have been proposed in other trade negotiations, such as with Japan[5]. However, sales of biologic drugs now account for approximately one-third of prescription drug spending in the US, and high prices for these products have led some policymakers and consumer advocates to consider reforms to the BPCIA[3,6–8].

Despite their policy importance, the development times for biologic drugs are poorly understood, primarily because patent data for biologics have not been easily accessible. Previous studies have measured the amount of time required for human testing (phase 1 to phase 2 or 3 trials and regulatory review), but these have not also accounted for development time before human testing[9,10]. To expand on this previous work, we used the key patent filing dates associated with small-molecule and biologic drugs to determine whether there is a difference in the amount of time these drugs spend in development before FDA approval (Box 1).

We found that, between 2007 and 2016, the FDA approved 275 new drugs, of which 212 (77%) were small-molecule drugs and 63 (23%) were biologic drugs (Supplementary Table 1 and Supplementary Data)[11]. Key patents could be identified for 92% (252) of these products using data from US Patent and Trademark Office (USPTO) patent term restoration data, and for 89% (245) of products using the Merck Index. Across the study cohort, median total development times—from first patent filing to FDA approval—were similar between the USPTO data (12.4 years; interquartile range (IQR), 9.7–15.3 years) and the Merck Index (12.1 years; IQR, 9.2–17.7 years). Total development times appeared to be stable or decreasing slightly over the past decade (Supplementary Fig. 1).

Median total pre-market development times were not different between biologic and small-molecule drugs using USPTO data (12.4 versus 12.4 years; $P = 0.68$) and were shorter for biologic drugs using the

Background

- Drug development requires considerable investment
  - Includes animal testing, clinical trials, regulatory review
  - Requires time, finances, personnel, patients, etc.
- Exclusive markets incentivize private investment
  - 2 mechanisms to ensure initial exclusive markets
    - **1. Patents**
    - **2. Data exclusivities**

Background continued

- Data exclusivities
  - Prevent regulatory authorities from approving (and/or reviewing) applications reliant on the originator's clinical trial data to demonstrate safety/effectiveness
  - Data exclusivities important when active ingredient no longer or not patentable
  - Data exclusivity periods vary by drug type (biologic vs small molecule), situation (e.g., PED), and between/within countries
  - In US currently, new small molecule drugs get 5 years of data exclusivity whereas biologics get 12 years
    - **Why the difference in New Chemical Entity exclusivities?**

Background continued

- Biologic (aka, large molecule) – 12-year data exclusivity
  - Biologic drugs are a category of pharmaceuticals derived from living organisms or from their cells and use relatively new biotechnology
- Small-molecule – 5-years data exclusivity
  - Chemically produced pharmaceutical drugs known as “small molecule drugs” (which represent the majority of drugs available today) can often be synthesized using a variety of processes by different manufacturers to derive an identical chemical structure.

Background continued

- Common arguments for longer exclusivity periods for biologics
  - 1. Biologics are particularly expensive to develop
    - Longer development times
  - 2. Patents offer less secure protection for biologics
    - Biologics are products-by-process, but product patents proved to be poor protection for small molecule drugs
- Research question: Do biologics take longer to develop than small-molecule drugs?

Methods - Design

- Drug product cohort selection
  - Constructed database of all new drugs (NMEs) approved by CDER within FDA in 2007-2016
- Key patent identification
  - USPTO database of products given patent term restoration period / certificate of suppl. protection
  - Merck Index entries containing patent information

Methods – Design

- Deriving development times
  - USPTO and Merck analysed separately
  - Development time = FDA approval – first patent filing
  - Each segment of development period also compared
    - Patent filing to clinical testing in humans (IND* date)
    - IND to initiating regulatory review (i.e., BLA/NDA** date)
    - IND date to FDA approval (i.e., regulatory review period)

