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The critical impact of time discounting on economic incentives to overcome the antibiotic market failure

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As summarized in a recent article (Antibacterial R&D incentives. *Nature Rev. Drug Discov.* **10**, 727–728 (2011))¹, numerous ‘push’ and ‘pull’ economic incentives have been proposed to rekindle the antibiotic pipeline^{2–6}. These have been the subject of discussions in both the United States and Europe^{1,4}.

Push incentives act early in research and development (R&D) and are generally of smaller monetary amounts than pull incentives, which do not become operative until after a drug is approved for use in humans. Until recently, the relative potency of push and pull incentives at promoting new R&D in the antibiotic area had been uncertain. However, an analysis by Sharma and Towse⁶ found that a key pull incentive — extended market exclusivity — had minimal impact on improving the net present value (NPV) of antibiotics. By contrast, push incentives may be of greater value. Because pull incentives should result in larger amounts of revenue than push incentives, the assertion that pull incentives are less economically valuable than push incentives may be counterintuitive. However, as we show below, push incentives may be 95% smaller than pull incentives and still yield similar value.

To explain this paradox, we developed a model to determine the present value (PV) of push and pull incentives. In the base case model, the extended exclusivity incentive began after patent expiration, which included the 20 years of patent term and 5 years of patent term restoration (a total of 25 years) afforded to drugs in the United States under the Hatch–Waxman Act (Supplementary information S1 (figure); panel a). As is standard, the model incorporated time discounting in calculating the NPV^{7,8}. Because a discount rate of 10–11% has become standard in pharmaceutical economic models as a way to adjust for risk^{5,9–11}, a discount rate of 10.5% was used in the current model, with sensitivity analyses run at 7% and 20%^{12,13}. Thus, in the base case estimate, future revenue from the extended exclusivity incentive was discounted by 10.5% compounded annually for 25 years before the incentive

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Competing interests statement

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began, which was consistent with a timeline including: preclinical development (4 years); clinical development (8 years) plus time for filing and approval of a new drug application (NDA) (1 year); and sales protected for a period of 12 years after initial approval by the initial patent on the compound (7 years remaining at the time of NDA filing) plus 5 years of patent term restoration^{5,10,12} (Supplementary information S1 (figure); panel a). Discounting continued during the period of extended exclusivity.

To model the impact of discounting on pull incentives, the base case estimate of annual antibiotic sales during the period of extended exclusivity was US\$400 million^{5,10}. Time discounting was applied to the difference between the total sales with extended exclusivity and the sales without extended exclusivity. To calculate this difference, a base case estimate of a 15% annual decline in sales following the expiration of exclusivity was modelled⁵. Total sales resulting from the extended exclusivity incentive were calculated by summing up the difference between the sales during the extended exclusivity incentive period (\$400 million per year in the base case model) and sales starting at \$400 million per year but declining at 15% per year without the incentive.

To model the impact of discounting on push incentives, a separate base case scenario was developed. The model did not distinguish among the different types of push incentives; it could equally apply to grants, contracts, R&D tax credits, matching funds, other forms of public-private partnerships (PPPs) or any other push incentive of the same dollar amounts and time period modelled.

In the base case pull incentive model, the total revenue generated during the 5 years of extended exclusivity was \$739 million (TABLE 1). However, this revenue did not become available until 26–30 years after the discovery of the drug (Supplementary information S1 (figure); panel b). Because of time discounting, the PV of these future total revenues was only \$43.1 million (TABLE 1).

In sensitivity analyses, changing the discount rate to 7%, which was reflective of a value published 20 years ago¹⁴, still resulted in an 86% erosion in the PV of the incentive (TABLE 1). Increasing the discount rate to 20%, which was more consistent with the higher R&D risk at small companies^{12–14}, resulted in a remarkable 99.4% erosion in the PV of the incentive (TABLE 1). However, acquisition of a drug from another company after some period of development had already occurred shortened the period of discounting. For example, drug acquisition after completion of preclinical development (filing an investigational new drug (IND) application), Phase I trials or Phase II trials led to discount periods of 21, 19 or 17 years, respectively, before the exclusivity extension began (Supplementary information S1 (figure); panel b), resulting in 91%, 89% or 87% PV erosions, respectively (TABLE 1).

Doubling the length of the extended exclusivity period from 5 to 10 years (Supplementary information S1 (figure); panel b) more than doubled the PV of the incentive to \$96 million (TABLE 1) because the annual 15% decline in sales after patent expiration is cumulative. Thus, the difference in sales with versus without extended exclusivity increases by 15% annually for each year of the exclusivity incentive (that is, it is 15% greater in year 30 than in year 29, and so on). For the same reason, combining a 10-year extended exclusivity incentive with a shortened duration of discounting due to acquisition of the drug after completion of preclinical development (filing an IND application), Phase I trials or Phase II trials resulted in synergistically higher absolute PVs (of \$143 million, \$175 million or \$214 million, respectively).

Changing the rate of declining sales after expiration of exclusivity had a minimal impact on the PV (TABLE 1). By contrast, the overall value of the extended exclusivity incentive was

affected by changing the peak antibiotic sales at the time the extended exclusivity began (TABLE 1). Finally, initiating extended exclusivity after the expiration of the 5-year Hatch–Waxman data exclusivity period (which begins once the drug is approved), rather than after patent expiration resulted in the extended exclusivity expiring 2 years before patent expiration (Supplementary information S1 (figure); panel c). The net effect was no period of extended exclusivity, and hence no additional revenue, resulting in a PV of \$0. R&D had to be prolonged beyond 15 years for the extended exclusivity to generate any value if it began after the expiration of data exclusivity.

