

## TPP and IP Pharmaceuticals

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## Background on TPP Biopharma Provisions

### Intellectual Property Chapter

Across the board, the TPP provides strong overall standards for intellectual property protection and enforcement with ground-breaking provisions that create new opportunities in TPP markets and raise the standard throughout the region, including for patents, trade secrets, and trademarks.

- ***Patentability of New Uses, New Methods of Using a Known Product, or New Processes of Using a Known Product:*** TPP establishes a requirement for patents for at least one of the following: new uses; new methods of use; or new processes of existing products – all of which promote and protect vitally important modifications that would not be developed without the incentives of the patent system. This provision was not included in many previous FTAs.
- ***12-month patent grace period:*** Inventors of pharmaceutical products will benefit from a 12-month grace period throughout the region. This grace period means inventors – such as in the biotech sector – can publish their research findings or present those findings at academic conferences without forfeiting their chances of patenting their inventions and raising capital for their innovation.
- ***Expedited patent procedures:*** TPP encourages Parties to have procedures to speed up patent examination and marketing approval processes. Ultimately, systemic efficiency is a primary element in successful market entry for innovative pharmaceuticals.
- ***Patent Term Adjustment for Patent Office Delays:*** TPP partners will have to provide patent term adjustment to compensate for unreasonable delays in the issuance of patents for all products, including pharmaceuticals.
- ***Patent Term Restoration for Marketing Approval Delays:*** TPP requires an adjustment for the patent term when the marketing approval process unreasonably cuts into the effective term of a patent on pharmaceutical products.
- ***Early Resolution of Patent Disputes (Patent Linkage):*** Early notice and patent dispute resolution mechanisms for pharmaceutical patents are critical to preventing the undermining of pharmaceutical investment. The TPP will require adequate time and opportunity for a patent holder to seek available remedies prior to the marketing of an alleged infringing product as well as procedures for the timely resolution of disputes.
- ***Data Protection for New Pharmaceutical Products:*** TPP sets a minimum standard of at least 5-years of data protection for new pharmaceutical products and clarifies that the period of protection will start on the date of approval in each market (rather than from the first marketing approval in the world).
- ***Recognition of Incremental Innovation:*** TPP will go beyond previous trade agreements to promote incremental innovation by providing data protection for combination products that

contain at least one new chemical entity (5 years) or new indications for a previously approved product (3 years), so that there are incentives to find new therapeutic applications for previously approved products.

- ***Enhanced Protection for Biologics:*** TPP will require, for the first time in a trade agreement, Parties to provide an extended term of effective market protection for biologic medicines. TPP gives partner countries two ways to meet that standard. One way is to provide a minimum of at least 8 years of data protection. The other way is to deliver a comparable outcome through both data protection of at least 5 years plus other measures (e.g., regulatory procedures or other administrative actions). TPP also specifies the types of biologic products subject to the enhanced protection, and ensures that the Parties can review the provisions to keep pace with technological changes and other developments, and recommend modifications, if appropriate.
- ***Trade Secrets:*** The innovative pharmaceutical industry has been a frequent target of trade secret theft, and TPP will be the first trade agreement to require criminal penalties and procedures for trade secret misappropriation, including by cyber means.
- ***Enforcement of Intellectual Property Rights:*** TPP includes strong civil, border, and criminal enforcement provisions against trademark counterfeiting, which is important to protect pharmaceutical brands and reputations, as well as consumer safety. TPP also includes strong civil remedies, including damages and injunctions, for patent infringement.

### **Market Access Chapter**

- ***Tariffs:*** TPP eliminates tariffs on medicines and medical devices. This will facilitate exports and decrease costs for hospitals, clinics, aid organizations and consumers, among others. TPP eliminates tariffs on all pharmaceuticals, APIs, medical devices (i.e., syringes, IV bags and tubes, testing equipment, etc.).
- ***Import Licensing:*** Complicated and unclear import licensing procedures can create costs and obstacles when exporting goods, and can result in significant barriers to trade. TPP requires countries to notify each other of their import licensing procedures, and to keep these notifications updated. In addition, countries cannot apply import licensing procedures to TPP goods without notifying all countries of the license requirement and the reason for it.
- ***Local Distributor Requirements:*** TPP prohibits countries from requiring that exporters establish contractual relationships with domestic distributors as a condition of importation. These requirements raise costs and introduce unnecessary complexity
- ***Commercial Samples:*** Some countries assess duties on commercial samples. TPP requires countries to eliminate those duties, helping to lower costs for commercial activity within the TPP region.

