

1 **Differential Legal Protections for Biologics vs. Small-Molecule Drugs in the US**

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39

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KEY POINTS

Question

What evidence supports greater legal protections from direct competition or price negotiation for biologics than for small-molecule drugs?

Findings

Compared to small-molecule drugs, biologics had higher clinical trial success rates, similar development times and costs, and denser patent thickets, which contributed to longer periods of market exclusivity. Biologics also had higher treatment costs and higher revenues.

Meaning

There is little currently available evidence to support longer market exclusivity periods and longer exemptions from Medicare price negotiation for biologics.

42 **ABSTRACT**

43

44 **Importance:** Biologics approved by the US Food and Drug Administration (FDA) receive 12
45 years of guaranteed protection from biosimilar competition compared to 5 years of
46 protection from generic competition for new small-molecule drugs. Under the 2022
47 Inflation Reduction Act, biologics are exempt from selection for Medicare price negotiation
48 for 11 years compared to 7 years for small-molecule drugs. Congress has chosen to codify
49 these differing legal protections on the premise that biologics require more time and
50 resources to develop and have weaker patent protection, necessitating additional
51 protections for manufacturers to recoup their development costs and generate adequate
52 returns on investment.

53

54 **Objective:** To review empirical evidence from the US experience with biologics to
55 determine whether they require longer market exclusivity or protection from price
56 negotiation compared to small-molecule drugs.

57

58 **Evidence Review:** Recent data on development times, clinical trial success rates, research
59 and development costs, patent protection, market exclusivity periods, revenues, and
60 treatment costs of biologics vs. small-molecule drugs were analyzed.

61

62 **Findings:** The FDA approved 599 new therapeutic agents from 2009-2023, of which 27%
63 (159) were biologics and 73% (440) were small-molecule drugs. Median development
64 times were 12.6 years (interquartile range [IQR]: 10.6-15.3 years) for biologics versus 12.7

65 years (IQR: 10.2-15.5 years) for small-molecule drugs ($P=0.76$). Biologics had higher
66 clinical trial success rates at every phase of development. Median development costs were
67 estimated to be \$3.0 billion (IQR: \$1.3 billion-\$5.5 billion) for biologics and \$2.1 billion
68 (IQR: \$1.3 billion-\$3.7 billion) for small-molecule drugs ($P=0.39$). Biologics were protected
69 by a median of 14 patents (IQR: 5-24 patents) compared to 3 patents (IQR: 2-5 patents) for
70 small-molecule drugs ($P<0.001$). The median time to biosimilar competition was 20.3 years
71 (IQR: 16.9-21.7 years) compared to 12.6 years (IQR: 12.5-13.5 years) for small-molecule
72 drugs. Biologics achieved higher median peak revenues (\$1.1 billion in year 13; IQR: \$0.5
73 billion-\$2.9 billion) than small-molecule drugs (\$0.5 billion in year 8; IQR: \$0.1 billion-\$1.2
74 billion) ($P=0.01$) and had higher median revenues in each year following FDA approval. The
75 median annual cost of treatment was \$92,000 (IQR: \$31,000-\$357,000) for biologics and
76 \$33,000 (IQR: \$4,000-\$177,000) for small-molecule drugs ($P=0.005$).

77

78 **Conclusions and Relevance:** There is little currently available evidence to support
79 biologics having extended market exclusivity or protection from negotiation. As a result of
80 differential treatment, US law appears to over-reward the development of biologics relative
81 to small-molecule drugs.

82 The US Food and Drug Administration (FDA) regulates new pharmaceuticals as
83 either small-molecule drugs, which are derived from chemical compounds, or biologics,
84 which are derived from living organisms or their cells. Biologics represent 2% of
85 prescriptions in the US,¹ but tend to be more expensive and account for approximately half
86 of total drug spending.^{2,3}

87 Manufacturers earn most of their revenue on brand-name prescription drugs during
88 periods of market exclusivity when they face no direct generic or biosimilar competition.⁴
89 The US government provides these time-limited monopolies to incentivize private
90 investment in pharmaceutical innovation via two types of protections: patents, which are
91 granted by the US Patent and Trademark Office and typically last for 20 years from the time
92 of filing, and non-patent exclusivities (also referred to as statutory or regulatory
93 exclusivities), which are granted by the FDA and prohibit the marketing of generic or
94 biosimilar products for varying amounts of time (depending on the type of approval
95 obtained).⁴ Generic and biosimilar firms must wait for these protections to expire or, in the
96 case of patents, successfully challenge them in court before entering the US market.⁴

97 Because of perceived risks associated with developing biologics and concerns about
98 their long-term profitability, Congress has provided longer periods of statutory exclusivity
99 for biologics than for small-molecule drugs. The Hatch-Waxman Act of 1984 provides up to
100 5 years of statutory exclusivity for newly approved small-molecule drugs before the FDA
101 can review applications for generic versions. By contrast, the Biologics Price Competition
102 and Innovation Act of 2009 grants biologics 12 years of statutory exclusivity before the
103 first biosimilar can be authorized for marketing.⁴ Proponents of a 12-year exclusivity
104 period for biologics argued that patents on biologics would be difficult to enforce and that

105 biosimilar competitors would therefore be able to enter the market before manufacturers
106 could recoup development costs and generate adequate returns on investment.^{5,6}

107 In 2022, Congress enacted legislation further enshrining differential periods of
108 protection for biologics vs. small-molecule drugs. The Inflation Reduction Act, which
109 directs Medicare to negotiate the prices of top-selling medicines, exempts biologics from
110 negotiation for the first 11 years after FDA approval compared to the first 7 years for small-
111 molecule drugs, with negotiated prices taking effect 2 years later for both types of
112 products.⁷ The justification for this difference was again that biologic developers need
113 longer protections to recoup their development costs.

