The Imperative of Protecting Life Sciences Innovation In the TPP

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The TPP will not be the high-standard, next-generation trade agreement it's been lauded to be if it does not include 12 years of data exclusivity protection for novel biologic drugs.

With negotiations to finalize the Trans-Pacific Partnership (TPP) agreement fast coming to a conclusion, it's imperative that America's trade negotiators preserve the strong intellectual property (IP) protections that provide the foundation for the global innovation ecosystem. This is particularly important in the area of life sciences. Paramount among these is ensuring that 12 years of data exclusivity protection on the clinical trial data that validates the safety and efficacy of novel biologic drugs becomes part of the final TPP agreement. That standard was enshrined in U.S. law by Congress after vigorous and extensive debate regarding the need to preserve incentives for life sciences innovation alongside the interests of affordability and competition.

STRONG IP RIGHTS UNDERPIN LIFE SCIENCES INNOVATION

America's biopharmaceutical industry provides a driving force for innovation, employment, and economic growth as well as an improved standard of living and quality of life for citizens throughout the world. The sector supports more than 7.4 million jobs and contributes $426 billion annually to U.S. GDP.[1] Exports from the U.S. biopharmaceutical industry totaled $52 billion in 2013.[2] The biopharmaceutical industry is one of the most research and development (R&D)-intensive in the United States, with the biopharmaceutical sector accounting for $78.7 billion, or 85 percent, of the estimated $92.6 billion in life sciences R&D conducted in the United States in 2014, according to Battelle's *2014 Global R&D Funding Forecast*.[3] Measured by R&D expenditure per employee, the U.S. biopharmaceutical sector leads all other U.S. manufacturing sectors,

investing more than ten times the amount of R&D per employee than the average U.S. manufacturing sector.[4] Moreover, America's life science industry—led by the biopharmaceutical sector—leads all industries in volume of research performed.[5] In total, U.S. pharmaceutical companies account for 80 percent of the world's R&D investment in health care biotechnology.[6]

Robust intellectual property protections constitute the fundamental foundation upon which private sector actors' intensive investment in biopharmaceutical R&D occurs. Intellectual property rights represent a grand bargain. In exchange for receiving exclusive rights for a limited period of time, innovators are required to disclose their knowledge, as opposed to keeping it secret, and this creates knowledge spillovers that help others to innovate. But by allowing innovators to capture an adequate portion of the benefits of their innovative activity, intellectual property rights (IPRs) endow innovators with the resources—and incentive—to pursue the next generation of innovative activities, engendering a virtuous cycle of innovation.[7] This virtuous cycle allows the profits earned from one generation of biomedical innovation to sow the seeds for investment in the next generation of biomedical innovation. This dynamic is vital for true innovation-based industries, such as the biopharmaceutical sector, for they compete not on making a product (i.e., a drug) cheaper, but by inventing the next-generation one.[8]

Robust intellectual property protections constitute the foundation upon which intensive private-sector investment in biopharmaceutical R&D occurs.

Without adequate intellectual property protection, private investors would never find it viable to fund advanced research, because lower-cost copiers would be in a position to undercut the legitimate prices (and profits) of innovators even while still generating substantial profits on their own.[9] In other words, without robust intellectual property protections, investment in next-generation medicines will be significantly curtailed and the world will be left only with today's existing cures for medical maladies and little hope for solving the challenges on the frontiers of medical science. And if the TPP does not get the rules setting the foundational framework for life sciences innovation right, then the long-term result will be less innovation and fewer cures for unsolved diseases, which will negatively impact not only U.S. citizens, but citizens throughout the broader TPP region and indeed the entire world.