## **Technical Barriers to Trade Chapter, Annex on Pharmaceuticals**

- ***Transparent and Open Regulations:*** TPP requires TPP participants to engage in transparent and open practices when regulating products in the sector.
- ***Scientific Basis for Regulations:*** TPP parties will have to consider relevant scientific and technical guidance when developing regulations, grant marketing authorizations based on specified and publically available criteria, provide reasons for rejecting applications, and establish due process procedures that allow for appeal.

## **Annex on Transparency and Procedural Fairness for Pharmaceuticals and Medical Devices**

- The Pharmaceuticals Annex of the Transparency and Anticorruption Chapter will raise standards in the Asia Pacific region, requiring TPP partners to ensure comparable levels of transparency, procedural fairness and due process in their national healthcare programs operated by national healthcare authorities as we do here in the United States. This approach will help level the playing field for pharmaceutical exports.

## **Customs Chapter**

- TPP's chapter on customs helps reduce border delays and streamline customs procedures, allowing Pharmaceutical products to move more quickly, efficiently, and cheaply across borders.

## **Government Procurement Chapter**

- TPP commitments on government procurement will enhance transparency and competition in the purchase of medicines by covered TPP government institutions, including government hospitals and other health entities. TPP opens purchases by these government institutions to competition from TPP suppliers and establishes fair, transparent procurement rules designed to ensure effective competition, including commitments related to provision of timely information on upcoming procurements, tender specifications and other requirements, and contract award and review procedures.

## **Other Provisions**

- TPP enhances consumer protection by requiring countries to adopt or maintain laws that ban fraudulent and deceptive commercial activities that can lead to mislabeled or deceptively advertised medicines, and hurt consumers, and reduce consumer confidence in pharmaceutical products and brands.

## CHAPTER 2

# TPP AND THE CONFLICT OVER DRUGS: INCENTIVES FOR INNOVATION VERSUS ACCESS TO MEDICINES

LEE BRANSTETTER

Well before talks were completed on the Trans-Pacific Partnership (TPP) agreement, a furor surrounded the negotiators as they attempted to reconcile two conflicting demands. Pressure from advocates for poor countries sought to ensure that innovative pharmaceutical products—especially “biologics” derived from genetic material, cells, or other biological sources—are quickly made available to poor countries in generic form at affordable prices. On the other side was the insistence of branded pharmaceutical companies that protection of their intellectual property (IP), through a long timetable before less expensive generic copies enter the market, is essential to their ability to innovate and produce more life-saving drugs in the future, for the benefit of everyone.

In the end, the agreement reached in 2015 satisfied neither side. For months it was subjected to withering criticism from nongovernmental organizations (NGOs), patient rights advocates, academics, and even Margaret Chan, the head of the World Health Organization, for allegedly yielding to the demands of “Big Pharma.” These critics faulted the TPP for providing overly generous IP protections for new drugs that reduce access to them by poor patients.

The pharmaceutical industry is not happy either. It argues that the TPP’s IP protections are too weak. When the outlines of the agreement were announced, in early October 2015, Jim Greenwood, president and CEO of the Biotechnology Industry Organization (BIO), declared that anything less than 12 years of protection for the data used to develop biologic drugs was “remarkably short-sighted and has the potential to chill global investment and slow development of new breakthrough treatments for suffering patients.”<sup>1</sup> The criticism of Senator Orrin Hatch, a longtime champion of the industry, which threatens to hold up approval of the TPP in the Senate, was equally tough. He declared that “this deal appears to fall woefully short”<sup>2</sup> and called for its renegotiation.