114 Now that 15 years have passed since the enactment of the Biologics Price
115 Competition and Innovation Act, we sought to determine whether special protections for
116 biologics remain justifiable. We systematically analyzed development times, clinical trial
117 success rates, research and development costs, patent protection, market exclusivity
118 periods, revenues, and treatment costs.

119

120 **Methods**

121 We used Drugs@FDA to identify all novel small-molecule drugs and biologics
122 approved from 2009 (when the Biologics Price Competition and Innovation Act was
123 passed) to 2023.⁸ We excluded vaccines and imaging and diagnostic agents. We adapted the
124 study period for some analyses, as described below, when data were unavailable. **eTable 1**
125 summarizes cohorts and study periods used in each analysis. Institutional review board
126 approval was not required for this study since we did not analyze patient-level data. We

127 followed the Strengthening the Reporting of Observational Studies in Epidemiology
128 (STROBE) guideline.

129

130 Development times

131 We calculated development times by subtracting the start of development from the
132 date of FDA approval for each product in the cohort. We used the date of the first
133 international patent filing as the beginning of development, since developers typically file
134 patent applications soon after a new compound or synthesis process is discovered.
135 Consistent with a prior study,⁹ we extracted all patent numbers for new molecular entities
136 in the US Patent and Trademark Office's database of applications for pharmaceutical patent
137 term extensions through 2021, the most recent year for which complete data were
138 available.¹⁰ We then searched the European Patent Office's international patent database
139 (Espacenet) for each patent to identify the earliest priority date, which reflects the first
140 international patent filing for the invention.

141 We used Mann-Whitney *U* tests to identify significant differences in median
142 development times between biologics and small-molecule drugs. We ran 2 sensitivity
143 analyses. First, we generated a null distribution of differences in means (5,000
144 replications). Second, we ran a linear regression model and calculated robust standard
145 errors to account for heteroskedasticity. The model controlled for special FDA pathways
146 (accelerated approval, breakthrough designation, fast track, priority review, or Orphan
147 Drug Act designation), patent filing year (as a continuous variable to account for potential
148 changes over time), and whether a product was first-in-class (based on data published by
149 the FDA^{11,12}). All tests were 2-tailed and used a type I error rate of 0.05.

150

151 Clinical trial success rates

152 To evaluate probabilities of success in phase 1, 2, and 3 clinical trials, we searched
153 PubMed for all English-language articles published from 2009-2023 containing the
154 following terms: “clinical approval success rates,” “clinical phase transition,” “clinical trial
155 success rates,” “clinical success rates,” or “phase transition probabilities.” We also searched
156 the websites of the 2 major US pharmaceutical trade associations—Pharmaceutical
157 Research and Manufacturers of America (PhRMA) and Biotechnology Innovation
158 Organization (BIO)—for literature on clinical trial success rates. Finally, we manually
159 reviewed the works cited in each included article to identify additional studies our PubMed
160 and website searches may have missed (**eFigure 1**). We only considered original studies
161 that quantitatively estimated clinical trial success rates at each phase of development, and
162 that reported rates separately for small-molecule drugs and biologics.

163

164 Research and development costs

165 We estimated research and development costs using information disclosed in filings
166 by pharmaceutical firms with the US Securities and Exchange Commission for new
167 therapeutic agents; these data were sourced from a prior study.¹³ We applied probability
168 adjustments to reflect the likelihood of success using published clinical trial success rates
169 for biologics and small-molecule drugs.¹⁴ As in previous studies, we applied a 10.5%
170 discount rate to reflect the cost of capital.^{13,15} We reported median research and
171 development costs for biologics and small-molecule drugs. All values were adjusted to
172 2023 dollars using the Consumer Price Index (All Urban Consumers). We used a 2-tailed

173 Mann-Whitney *U* test (type 1 error rate of 0.05) to identify statistically significant
174 differences.

175

176 Patent protection

177 We used the FDA's Purple Book to identify all publicly disclosed patents on
178 biologics. Unlike for small-molecule drugs, patents are only linked to individual biologics
179 and listed in the FDA's Purple Book when a potential biosimilar competitor makes a formal
180 request or initiates litigation against a brand-name manufacturer.¹⁶ We then used Lex
181 Machina, a commercial patent litigation database, to identify additional patents on biologics
182 disclosed during litigation, as well as to calculate the number of litigated patents per
183 biologic. Because patent information was only available for 13 biologics approved by the
184 FDA from 1989 (Epogen) to 2011 (Eylea), we used the FDA's Orange Book to identify all
185 patents on small-molecule drugs approved by the FDA from 1989 to 2011. We used Lex
186 Machina to identify patents on small-molecule drugs disclosed during litigation. We used
187 Mann-Whitney *U* tests to identify significant differences between small-molecule drugs and
188 biologics.