And the reality is that intensive private-sector investment in life sciences R&D has generated tremendous results, with the Tufts Center for the Study of Drug Development finding that, among 35 drugs and drug classes, private-sector research was responsible for central advances in basic science for 7, in applied science for 34, and in the development of drugs yielding improved clinical performance or manufacturing processes for 28.[10] In fact, today there are more than 5,000 medicines in development globally. At the forefront of these stand biologics—large, complex molecules derived from living cells that are manufactured from living organisms.[11] Biologic medicines—which include therapeutic proteins, DNA vaccines, monoclonal antibodies, and fusion proteins—are significantly more complex structurally than traditional "small molecule" pharmaceutical drugs and are often 200 to 1,000 times larger. To date, almost 200 biologic medicines have transformed the lives of over 800 million patients, including the breakthrough anti-cancer medicines Avastin, Herceptin, and Rituxan.[12] As Figure 1 shows, more than 900 novel biologic drugs targeting more than 100 different diseases are under development today, addressing a range

of conditions from cancers such as leukemia and melanoma to diabetes and infectious diseases.[13] By 2017, analysts expect that biologics will account for 30 percent of the pharmaceutical industry pipeline and that biologics will comprise seven of the top ten global pharmaceuticals.[14]

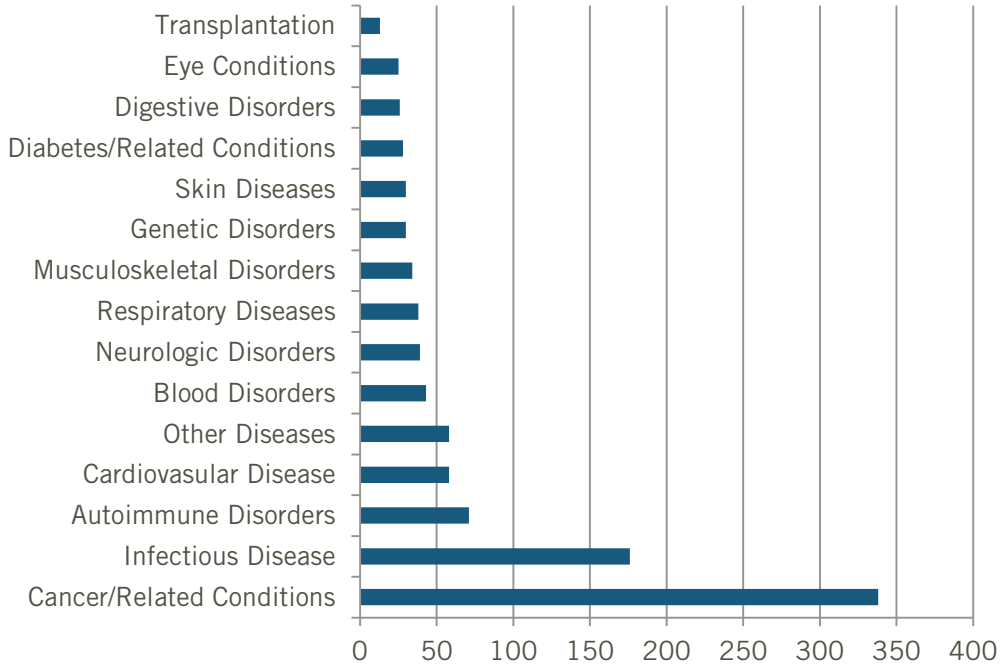

Figure 1: Biologics Medicines in Development, By Therapeutic Category[15]

Unlike traditional pharmaceutical drugs, which involve smaller molecules that operate largely on the basis of chemical reactions and that work by treating the consequences of a disease, biologics work by blocking diseases earlier in their development, in the immune system. And since they can be tailored to individuals taking the medicine, biologics constitute an important step toward realizing the vision of personalized medicine.[16] But as biologics are large, complex molecules that must be manufactured within living tissues, the resulting protein is unique to the cell lines and the specific process used to produce it, and even slight differences in the manufacturing of a biologic can alter its nature.[17] Indeed, the sensitivity of these complex proteins make them more difficult to characterize and to produce such that even minor differences in manufacturing processes or cell lines may result in variations in the resulting protein.[18] Accordingly, the intellectual property components of a biologic include both the structure of the molecule itself and the process for how to reliably, safely, and consistently manufacture the molecule at scale in living tissues.