*IND = Investigational new drug application

**BLA = Biologic licensing application, NDA = New Drug Application (small molecule)

Methods - Analysis

- Statistical analysis
  - Comparing development times by drug type
    - Unadjusted non-parametric Mann–Whitney test
    - Adjusted multivariable linear regression, included controlling for:
      - Special FDA programs to expedite regulatory approval
      - Orphan drug designation
      - First-in-class status
    - Sensitivity testing re-running analysis for each segment
    - Statistical significance was two-tailed $P < 0.05$

Results – overall cohort

- Final cohort
  - 275 new drugs
    - 212 (77%) small-molecule drugs
    - 63 (23%) biologic drugs
- Key patent data
  - 92% (252) using USPTO patent term restoration data
  - 89% (245) using Merck Index data
- Total development times (pat filing to approval)
  - USPTO data: Median = 12.4 years; IQR = 9.7–15.3
  - Merck Index: Median = 12.1 years; IQR = 9.2–17.7

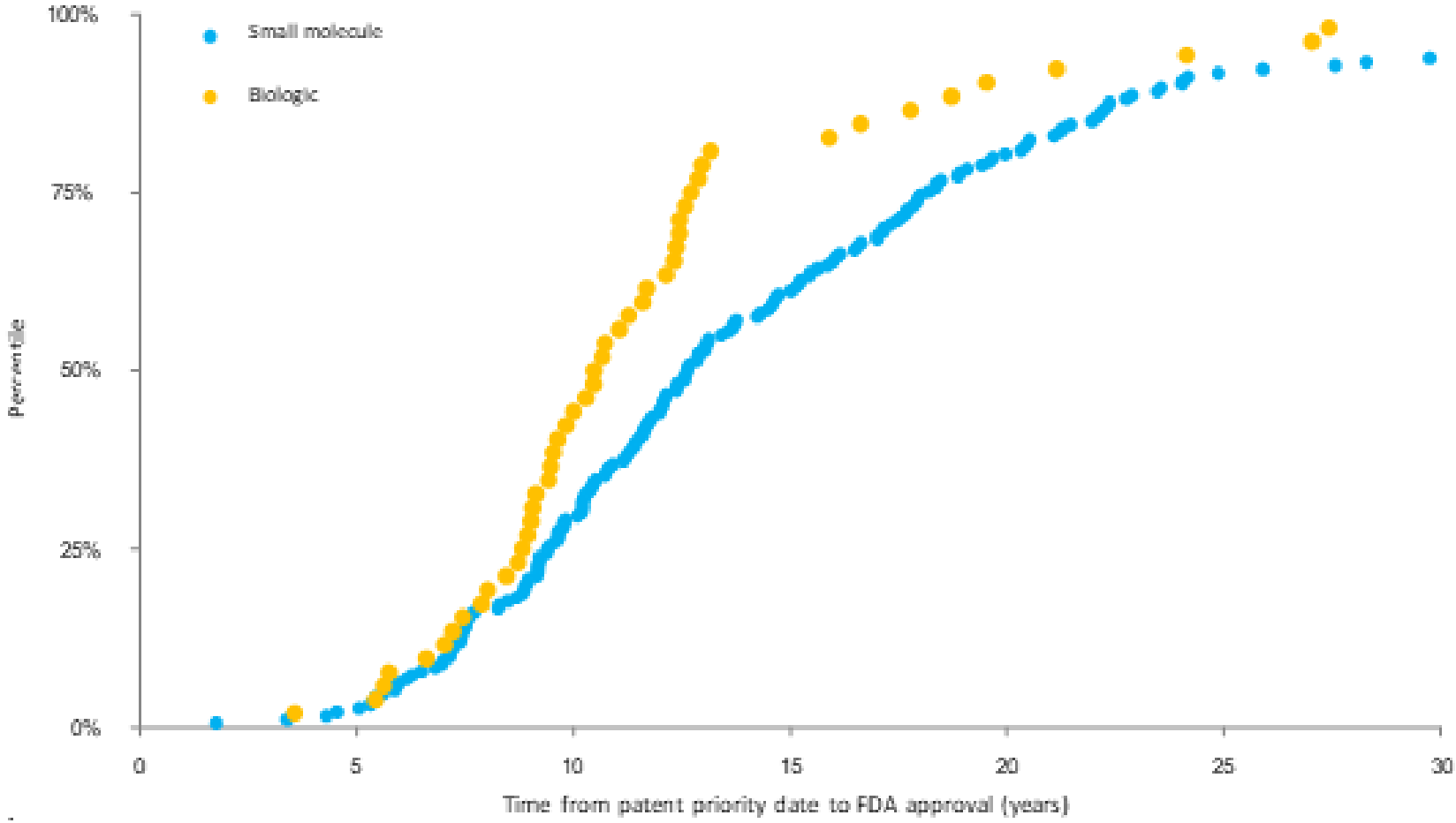
Results – small molecule vs biologics

- Total development time biologic vs small-molecule
  - USPTO: BLA = 12.4 years vs NDA = 12.4 years (p = 0.68)
  - Merck: BLA = 10.6 years vs NDA = 12.6 years (p = 0.01)
- Results of after controlling for confounders:
  - USPTO: findings held
    - no difference in times overall or by time segment
  - Merck: findings held
    - Biologics: 2.5–2.9 years shorter total development times
  - No clear time trends

Results – small molecule vs biologics

Figure 1. Cumulative distribution of time from first patent filing to FDA approval for biologics vs small-molecule