189

190 Market exclusivity periods

191 To evaluate the relative length of market exclusivity for small-molecule drugs vs
192 biologics, we used a two-pronged approach. First, we determined the length of market
193 exclusivity for all biologics that faced biosimilar competition as of December 31, 2023,
194 using approval dates from Drugs@FDA and biosimilar entry dates reported by
195 manufacturers to Medicaid.¹⁸ The duration of market exclusivity was calculated as the time

196 between initial FDA approval and the date of market entry of the first biosimilar
197 competitor.

198 Second, to estimate market exclusivity periods for small-molecule drugs, which have
199 been studied extensively in the literature, we searched PubMed for all English-language
200 articles published from 2009-2023 containing the following terms: “exclusivity period,”
201 “data exclusivity,” “market exclusivity,” “regulatory exclusivity,” or “statutory exclusivity”
202 (and reviewed their references). We only included original studies that quantitatively
203 estimated market exclusivity periods for small-molecule drugs (**eFigure 2**).

204

205 Revenues and treatment costs

206 We used data from SSR Health to track drug prices and sales revenues for all new
207 small-molecule drugs and biologics approved from 2009 to 2022; we stopped in 2022 to
208 allow for at least one year of revenue data. SSR Health obtains data, reported quarterly
209 through 2023, from public disclosures by manufacturers, capturing more than 90% of US
210 prescription drug revenues. All values were adjusted to 2023 dollars using the Consumer
211 Price Index (All Urban Consumers). We excluded products with less than 1 full year of
212 revenue data.

213 We calculated median net revenues for biologics and small-molecule drugs in each
214 year since FDA approval starting with the quarter of each product’s FDA approval. We
215 ended our analysis in year 13, the last year for which there were more than 5 observations
216 for both types of products. We then calculated the present value of revenues under each
217 curve using a 10.5% discount rate, the same rate we used for estimating development
218 costs.

219 We calculated the median annual cost of treatment for biologics and small-molecule
220 drugs (rounded to the nearest \$1000). SSR Health estimated annual treatment costs by
221 multiplying net unit prices (reflecting rebates and discounts across all payers) by the
222 number of units in a yearly regimen or course of therapy as indicated on the FDA-approved
223 labeling.^{2,19} **eText 1** provides additional information about the methods used to calculate
224 treatment costs. We used 2-tailed Mann-Whitney *U* tests (type 1 error rate of 0.05) to
225 identify significant differences in both revenues and treatment costs.

226

227 **Results**

228 The FDA approved 599 new therapeutic agents from 2009-2023, of which 27%
229 (159) were biologics and 73% (440) were small-molecule drugs. The annual number of
230 new biologics approved increased from a median of 7 in 2009-2015 to 13.5 in 2016-2023
231 (93% increase); the annual number of new small-molecule drugs approved increased from
232 a median of 25 in 2009-2015 to 37 in 2016-2023 (48% increase) (**Figure 1**).

233

234 Development times

235 Median development times were 12.6 years (interquartile range [IQR]: 10.6-15.3
236 years) for biologics (n=100) compared to 12.7 years (IQR: 10.2-15.5 years) for small-
237 molecule drugs (n=302) ($P=0.76$) (**eFigure 3**). No significant differences were observed in
238 the sensitivity analyses (**eText 2**).

239

240 Clinical trial success rates

241 Five studies reported clinical trial success rates for biologics vs. small-molecule
242 drugs.^{14,20-23} All found higher success rates for biologics throughout the development
243 process (**Figure 2**). For products entering phase 1 trials, the median estimate across the 5
244 studies was that 14% (range 9%-32%) of biologics and 8% (range 6%-13%) of small-
245 molecule drugs were approved by the FDA. For products entering phase 2 trials, the median
246 estimate increased to 24% (range 17%-38%) of biologics and 15% (range 10%-21%) of
247 small-molecule drugs. For products entering phase 3 trials, the median estimate increased
248 further to 57% (range 51%-71%) of biologics and 49% (range 38%-58%) of small-
249 molecule drugs. **eTable 2** provides data on the sample size of each study.

250

251 Research and development costs

252 Research and development spending was publicly disclosed for 63 new therapeutic
253 agents (16 biologics and 47 small-molecule drugs). Median development costs were \$3.0
254 billion (IQR: \$1.3 billion-\$5.5 billion) for biologics and \$2.1 billion (IQR: \$1.3 billion-\$3.7
255 billion) for small-molecule drugs ($P=0.39$) (**Figure 3**).

256

257 Patent protection

258 Patent information was publicly disclosed for 13 biologics and 565 small-molecule
259 drugs. Biologics had a median of 14 patents (IQR: 5-24 patents) per product compared to 3
260 patents (IQR: 2-5 patents) per small-molecule drug ($P<0.001$). Among the 13 biologics and
261 166 small-molecule drugs with any litigation, brand-name firms claimed infringement on a
262 median of 12 patents per biologic (IQR: 5-24 patents) compared to a median of 1 patent per
263 small-molecule drug (IQR: 0-3 patents) ($P<0.001$).