Unfortunately, the process of developing a biologic drug is extremely risky, time-consuming, and expensive. In fact, the vast majority of biologic medicines never make it to the approval stage, with less than 15 percent moving from initial pre-clinical studies to clinical trials.[19] Yet the cost to develop a new prescription medicine that gained marketing approval in 2013 was $2.6 billion (a 145 percent increase over 2003 costs), while estimated

post-approval R&D costs of $312 million "boosts the full product life cycle cost per approved drug" to close to $3 billion.[20] Moreover, for biologic drugs that are approved, development of manufacturing facilities represent an additional cost beyond R&D that can range from $90 million to $450 million or more. Given the time, risk, and expense involved in developing biologics, studies find that the break-even time to recover development, manufacturing, promotion, and capital costs averages 14.6 years.[21] This long break-even timeframe means that biologics makers have a limited amount of time in which to recoup their investment before a biologic drug's intellectual property rights expire.

Biologic drugs reaching the marketplace require on average almost fifteen years to develop at a cost approaching $3 billion.

While patents constitute one important form of IP protection for biologics, they are not sufficient to support the environment needed to promote large-scale investment in biologic R&D, for two principal reasons. First, because biologics are structurally complex molecules which are closely tied to a specific manufacturing process, many biologic patents are process patents or relatively narrowly constructed product patents. This means that biologics patents are susceptible to being circumvented by small changes to the molecule or to the process of making it.[22] Because patents fail to provide the same certainty for biologics as they do for traditional pharmaceutical drugs, they do not necessarily assure that biologics will enjoy the same length of time on the market before facing competition from generics. Second, patents do not safeguard the intellectual property involved in developing the extensive clinical trial data and results required to prove the safety and efficacy of a biopharmaceutical product (e.g., the regulatory data).

This creates a situation in which, as Kathleen Kelleher explains in the *Michigan Telecommunications and Technology Law Review*, "The complexity of most biologics may allow a biogeneric manufacturer to design around an innovator's patents, but still secure regulatory approval through its "biosimilarity" to the pioneer (original) biologic."[23] In other words, because regulatory approval for biosimilar drugs does not require identity with the pioneer biologic drug it references, without an extended period of data exclusivity—which protects the actual investment needed to prove the safety and efficacy of a biopharmaceutical product—a competing biosimilar product could elude the innovator's patent while still relying on the innovator's clinical data for regulatory approval, thus creating a "patent protection gap."[24] (This gap does not exist for small molecule drugs, which receive five years of data exclusivity protection, because generic drugs are required to have the *identical* active ingredient.)[25] As the Biotechnology Industry Organization (BIO) writes, the likelihood of generics competitors exploiting this patent protection gap is exacerbated by two key facts:

> First, because of the nature of biologic products—large molecules produced by living cells and organisms through highly specific processes—patent protection is often narrower than that of small molecule drugs. Second, the creation of an abbreviated pathway for approval of similar biological products creates new and strong incentives for competitors to exploit this patent protection gap.[26]

As Professor Kristina Lybecker concludes, "Although patent protection and data exclusivity may be considered complementary forms of protection, they serve distinct purposes. Patents are granted for innovations that are novel, non-obvious and useful…while data

protection incentivizes the lengthy development work which is necessary to establish safety and efficacy regulatory approval of a new product."[27]

Recognizing the need to strike a balance between innovators' incentives for investment in expensive and risky novel drug development while at the same time making room for competition by creating a path for biosimilar manufacturers to bring biosimilar products to market, the U.S. Congress extensively debated the appropriate length of regulatory data protection for biologic drugs in the late 2000s. In 2009, recognizing that biologics constitute unique products that merit high levels of intellectual property protection, Congress passed the bipartisan Biologics Price Competition and Innovation Act (BCIPA), which enshrined 12 years of data exclusivity protection for novel biologic medicines. This protection means that biosimilar manufacturers must independently conduct the comprehensive pre-clinical and clinical trials for their own product, or wait the 12 years required by the Biologics Act before requesting a regulatory shortcut to approval based on the innovator's prior approval and data.[28]

Twelve years of data protection strikes an appropriate balance between promoting competition and providing adequate incentives to support continued innovation of new treatments and cures.