In the base case push incentive model, the full amount of the push incentive was applied to year 1, which is consistent with an incentive that is intended to encourage a new antibiotic discovery programme. As the incentive was applied in year 1, there was no discounting. Thus, a push incentive of only \$43.1 million was sufficient to equal the PV of a 5-year extended exclusivity pull incentive that generated an additional \$739 million in sales (TABLES 1,2).

Owing to the erosive power of discounting, if the full amount of the push incentive was instead applied in year 5 (after IND filing), year 7 (after Phase I trials) or year 9 (after Phase II trials) the size of the incentive had to be \$71 million, \$86 million or \$106 million, respectively, to exceed the PV of a 5-year extended exclusivity (TABLE 2). If the push incentive was spread over a 5-year period, rather than as a lump sum in a single year, a cash input of \$11.5 million per year during the first 5 years (\$57.6 million in total) resulted in a PV that exceeded the PV of the 5-year extended exclusivity (TABLE 2). If the push incentive was instead applied to years 6–10 of development, the size of the incentive had to increase to \$19 million per year (\$95 million in total) to achieve a PV in excess of the 5-year extended exclusivity (TABLE 2). Finally, if the incentive was spread over the entire period of development (years 1–13) — as would be the case for R&D tax credits, for example — only \$6.25 million per year (\$81.25 million in total) was required to exceed the PV of a 5-year extended exclusivity pull incentive (TABLE 2).

In summary, because of the power of discounting to erode the value of incentives over time, a push incentive that was 95% smaller in total dollar amount still exceeded the PV of a pull incentive (extended exclusivity) in the current model. Prolonging the extended exclusivity incentive to 10 years, especially when combined with acquisition of the drug after key milestones, rather than internally discovering and developing the drug, was very effective at improving the absolute PV. However, the extended exclusivity incentive lost most or all of its value (depending on how long R&D took) if it was initiated after the expiration of the standard 5-year data exclusivity period and therefore ran concurrently with existing patent life. Thus, if the goal of an extended exclusivity incentive is to improve the economics of antibiotic discovery and development, it should be provided by a mechanism that begins after the expiration of the total effective period of exclusivity provided by current mechanisms, which include patent term, patent restoration and data exclusivity. Ultimately, a mixture of both push and pull incentives, including extended exclusivity for more than 5 years starting after patent expiration, is likely to be optimal for reversing the failure of the market to provide sufficient incentives to develop new antibiotics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Impact of discounting on pull incentive (extended exclusivity)

Variables	Values	Incentive present value (US\$)	Erosion in value caused by discounting (%)
<i>Base case model</i>			
Discount rate	10.5%	\$43,089,799	94%
Years of discounting [†]	25		
Years of extended exclusivity	5		
Annual decline in sales after exclusivity expiration (%)	15% per year		
Annual sales at initial exclusivity extension	\$400 million		
Base case total sales without discounting	\$739,065,375		
<i>Sensitivity analyses</i>			
Discount rate	7–20%	\$107,516,373– \$4,172,459	86%–99%
Years of discounting:			
Acquisition after IND application	21 years	\$64,242,670	91%
Phase I trials	19 years	\$78,441,906	89%
Phase II trials	17 years	\$95,779,529	87%
Years of extended exclusivity	10 years	\$96,353,281	96%
Acquisition after IND application		\$143,653,305	93%
Phase I trials		\$175,404,277	92%
Phase II trials		\$214,173,007	90%
Annual decline in sales after exclusivity expiration (%)	7.5–30%	\$22,173,124– \$72,211,117	97%–90%
Annual sales at initial exclusivity extension	\$100 million – \$1 billion	\$10,772,450– \$107,724,498	94%–94%
Exclusivity extension concurrent with patent:			
R&D takes 13 years (base case)		\$0	
R&D takes 15 years		\$0	
R&D takes 17 years		\$11,965,400	98%
R&D takes 20 years		\$43,089,799	94%

IND, investigational new drug; R&D, research and development.

* Years of discounting before patent expiration (that is, before the generation of additional revenue during the extended exclusivity; discounting continues during the extended exclusivity period). The base case estimate accounts for 4 years of preclinical discovery and development, 9 years of clinical development plus new drug application (NDA) filing and approval, and 12 years of sales before the extended exclusivity would begin (25 years in total). Shorter periods were modelled for acquisition of a compound after another company completed preclinical development and filed an IND application (21 years), after Phase I clinical trials (19 years) or Phase II clinical trials (17 years) but the model does not account for the cost of that acquisition and the actual NPV would need to be reduced by that amount.

[†]In the base case model the cash inputs are made available in year 1, so there is no discounting. In the sensitivity analyses a 10.5% annual discount rate was applied.

Table 2

Impact of discounting on push incentive

Variables	Values	Incentive present value (US\$)	Erosion in value caused by discounting (%)
<i>Base case model</i>			
Discount rate	10.5%	\$43,100,000	0%
Year incentive applies	Year 1		
<i>Sensitivity analyses</i>			
Total cash inputs	\$43,100,000		
Year incentive applies:			
Year 5	\$71,000,000	\$43,100,000	39%
Year 7	\$86,700,000		50%
Year 9	\$105,900,000		59%
Years incentive applies (annual amount in millions):			
Years 1–5 (\$11.5 million per year)	\$57,575,000	\$43,100,000	25%
Years 6–10 (\$19 million per year)	\$95,000,000	\$43,100,000	55%
Years 1–13 (\$6.25 million per year)	\$81,250,000	\$43,269,000	47%
Years 1–13 (\$12.5 million per year)	\$162,500,000	\$86,538,058	47%
Years 1–10 (\$6.25 million per year)	\$62,500,000	\$37,592,330	40%