264

265 Market exclusivity periods

266 By the end of 2023, the FDA had approved 45 biosimilars for 14 biologics; for 4 of
267 these biologics, the approved biosimilars had not yet entered the market (**Table 1**). Among
268 these 14 biologics, there was a median of 2.5 biosimilar competitors launched in the market
269 (IQR: 0.3-3.8 biosimilars). The median time to biosimilar market entry was 20.3 years (IQR:
270 16.9-21.7 years). Among 5 prior studies analyzing small-molecule drugs, the median time
271 to generic market entry was 12.6 years (IQR: 12.5-13.5 years) (**eTable 3**).²⁴⁻²⁸

272

273 Revenues and treatment costs

274 Biologics had higher median revenues every year after approval and achieved higher
275 median peak revenues (\$1.1 billion in year 13; IQR: \$0.5 billion-\$2.9 billion) than small-
276 molecule drugs (\$0.5 billion in year 8; IQR: \$0.1 billion-\$1.2 billion) ($P=0.01$) (**Figure 4**).
277 The discounted (present) value of cumulative median annual revenues for biologics was
278 \$3.7 billion (IQR: \$1.5 billion-\$10.3 billion) compared to \$2.0 billion (IQR: \$0.8 billion-\$5.2
279 billion) for small-molecule drugs ($P<0.001$). The median annual net cost of treatment for
280 biologics was \$92,000 (IQR: \$31,000-\$357,000), compared to \$33,000 (IQR: \$4,000-
281 \$177,000) for small-molecule drugs ($P=0.005$).

282

283 **Discussion**

284 The differential treatment of biologics under the Biologics Price Competition and
285 Innovation Act and the Inflation Reduction Act was based on assumptions regarding
286 development costs, risks, and revenue potential. From a broad review of data and studies

287 spanning the last 15 years, we found that biologics had higher clinical trial success rates
288 than small-molecule drugs at each phase of development and similar development times
289 and costs. After approval, biologics had denser patent thickets, more patent infringement
290 claims per product, and longer periods of market exclusivity than small-molecule drugs.
291 Biologics were also more expensive and earned substantially higher revenues. These
292 results call into question the need for policies that protect biologics from competition or
293 price negotiation for longer periods of time than small-molecule drugs.

294 When Congress considered the Biologics Price Competition and Innovation Act,
295 proponents of 12-year statutory exclusivity for biologics asserted that patents on biologics
296 would not limit competition as effectively as patents on small-molecule drugs.²⁹⁻³¹ We
297 found 4 times more patents per biologic than per small-molecule drug. Litigation is a key
298 tool that brand-name manufacturers use to delay entry of competitors, and our data
299 indicate that manufacturers of biologics have claimed infringement of 12 times as many
300 patents per litigated product as small-molecule manufacturers. Contrary to expectations
301 when the Biologics Price Competition and Innovation Act was passed, patents on biologics
302 may be more effective at delaying biosimilar entry than patents on small-molecule drugs
303 are at delaying generic entry.³²⁻³⁴ One strategy, for example, has been to obtain new
304 patents on methods of manufacture just as 12-year exclusivity periods expire, thereby
305 creating uncertainty for biosimilar firms seeking to challenge biologic patents.³⁵ Such
306 strategies help explain why market exclusivity periods, on average, appear to be several
307 years longer for biologics than for small-molecule drugs, based on the data analyzed in this
308 study.

309 Other barriers to biosimilar entry also contribute to longer periods of market
310 exclusivity for biologics.³⁶⁻³⁸ For example, unlike most generic small-molecule drugs,
311 biosimilars require advanced clinical trials to obtain FDA approval, increasing the time and
312 resources needed to enter the market. Once approved, biosimilars do not benefit from
313 automatic substitution like generic small-molecule drugs unless the FDA grants a
314 biosimilar the rare designation of “interchangeable,” which typically requires further
315 studies. Even then, many states do not require substitution of interchangeable biosimilars
316 at the pharmacy in the way that generic drugs must be dispensed when available.³⁹
317 Physicians have also shown greater reluctance to switch patients from brand-name
318 biologics to biosimilar versions compared to generic drugs.⁴⁰ The result is that biosimilars
319 have historically captured just 25% of the biologic market within 2 years of first biosimilar
320 entry, with average price reductions on biologic reference products of less than 10%.^{41,42}
321 By contrast, generic small-molecule drugs generally capture 65-90% of the market within a
322 year of first generic entry, with average price reductions of 50%.^{43,44} Although policies to
323 address patent thickets are vital to facilitate timely biosimilar entry, other policies focused
324 on FDA interchangeability requirements, state substitution laws, and physician education
325 could help better incentivize biosimilar development. Given the evolving regulatory
326 landscape for biosimilars, as well as changing perceptions among physicians, patients, and
327 insurers about the substitutability of these products, exclusivity periods and revenues for
328 originator biologics may decrease in the future.

329 Longer periods of market exclusivity for biologics have contributed to higher overall
330 revenues compared to small-molecule drugs. The \$3.7 billion in median revenues earned
331 by biologics over their lifetime (discounted to reflect the net present value to companies at

332 the time of launch) was nearly double the \$2.0 billion (also discounted) in median revenues
333 earned by small-molecule drugs. When compared to the median capitalized development
334 cost for biologics (\$3.0 billion) and small-molecule drugs (\$2.1 billion), biologics appear, on
335 average, to be more valuable assets to drug makers than small-molecule drugs. For small-
336 molecule drugs, estimated median development costs exceeded median revenues, likely
337 due to the heavy skewness of revenues, which followed a roughly lognormal distribution.