Yet the U.S. Congress was not alone in concluding, after extensive deliberation, that biologic drugs merit extended data protection rules. Congress's decision relied in part on findings from the National Academies of Science and Engineering report *Rising Above the Gathering Storm* which wrote that, "It is critical that a balance be struck in finding an appropriate period of exclusivity such that innovation is stimulated and sustained but patients have access to generic-drug-pricing structures" and recommended that this data exclusivity period should be "at least 10 to 11 years."[29] It's worth noting that a similar debate played out in European capitals much to the same recognition, with the European Union enacting a 10-year data exclusivity period for both new chemical entities and new biological entities before generic copies or biosimilars can be approved, with an eleventh year of data exclusivity available for significant new indications that are approved within the first 8 years after approval.[30]

Unfortunately, some believe that reducing the data protection period for biologics may lower medical costs. For instance, the Obama Administration's FY 2016 budget proposal contends that "by awarding brand biologic manufacturers seven years of exclusivity, rather than 12 years under current law, and by prohibiting additional periods of exclusivity for brand biologics due to minor changes in product formulations...these two proposals will save the Federal Government $16 billion over 10 years."[31] But this is a short-term calculation that fails to consider or include the far more significant economic benefits that can be achieved if innovative biologic medicines can make progress toward addressing some of the most intractable diseases. For instance, a 1 percent reduction in mortality from cancer would deliver roughly $500 billion in net present benefits, while a cure would deliver $50 trillion in present and future benefits.[32] Likewise, the financial impact of Alzheimer's disease is expected to soar to $1 trillion per year by 2050, with much of the cost borne by the federal government, according to the Alzheimer's Association report, *Changing the Trajectory of Alzheimer's Disease*.[33] However, the United States could save $220 billion within the first five years if a cure or effective treatment to Alzheimer's disease were found. Innovative biologic medicines will play a central role in trying to develop solutions for these diseases. Short-circuiting the ecosystem underpinning biomedical

innovation by switching to seven years of data protection for biologics for the meager savings of $600 million a year would sacrifice potentially much larger financial benefits in the long term.

Moreover, even those savings may be overstated. In the case of conventional "small molecule" drugs, over three to five years the cost of developing a generic is approximately $1 to $5 million, providing a lower-cost alternative for patients.[34] But as Lybecker explains, "In contrast, many of the shortcuts available to generic manufacturers will not be available to biosimilar producers who are expected to need to invest in clinical trials as well as manufacturing and post-approval safety monitoring programs similar to those of the innovative biologic company. Consequently, biosimilar products are estimated to take eight to ten years to develop at a cost of $75-250 million."[35] Lybecker notes that, "Current studies estimate cost savings from biosimilars will be between 10 and 20 percent less than the cost of the pioneer biologic." In fact, European data suggests that biosimilars may offer just a 10 percent discount from a branded pioneer biologic.[36] As Lybecker concludes, "It is not worth undermining the future of this technology [biologics] with weakened intellectual property protection for the limited cost savings anticipated through biosimilar competition."[37]

These understandings led a diverse group of more than 100 organizations in February 2015 to sign onto *The Declaration Supporting Incentives for Medical Innovation in Trade Agreements.*[38] The organizations represented include a wide variety of health care associations and providers, chambers of commerce, university health organizations, and non-profits from across the United States, all recognizing that the trade agreements the United States enters into need to preserve the incentives for investment in biomedical innovation that are vital to finding cures or treatments to a wide range of diseases that currently have no solution. Moreover, they recognize that our trade negotiators aren't seeking a different standard in the Trans-Pacific Partnership, rather they are seeking inclusion of a standard that has already been established by U.S. law.[39]

Many opponents of the 12 year data exclusivity period have offered "the May 10th agreement"—a pact between the Bush Administration and Congress that helped complete free trade agreements (FTA) the United States concluded with Colombia, Panama, Peru, and South Korea—as a viable alternative. The Agreement strengthened environmental and labor protections but significantly reduced IP protections for biopharmaceuticals. These reduced standards, which were well below U.S. law and those of previous FTAs, decreased biopharmaceutical companies' competitiveness and did not provide any incentives for improving patient access to medicine. Should similar provisions be included in the TPP, medical innovation would continue to suffer but the consequences would be felt on a much larger scale.