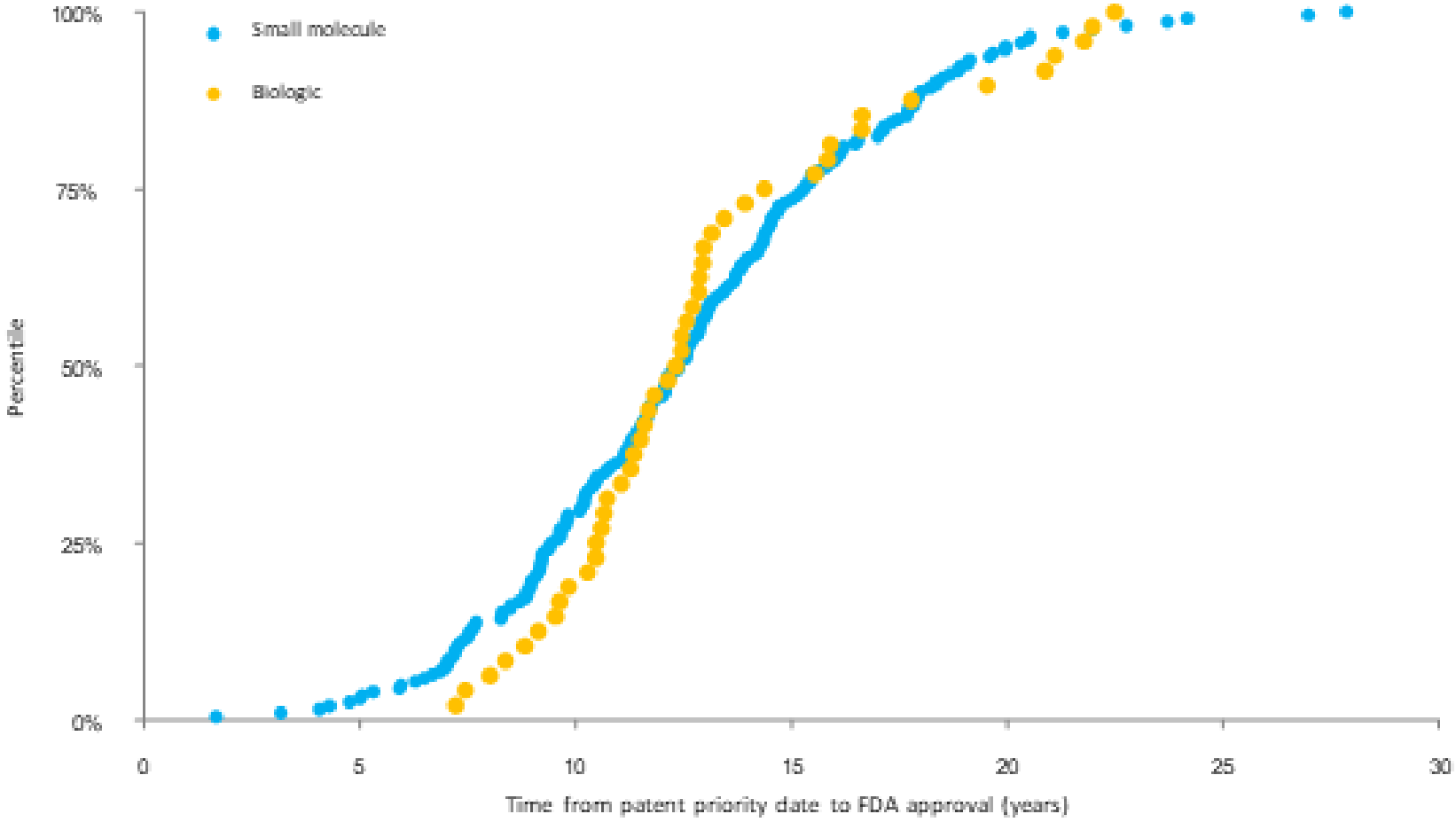
a. Merck Index



Results – small molecule vs biologics

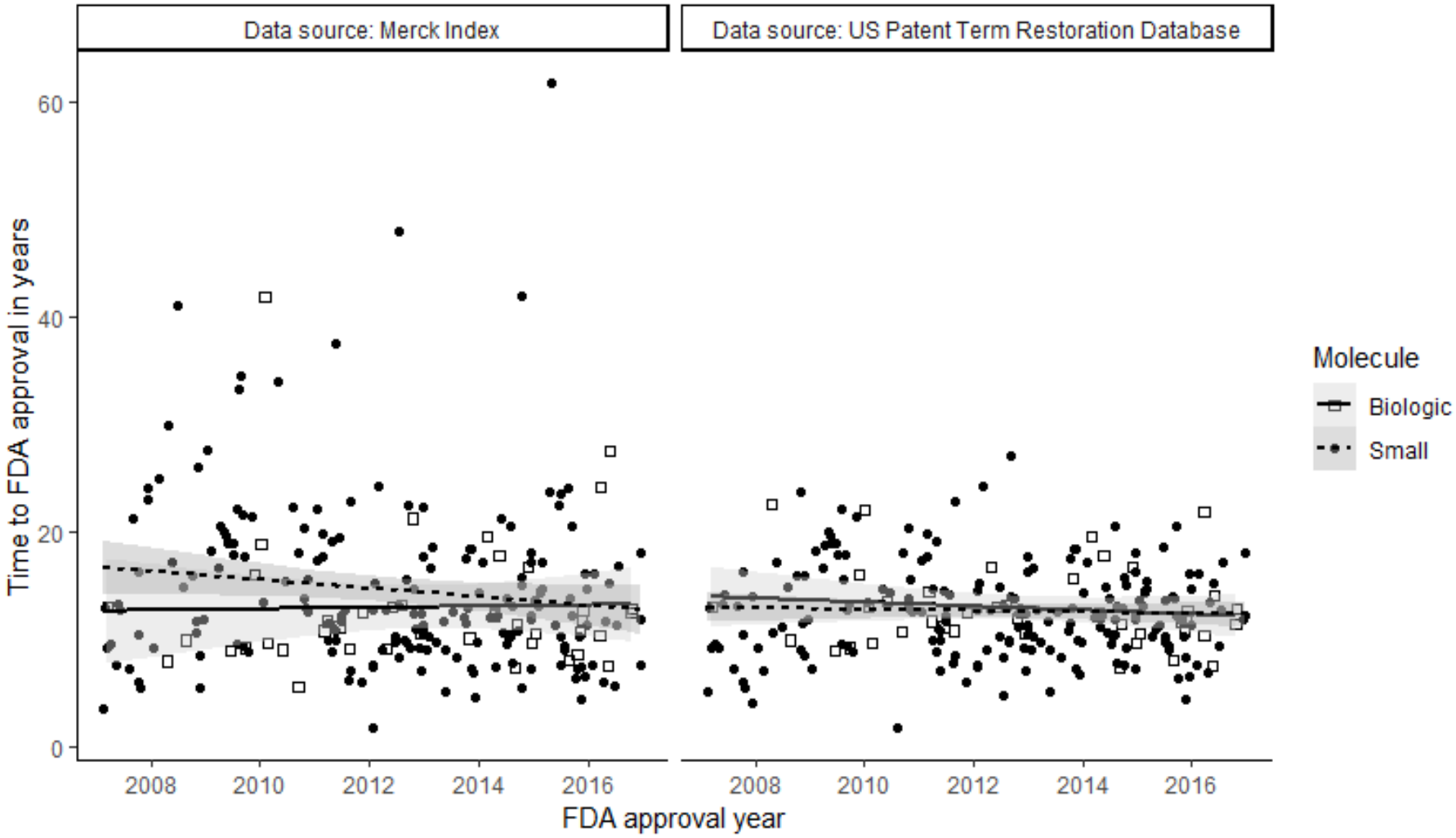
Figure 1. Cumulative distribution of time from first patent filing to FDA approval for biologics vs small-molecule