338 Concerned about the rising costs of biologics, the Obama Administration pushed to
339 reduce the statutory exclusivity period from 12 to 7 years so that it would be more aligned
340 with small-molecule drugs.⁴⁵ That effort was unsuccessful. Instead, Congress further
341 entrenched differential treatment with the Inflation Reduction Act of 2022, exempting
342 biologics from Medicare price negotiation for 4 years longer than small-molecule drugs (11
343 years vs. 7 years), even though Medicare spending is heavily concentrated on biologics.⁴⁶
344 Legislative efforts are currently focused on changing the timelines for price negotiation in
345 the Inflation Reduction Act. One proposal would exempt all drugs from price negotiation
346 for 11 years (House bill H.R. 7174: Ensuring Pathways for Innovative Cures Act), while a
347 competing proposal would reduce the exemption period to 5 years for all products (Senate
348 bill S. 1246: Strengthening Medicare and Reducing Taxpayer Prices Act).

349 Our study does not address the optimal duration of statutory exclusivities for
350 pharmaceuticals nor the timing of Medicare price negotiation. However, currently available
351 evidence does not support extended protection for biologics relative to small-molecule
352 drugs. Further research is needed to better understand the types of protections that are
353 needed to incentivize private investment in innovation while ensuring timely competition
354 from biosimilar and generic drugs for the benefit of patients and the health-care system.

355

356 Limitations

357 Our analyses of research and development costs, patents, and revenues were limited
358 to data in the public domain. Although we found no statistically significant difference in
359 development costs between small-molecule drugs and biologics, our analysis was based on
360 a small sample. It is possible that a larger study would observe a significant difference
361 given the divergent distributions observed between the two groups. Our development cost
362 estimates undercounted pre-clinical expenditures, and our analysis of development times
363 was restricted to products with applications for patent term extensions, some of which may
364 have been attached to secondary patents rather than primary patents.⁴⁷ However, these
365 issues affected both types of products, reducing the potential for bias.

366 Data on biologic patents are only disclosed when patents are litigated, and not every
367 patent associated with a biologic drug is litigated. The disparity between overall patent
368 protection for biologics and small-molecule drugs may therefore be larger than reported in
369 this study.

370 Our estimate of the median and mean market exclusivity period for biologics may
371 have been biased upwards by the inclusion of older biologics. The earlier biologics in our
372 sample were approved before the biosimilar pathway existed. After becoming law, the
373 biosimilar pathway was slow to be implemented, but as this pathway has matured,
374 biosimilar market entry has been occurring sooner than in the past.

375 Because the SSR Health dataset did not capture revenues in all years for all products
376 (due to lack of reporting by companies), we used median values to mitigate the impact of
377 outliers arising from year-to-year changes to the sample composition. We did not examine

378 manufacturing costs due lack of publicly available data; existing analyses suggest that these
379 costs are higher for biologics than for small-molecule drugs, but are trivial relative to
380 revenue for both types of products.^{48,49}

381 Finally, although we restricted our literature reviews on clinical trial success rates
382 and exclusivity periods to studies published since 2009, some of the included studies relied
383 on earlier data.

384

385 **Conclusions**

386 There is little currently available evidence to support biologics having extended
387 market exclusivity or protection from negotiation. As a result of differential treatment, US
388 law appears to over-reward the development of biologics relative to small-molecule drugs.