ROBUST IPR PROTECTIONS BENEFIT ALL TPP PARTNERS

America's TPP negotiators should insist on the strongest IPR protections in the TPP not only because it is in the United States' interests, but also because doing so is in partner TPP countries' interests, and indeed those of the world. If TPP-member countries wish to create the region in which innovation flourishes most vibrantly in the world, then they should seek to secure strong intellectual property rights protections.

Effective intellectual property rights systems have always been about finding the right balance between creating the incentives for innovation while promoting the diffusion of knowledge and technical discoveries.[40] For instance, an effective copyright system attains a balance between sharing and innovation and protection; it does so by prohibiting outright theft and piracy while at the same time providing some safe harbor for legitimate digital providers.[41] A good example of a system that generally gets the balance mostly right is the U.S. Digital Millennium Copyright Act (DMCA). The DMCA provides safe harbors limiting copyright liability, thereby helping to ensure that legitimate providers of user-generated content sites, cloud computing, and a host of other Internet-related services firms that act responsibly can thrive online. (It also allows for take down of infringing material.)

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And so it is in the life sciences. Effective IP systems in the life sciences sector must balance incentives to invest in risky, lengthy, and expensive drug development efforts with the global public's desire to have affordable access to medicines. Fortunately, the literature increasingly shows that stronger IP systems throughout the world are leading to greater rates of R&D, innovation, and solutions to medical challenges.

Indeed, academic evidence finds a strong relationship between the strength of an economy's (or in this case, a region's) intellectual property protections and the extent to which it participates in trade, foreign direct investment, technology transfer, and local research and development and innovation activity. For example, Cavazos Cepeda et al. find that every 1 percent increase in the level of protection of IPRs in an economy (as measured by improvements to an economy's score in the Patent Rights Index), contributes to on average a 0.7 percent increase in the domestic level of R&D. Stronger IPRs in developing economies are also associated with increased levels of technology-intensive foreign direct investment (FDI).[42] Branstetter, Fisman, and Foley find that stricter patent laws increase FDI, which increases economic growth more than the imitation growth potential of less robust patent laws.[43] By contrast, the United Nations Commission on Transnational Corporations (UNCTC) has found that weak IPRs reduce pharmaceutical and software investment.[44]

There's also evidence that developing countries which strengthen their IPR regimes increase incentives for novel biomedical innovation. For example, Ryan, in a study of biomedical innovations and patent reform in Brazil, finds that patents provided incentives for biomedical technology entrepreneurs to make risky investments into innovation and facilitated technology markets among public-private technology innovation networks.[45] Delgado, Kyle, and McGahan likewise find that patent protection may foster the development of local firms in developing countries as well as partnerships between local and foreign firms from wealthier countries, thus promoting technology transfer and the dissemination of research.[46] Put simply, as a study by Charles River Associates, *Policies that Encourage Innovation in Middle-Income Countries,* finds, "for countries whose objective is to develop an innovative biopharmaceutical industry (either by domestic companies or investment by international companies), intellectual property is a necessary building block."[47] In contrast, developing countries such as Colombia and Malaysia that perform poorly relative to peers in innovation indicators, such as biopharmaceutical R&D spending, number of biopharmaceutical patents filed, journal articles published, and

clinical trials carried out, have fallen behind because they "lack a consistent system for securing intellectual property rights."[48]

Nevertheless, some in the global health community allege that the prices of new innovative drugs under patent make them unaffordable to most people in developing countries because of the absence of generic competition. This makes understanding the effects of IPRs on access and affordability important for researchers, policymakers, and firms. A new December, 2014 report from the National Bureau of Economic Research titled *Intellectual Property Rights and Access to Innovation: Evidence from TRIPS* by Margaret Kyle and Yi Qian sheds light on this subject by examining the effect of pharmaceutical patent protection on the speed of drug launch, price, and quantity in 60 countries from 2000 to 2013.[49]

While access to medicines is important, so is the very existence of medicines as well as their continued improvement.