b. USPTO patent term extensions



Results – small molecule vs biologics

Supp figure 1. Time trends



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Discussion – Main takeways

- Main takeaway:
  - Biologic development is not relatively more time-consuming as compared to small-molecule drugs.
- Policy relevance
  - One rationale for longer exclusivity periods has been longer development times
  - But our results reflect no difference (at least since 2007)
  - Proposals to lower data exclusivity from 12 to 5–10 yrs in US
    - Harmonize with peer countries (e.g., EU, Canada, Australia, NZ)
    - Boost biosimilar competition to reduce spending
    - Disparities in exclusivities send signal of societal preference in molecule size

Discussion – limitations

- Limitations
  - Methodological
    - Only one way to measure of development times
    - Small-molecule tradition older than biologics
    - CBER
    - Only considers drugs that made it to market
  - Policy concerns
    - Does not directly address the matter of cost
    - Study does not address other arguments for longer data exclusivities (i.e., patents inadequate protection)
      - Note biosimilar competitions relatively rare relative to generic competition (study pending on this question)

Post publication updates

116TH CONGRESS
1ST SESSION

H. R. 3379

To amend the Public Health Service Act to shorten the exclusivity period for brand name biological products from 12 to 5 years.

IN THE HOUSE OF REPRESENTATIVES

JUNE 20, 2019

Ms. SCHAKOWSKY (for herself, Mr. WESTERMAN, Ms. DELAURO, Ms. CRAIG, Mr. DOGGETT, Mr. KRISHNAMOORTHI, Mr. KHANNA, Mr. CICILLINE, Mr. POCAN, Mr. RUSH, Mr. LEVIN of Michigan, Mr. MORELLE, Ms. JAYAPAL, Ms. TLAIB, Ms. KAPTUR, Mr. WELCH, and Mr. GARCÍA of Illinois) introduced the following bill; which was referred to the Committee on Energy and Commerce

OFFICE OF THE PARLIAMENTARY BUDGET OFFICER
BUREAU DU DIRECTEUR PARLEMENTAIRE DU BUDGET

The impact of the Canada – United States – Mexico Agreement on prescription drug expenditures in Canada

Ottawa, Canada
2 April 2019
www.pbo-dpb.gc.ca

Contact details for follow up questions:

Reed F. Beall, Ph.D.

Assistant Professor, Healthcare Policy

Community Health Sciences

Cumming School of Medicine & O'Brien Institute for Public Health

3280 Hospital Drive, TRW 3E46

Calgary, AB T2N 4Z6 Canada

mail: Reed.Beall@ucalgary.ca

Web: http://reed-beall.squarespace.com

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