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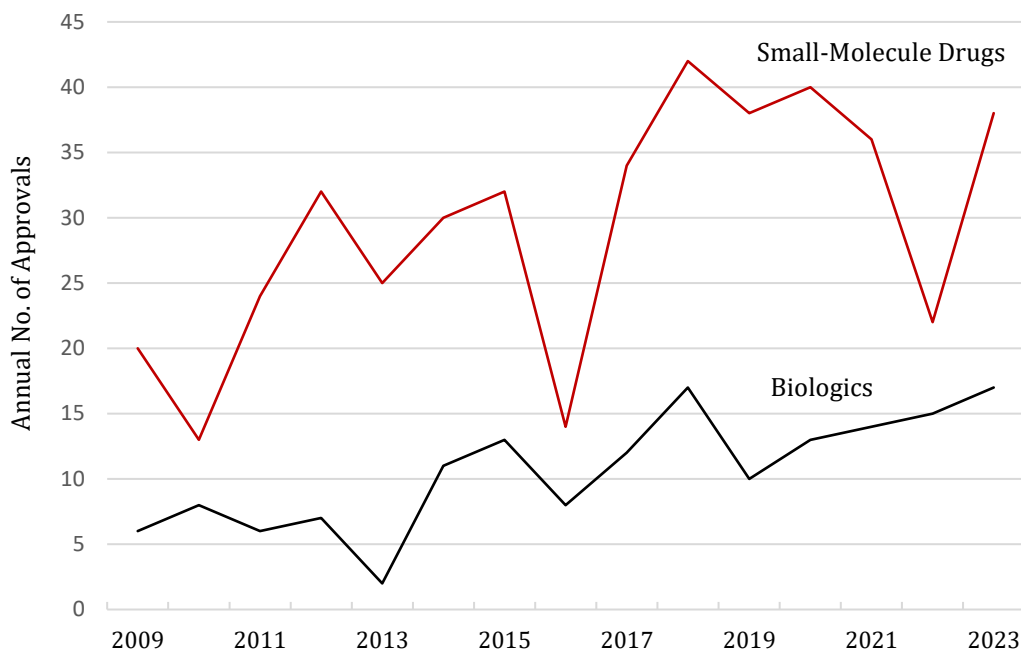
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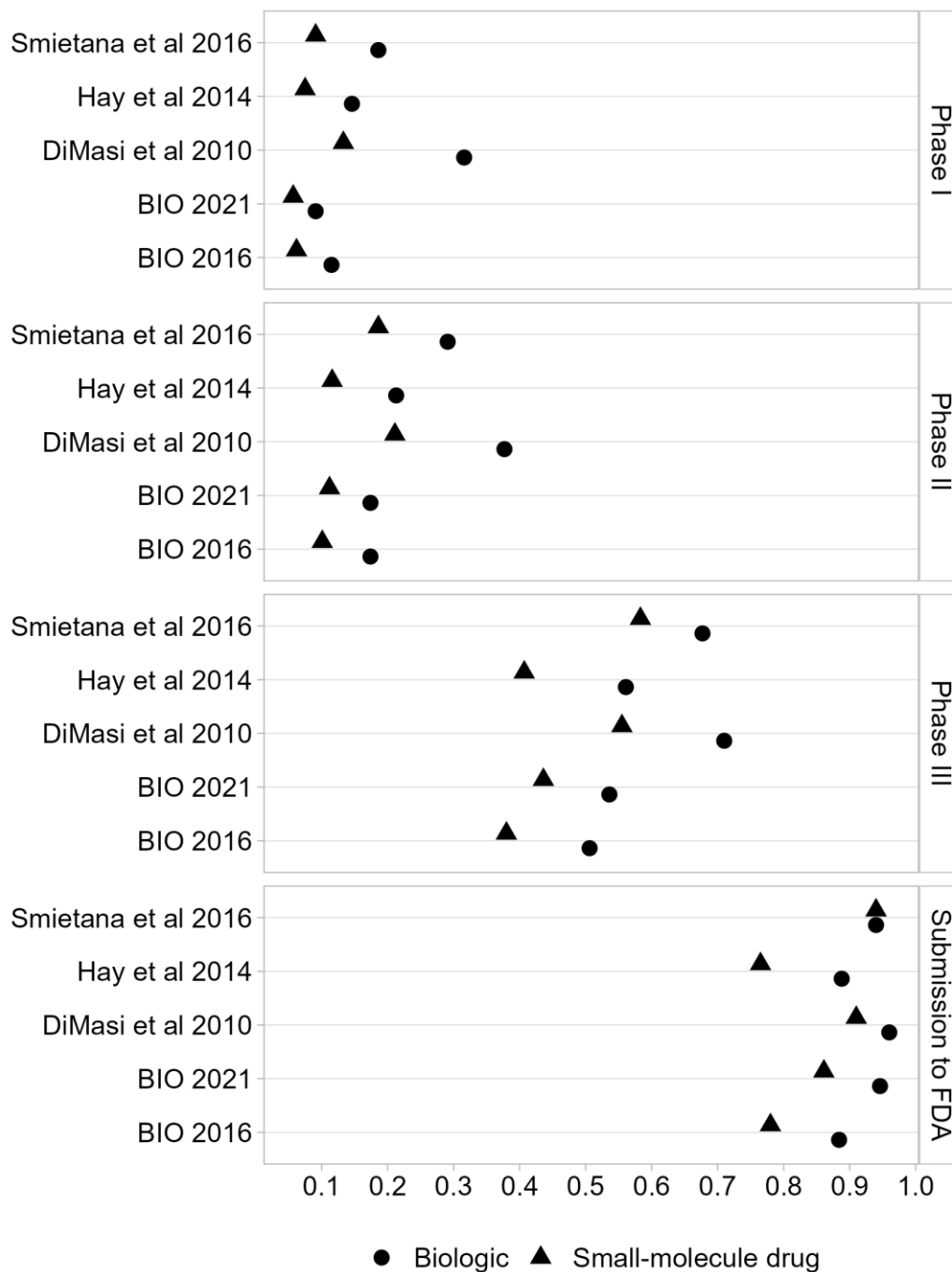
543 **FIGURES AND TABLES**

544 **Figure 1.** Small-molecule drugs and biologics approved by the US Food and Drug
545 Administration, 2009 to 2023



546
547 *Legend:* In March 2020, the Food and Drug Administration’s Center for Drug Evaluation and Research
548 reclassified some drugs previously approved under New Drug Applications as Biologics License
549 Applications;⁵⁰ these are counted as Biologics License Applications in the figure. The data were sourced from
550 Drugs@FDA.⁸

551 **Figure 2.** Clinical trial success rates by phase for small-molecule drugs vs. biologics

