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A plan for sustainable funding for US biomedical research

Preston Hensley and John L. LaMattina

The United States is facing two healthcare challenges — the equitable distribution of healthcare, and to support it, a sustainable biomedical research foundation for the discovery of new therapies and diagnostics. Although the US biomedical research infrastructure is currently strong, it is not a foregone conclusion that it will remain this way. As highlighted in a recent article[1] (An audience with…Story Landis. *Nature Rev. Drug Discov.* **13**, 718–719 (2014)), as well as by the American Society of Biochemistry and Molecular Biology[2], federal funding for biomedical research in the United States has been decreasing for more than a decade (FIG. 1) and, considering the current political climate, the situation is likely to get even worse for at least the next few years.

Over the same period, the private sector research and development (R&D) ecosystem in the United States has changed[3]. With increased globalization have come increased competition, pressure for short-term advantage and a shift in industry from early-stage research to later-stage development. This has resulted in increased offshoring of early- and late-stage research efforts, with potential long-term negative consequences. Additionally, universities, research institutes and research hospitals have become more translationally focused and some have become proof-of-concept centres for new drug discovery ideas. These events have changed the dialogue between those who create biological knowledge and those who apply it, and suggest that successful drug R&D in the future will require new modes of interaction among academic, industrial and governmental organizations. Here, we propose a plan to help provide the funding needed to address the associated challenges: extending patents on drugs by one year and using the additional revenue to support biomedical R&D.

Characteristics of the plan

The accounting for the sales of branded drugs in the United States during their extra year of patent protection would be the same as for a normal year. Profits (that is, excess over operational costs) would be reported as usual to the US Securities and Exchange Commission (SEC; see Further information). This accruing resource — estimated to be US$13 billion–$18 billion per year in recent years (FIG. 2) — would be escrowed and used to support federally and industrially driven R&D efforts, as well as efforts to expose junior and senior scientists to the differing academic, industrial and governmental research cultures and opportunities. If 50% of this resource (that is, about $6 billion–$9 billion per year, on average) could be directed back to the companies affected, and 50% directed to the US National Institutes of Health (NIH), a sustainable increase in the latter's budget — of roughly 25% per year — would be produced.

This resource would not be used for profit, or for business as usual on either side. For the NIH, it could be directed towards innovative programmes like the recently announced Accelerating Medicines Partnership (AMP), which focuses on the identification of new drug discovery targets and biomarkers, or the Toxicology in the 21st century (Tox21) collaboration between the NIH, the Environmental Protection Agency and the US Food and Drug Administration (FDA), which is focused on drug safety. Other programmes could focus on the discovery of diagnostics for patient stratification; threats where potential crises (such as Ebola and drug-resistant bacteria) loom; neglected diseases; and drug repurposing. From 2011 and 2012 alone, there were 148 clinical-trial failures between Phase II and FDA submission[4]. The rescue or repurposing of just one high-value failed drug candidate would have a positive impact on healthcare and could potentially create billions of dollars of market value.

On the industry side, these funds could be used to strengthen the academia–industry interface. They could fund academic research efforts that are directed at some of the same issues noted above, secondments in either direction, educational programmes or any of a number of activities that would bring industrial and academic researchers into closer conversation.

The devil, of course, is in the details. First, who will pay to keep the original branded version of these medicines on the market without competition for an extra year? That burden is distributed, but will fall largely on the insurance industry in the United States. The breakdown is commercial third party (insurance), 57%; Medicare Part D, 26%; Medicaid, 9%; and cash, 8% (REF. 5). But, the ultimate payers will be insurance subscribers and tax payers. So, this will amount to a small increase in consumer cost. However, it should be noted that the cost of pharmaceuticals represents only about 10% of the total US healthcare bill (a proportion that has been roughly constant over decades) and this proposed increase would be a very small percentage of that. This would not show up