The authors find that IPRs have a very large bearing on product launch and that on-patent products are most likely to be launched and to sell in higher quantities, but also command the highest prices. Products with expired patents sell in lower quantities and at lower prices than those that are on patent, but higher prices and quantities relative to those that were never protected. In fact, drugs that are never patented are unlikely to be marketed, regardless of country income level. Thus, it appears that IPRs may increase the availability of new treatments to populations in developing countries.[50] The authors further explored whether the WTO Trade-Related Intellectual Property Rights (TRIPS) Agreement changed the value of patents. They found that, overall, drugs are more likely to be launched if they have post-TRIPS patents, as well as to sell in higher quantities. However, the most surprising result from their research is that the price of such drugs is lower than pre-TRIPS patented products, on average, in the poorest category of countries.

To be sure, it's important that citizens worldwide have access to affordable medicines. In this regard, it's worth noting that 98 percent of the drugs on the World Health Organization's (WHO) Essential Medicines List are already off-patent, including ones treating the largest causes of mortality in developing counties, and also that the Doha Declaration put in place measures to provide access to medicines in case of national health emergencies.[51] But it's also critical that medicines exist to treat a wide variety of diseases and conditions; and that requires substantial investment in biopharmaceutical R&D. If countries wish to stimulate innovation in potentially groundbreaking biologic medicines that hold the promise to tackle some of the most intractable diseases, including cancer and Alzheimer's, it's vital they structure a system that affords innovators fair incentives to invest in biological R&D while at the same time ensuring reasonable patient access, in developed and developing countries alike, to biologic medicines. As ITIF notes in *Innovation Economics: The Race for Global Advantage*, innovation is in part about balancing the interests of current and future generations.[52] A nation focused only on the present generation would not invest in the future (and conversely a nation focused only on the future would not invest in the present). And so it is with medicines; while we must be concerned with addressing current challenges with the medicines available today, we must also be concerned with continuing to invest in solutions to diseases and conditions which have not yet been solved. Doing so requires preserving sufficient incentives to invest in

biomedical research. As the report *Wealth, Health and International Trade in the 21st Century* concludes, "Conferring robust intellectual property rights is, in the pharmaceutical and other technological-development contexts, in the global public's long-term interests. Without adequate mechanisms for directly and indirectly securing the private and public funding of medicines and vaccines, research and development communities across the world will lose future benefits that would far outweigh the development costs involved."[53]

CONCLUSION

The final terms of the Trans-Pacific Partnership Agreement will have tremendous implications not just for the future of global trade and the competitiveness of America's industries and economy but also for the future of life sciences innovation. The TPP has been lauded as a high-standard, 21st-century trade agreement that will both serve as a model for regional integration throughout the Asia-Pacific region and as a foundation upon which a stronger set of global trade rules can be built. The TPP's ambition to tackle emerging trade issues such as localization barriers to trade, trade secret theft, benefits for state-owned enterprises, and opening up markets for service trade represent important and laudable steps forward toward strengthening the global trade regime and creating a platform on which 21st century data- and knowledge-enabled commerce can occur. But the TPP will not be the high-standard trade agreement it can be if it fails to ensure the framework in which life sciences innovation flourishes throughout the TPP region by including 12 years of data protection for novel biologic drugs. Not only would such a decision threaten the competitiveness of America's biopharmaceutical companies but it would compromise their ability to deliver breakthrough medicines that benefit citizens throughout the world by providing cures or treatments for diseases that don't yet exist.

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