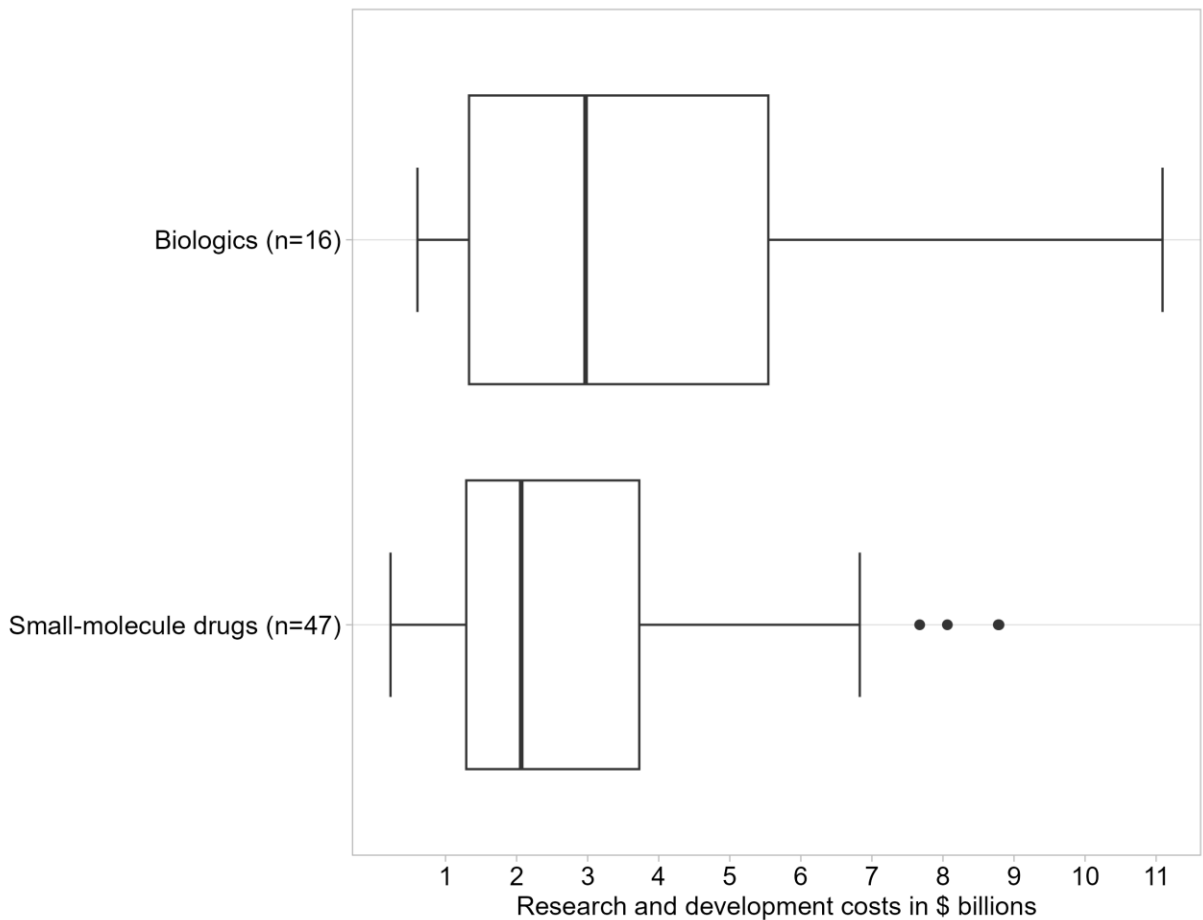


552

553 BIO indicates Biotechnology Innovation Organization; FDA, Food and Drug Administration.

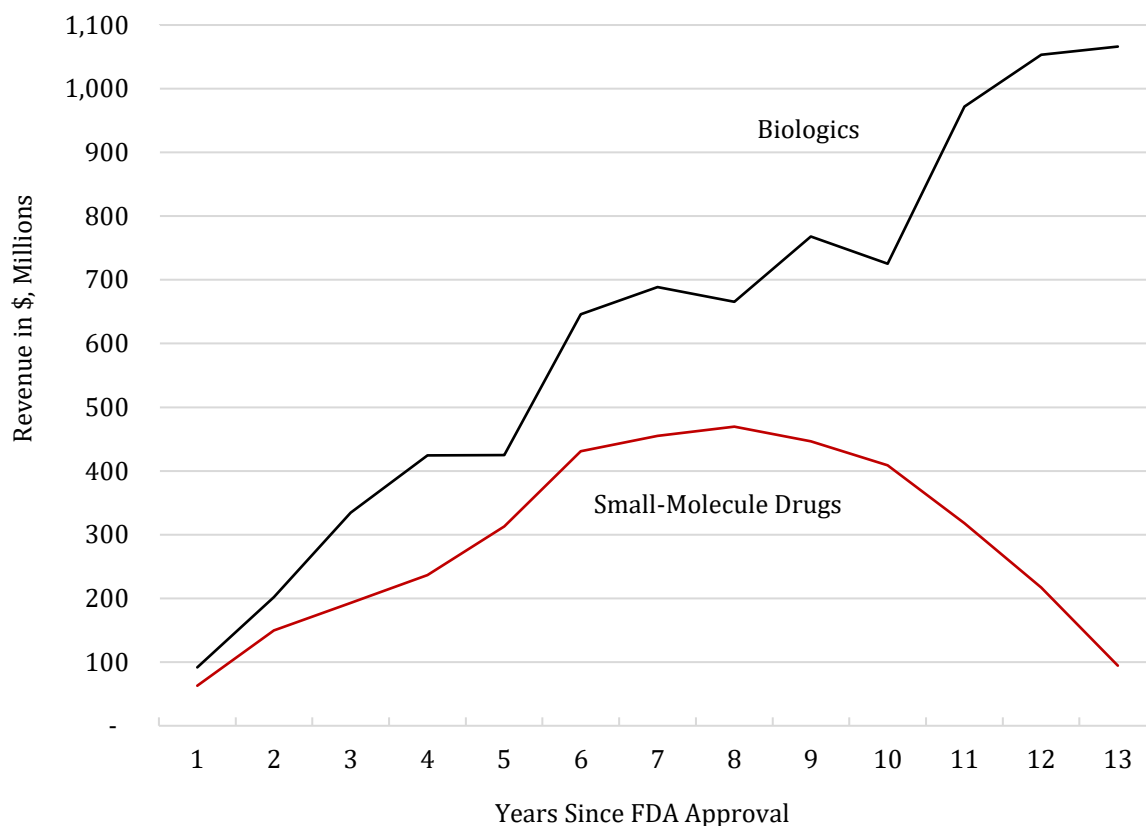
554 *Legend:* The estimates shown in the figure were sourced from multiple studies identified through a PubMed
 555 search of all English-language articles published from 2009-2023 and a targeted search for grey literature on
 556 the topic.^{14,20-23} eTable 2 provides data on the sample size of each study.

557 **Figure 3.** Estimated research and development investments for biologics vs. small-
558 molecule drugs
559



560
561 *Legend:* Research and development costs were extracted from filings by pharmaceutical firms with the US
562 Securities and Exchange Commission for novel biologics (n=16) and small-molecule drugs (n=47) approved
563 from 2009 to 2018.¹³ To estimate spending on failed trials, we applied probability adjustments to reflect the
564 likelihood of success using the most recently published clinical trial success rates for biologics and small-
565 molecule drugs.¹⁴ As in previous studies, we applied a 10.5% discount rate to reflect the cost of capital.^{13,15} All
566 values were adjusted to 2023 dollars using the Consumer Price Index (All Urban Consumers). The whiskers
567 on the left indicate the smallest values (excluding outliers), the left sides of the boxes indicate the lower
568 quartiles (25th percentile), the middle lines indicate the medians (50th percentile), the right sides of the boxes
569 indicate the upper quartiles (75th percentile), the whiskers on the right indicate the largest values (excluding
570 outliers), and any points beyond the whiskers indicate outliers.