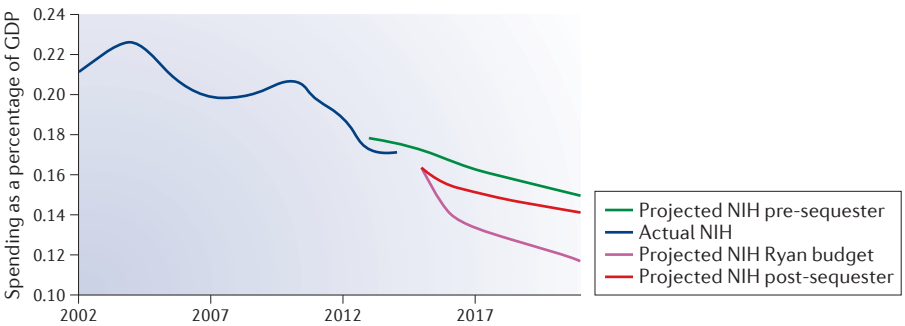

Figure 1 | **Actual and projected NIH spending 2002–2020.** All projected US National Institutes of Health (NIH) spending levels assume that the percentage of non-defence discretionary spending that is dedicated towards the NIH remains at the 2014 level. The decline in spending in all of the projections is due to the decline in non-defence discretionary spending[14]. The Ryan Budget is the budget passed by the House of Representatives for fiscal year 2015, which contains the House set spending and revenue targets for 10 years. The spending targets are for broad categories of spending, which can be different from the annual appropriations. The pre-sequester spending level assumes that the Budget Control Act pre-sequester spending caps remain in place through 2021. The post-sequester spending level assumes that the Budget Control Act post-sequester level spending caps remain in place through 2021. The gross domestic product (GDP) was ~US$17.5 trillion in 2014. Adapted with permission from the Office of Congresswoman Rosa Delauro[14].

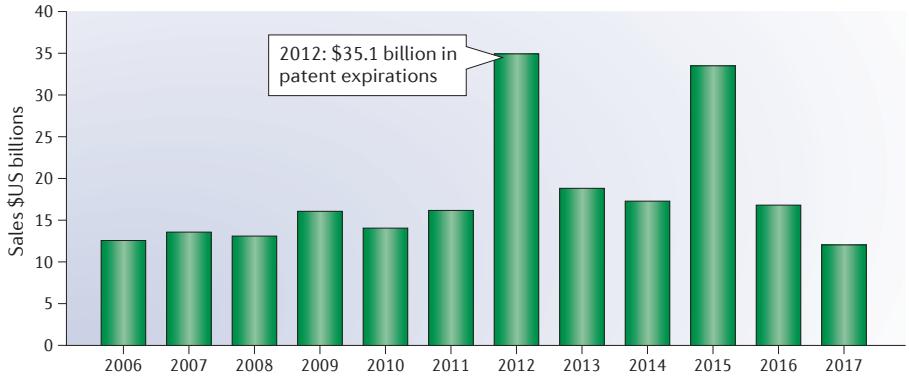

Figure 2 | **Estimated annual drug sales in the United States at risk due to loss of patent exclusivity from 2006 to 2017.** Adapted with permission from Casey Research[15].

as a significant out-of-pocket expense, as more than three quarters of all prescriptions cost patients less than ten dollars[5].

Another issue relates to the market entry of biosimilar versions of biologics, which now make up a substantial proportion of the medicines that generate the most revenue for the industry (and which would thus provide a substantial proportion of the annual amount that would become escrowed in the additional year of patent-protected sales). The arithmetic of the proposed scheme with regard to the dates over which revenue would be escrowed for small-molecule drugs is straightforward; the patent expiration dates (nominally 20 years from filing; see Further information) and profits (filed with the SEC) are known. However, although the same is true in principle for biologics, the situation is complicated by the lack of certainty over the market entry pathway for biosimilars in the United States[6,7]; at present, it could be anticipated that branded biologics may continue to have no biosimilar competitors for some time after the expiry of the relevant patents. Moreover, in Europe (where mechanisms for biosimilar approval have been established for several years), biosimilars have only won 25–30% of the market share, compared with up to 80% for generic versions of small-molecule drugs[8]. Nevertheless, the worst-case scenario, once these issues are resolved, is that the full estimated annual benefit of $13 billion–$18 billion will not be realized; a substantial portion will be, though. Time will tell in the United States, but optimistically, the issues surrounding biosimilar market entry may be resolved in roughly the period of time it will take for legislation around the proposed plan to get to the US Congress.

A related issue is that profits from the original branded version of drugs do not fall immediately to zero in the first year after patent expiry (when generic competitors begin to enter the market). It is not unusual for branded versions to retain 20% of their previous year's sales in that year ('year 21', assuming 20 years from patent filing). In this proposal, 100% of the profits from sales of the original branded version in year 21 will be escrowed, but the 20% of sales would still be realized in year 22. We feel that the delay in realizing the associated profit (which could be a substantial amount for blockbuster products) for the companies concerned is more than made up for by the substantial infusion of funds from the plan.

Precedents and support

There is a modern precedent for extending drug-patent lives to benefit the general public. In 1997, as part of the FDA Modernization Act (FDAMA)[9], the US Congress enacted the Pediatric Exclusivity Provision (PEP)[10]. The PEP allowed an extra 6 months of patent life in exchange for carrying out paediatric studies requested by the FDA, with the aim of encouraging drug makers to perform clinical trials in children. Before 1997, few drugs were studied in patients under the age of 16. Post-FDAMA, this situation changed, resulting in patients and physicians knowing the pros and cons of many more drugs for paediatric use. It proved to be a win–win. The parallel is not exact, but this is an example of where patent extension was used to achieve an end with social value.

It is also not unusual for the US Congress to turn to funding from pharmaceutical companies to provide extra resources for a government agency. When struggling to find funds to bolster a poorly funded FDA back in the 1990s, the US Congress passed the Prescription Drug User Fee Act (PDUFA; see Further information). The PDUFA calls for the levying of 'user fees' whenever a company files a New Drug Application (NDA) for FDA approval. These user fees were then used to hire more medical officers, chemists, pharmacologists and other experts that are needed to provide proper and complete reviews of NDAs. Since 1992, the PDUFA has been reauthorized four times, with the latest version being PDUFA-V, which was approved in 2012. The user fees — which now exceed $2 million for each NDA that is filed with the FDA, and totalled $713 million in fiscal year 2013 (REF. 11) — provide sustainable funding for the FDA. So the proposed plan, in effect, combines aspects of both the FDAMA PEP and the PDUFA legislation.

There is also historic precedent for such programmes[3]. Over a century ago, in response to a need to develop the US economy in new directions, Abraham Lincoln signed the Morrill Act of 1862 into law. At that time, the United States made a choice that it was necessary to increase scholarship and education in agriculture, engineering, the military (such as the Reserve Officers' Training Corps (ROTC)) and home economics. This Act ultimately produced 106 institutions of higher learning, including the University of California, the Massachusetts Institute of Technology, the University of Wisconsin, and a host of other state universities and colleges, including 31 tribal colleges. In so doing, it helped to fuel the industrial revolution of the late 1800s. The US Congress has established similar programmes for sea grant colleges (for aquatic research, the programme for which was established in 1966), urban grant colleges (urban research, in 1985), space grant colleges (space research, in 1988), and sun grant colleges (sustainable energy research, in 2003). These are all examples of academic-institution–industry–government partnerships — the goal of which is to enhance the nation's education, economy and environment in the twenty-first century.

As has been pointed out, increased biomedical research support is necessary but not sufficient to help the United States to realize its full potential. Attention should also be paid to structural aspects of sustainability — namely that aspects of the grant-awarding mechanisms be updated and that the trainee pipeline is adjusted so that the doctorates (currently 8,000 produced per year in the biological sciences) and postdoctoral fellows (currently 40,000 in the US biomedical research system) have a realistic chance for developing productive careers in biomedical research, or to make a creative impact in related fields[12].

Although the pharmaceutical industry directly employs 674,000 people, supports more than 4 million jobs and contributes more than $900 billion to the US gross domestic product (GDP) annually[13], and thus deserves attention, its struggles are just one aspect of a larger problem facing the United States, as has been discussed by the US President's Council of Advisors on Science and Technology (PCAST)[3]. Their analysis makes several recommendations, the first of which is: "The Nation has the opportunity to maintain its world-leading position in R&D investment, structured as a mutually supporting partnership among industry, the Federal Government, universities, and other governmental and private entities."

Specifically: "PCAST recommends reaffirming the President's goal that total R&D expenditures should achieve and sustain a level of 3 percent of GDP [which would be ~$525 billion for 2014]. Congressional authorization committees should take ownership of pieces of that goal, with the Executive Branch and Congress establishing policies to enhance private industry's major share."

US innovation centres are national resources. They were created in the last century, as a result of decades of investment in scholarship and infrastructure. The task now is to forge legislation that takes advantage of historic strengths and which supports and expands these strengths in a stable and predictable way — potentially as suggested here — and that will do this in an environment in which new partnerships will play an increasingly important, if yet to be fully defined, part.

What should the US economy look like in 2030? If technology is going to have a key role, especially in the balance of payments, the United States need s to begin seriously strengthening that sector now, and to scale its investment to match both the current need (especially in healthcare) and the goals for the economy in all technology sectors in the next few decades.

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Competing interests statement
The authors declare no competing interests.

FURTHER INFORMATION
United States Securities and Exchange Commission Annual Report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934: http://www.sec.gov/Archives/edgar/data/1003124/000119312511046748/d10k.htm
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