571 **Figure 4.** Median annual revenues following Food and Drug Administration approval for
572 biologics vs. small-molecule drugs



573
574 *Legend:* FDA indicates the Food and Drug Administration. We used data from SSR Health to track sales
575 revenues from 2009 to 2023. We calculated median net revenues for biologics and small-molecule drugs in
576 each year since FDA approval. All values were adjusted to 2023 dollars using the Consumer Price Index (All
577 Urban Consumers).

578 **Table 1.** Market exclusivity timelines for all biologics with biosimilars approved by the US
579 Food and Drug Administration
580

Reference Biologic		Date of First Biosimilar		Years Until First Biosimilar		Total Number of Biosimilars	
Generic Name (Brand Name)	Approval	Approval	Entry	Approval	Entry	Approval	Entry
Epoetin alfa (Epoegen/Procrit)	6/1989	5/2018	11/2018	29.0	29.4	1	1
Filgrastim (Neupogen)	2/1991	3/2015	9/2015	24.0	24.5	3	3
Rituximab (Rituxan)	11/1997	11/2018	11/2019	21.0	22.0	3	3
Infliximab (Remicade)	8/1998	4/2016	11/2016	17.6	18.2	4	3
Trastuzumab (Herceptin)	9/1998	6/2019	7/2019	19.2	20.8	5	5
Etanercept (Enbrel)	11/1998	8/2016	n/a	17.8	n/a*	2	n/a*
Insulin glargine (Lantus)	4/2000	6/2020	9/2020	20.1	20.4	2	2
Pegfilgrastim (Neulasta)	1/2002	6/2018	7/2018	16.3	16.4	6	6
Adalimumab (Humira)	12/2002	9/2016	1/2023	13.7	20.1	9	9
Bevacizumab (Avastin)	2/2004	9/2017	7/2019	13.5	15.4	5	4
Natalizumab (Tysabri)	11/2004	8/2023	n/a	18.7	n/a*	1	n/a*
Ranibizumab (Lucentis)	6/2006	9/2021	9/2021	15.2	15.2	2	2
Ustekinumab (Stelara)	9/2009	10/2023	n/a	14.1	n/a*	1	n/a*
Tocilizumab (Actemra)	1/2010	9/2023	n/a	13.7	n/a*	1	n/a*
Median				17.7	20.3	2.5	3.0

581
582 * No market entry as of December 31, 2023, for biosimilar versions of etanercept, natalizumab, ustekinumab,
583 or tocilizumab.