The 74-page Chapter 18 on Intellectual Property is long, complex, and multifaceted, addressing a very complicated set of policy domains. The most controversial provision relates to “data protection” or “data exclusivity” in the development of drugs, which refers to the period during which a generic pharmaceutical company may not market a competing generic drug on the basis of the data previously submitted by a branded

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1. Jim Greenwood, president and CEO, Biotechnology Innovation Organization, “BIO Statement on Data Exclusivity Provisions Within the Trans-Pacific Partnership,” October 4, 2015, Washington, [www.bio.org/media/press-release](http://www.bio.org/media/press-release).
2. “Hatch Statement on Trans-Pacific Partnership Negotiations,” press release, October 5, 2015, Washington, [www.hatch.senate.gov/public/](http://www.hatch.senate.gov/public/).

pharmaceutical company to demonstrate the safety and efficacy of the original drug. Drug companies wanted this protection for their new biologic drugs for 12 years. Opponents wanted to reduce it to five years. In the end the compromise provided eight years of protection. This chapter summarizes TPP Chapter 18's most important provisions and explains why the compromise accommodates the needs for both innovation and access. It concludes that the compromise reached is a good one, strengthening incentives for innovation, especially in the pharmaceutical space, while incorporating important safeguards to ensure access to essential medicines.

## PATENTS, PHARMACEUTICAL INNOVATION, AND HUMAN HEALTH

Most economists believe that innovation, broadly defined, is the primary driver of long-run economic growth in advanced countries.<sup>3</sup> They generally accept the usefulness of a patent system for new inventions as a means of promoting innovation. Under such a system, innovators receive a temporary monopoly right over the new technology they create. This monopoly raises the price of new inventions in the short run but induces more innovation and, therefore, more growth in the longer run.<sup>4</sup>

Empirical research shows that pharmaceutical innovation is especially dependent on patent protection.<sup>5</sup> The development of new drugs requires long-term, expensive, risky investments and the engagement of large teams of very talented researchers and clinicians. Most candidate drugs never make it through the clinical testing process. The cost of developing new drugs, inclusive of the cost of failures, lies in the billions of dollars per successful drug.<sup>6</sup> Patents allow firms to recoup these costs, inducing the development of inventions that have a unique impact on human welfare.

As a salient example, consider the modern drugs that keep AIDS at bay. The tens of millions of people with HIV/AIDS who are living normal lives have many to thank for this modern miracle, but it was a pharmaceutical company, making a risky bet with shareholders' capital, that first developed the antiretroviral treatments that proved to be effective. Without some degree of IP protection for these drugs, the treatment would never have seen the light of day.

Many economists and other policy analysts accept the rationale for reasonably strong patent protection in general—and drug patent protection in particular—in rich countries. Consensus regarding the imposition of stronger patent rights in poor developing countries is much weaker. The idea that the rich should pay for innovation but that its fruits should be shared at very low cost with the global poor sounds particularly appealing in the context of medical innovation, where access can mean the difference between life and death.

The creation of the pharmaceutical arsenal that exists today has relied very heavily on profits earned by the drug industry in a single rich country, the United States. The historical reliance of the global pharmaceutical industry on profits earned in the US market is likely to prove unsustainable in the face of an aging American population, mounting government fiscal challenges, and incomes that are growing much more slowly than health care costs (as discussed in appendix 2A). The willingness of American consumers to underwrite

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3. This consensus rests in part on the classic work of Solow (1957). Paul Romer (1986, 1990) is credited with (re)focusing the attention of the profession on the role of innovation. The modern theory of economic growth, with innovation at its core, is summarized in the graduate textbook by Acemoglu (2009).

4. Jaffe and Lerner (2004) provide a critical assessment of the US patent system as it existed at the end of the 20th century and advance a convincing (and accessible) version of the mainstream defense of a well-functioning patent system as an essential policy tool for promoting innovation. Boldrin and Levine (2007) are perhaps the best-known patent skeptics within the economics community; they go so far as to suggest that patents can actually be a barrier to innovation.

5. Cohen et al. (2002) present survey evidence supporting the view that managers in the pharmaceutical industry regard patent protection as particularly important. Branstetter, Chatterjee, and Higgins (2014) and Budish, Roin, and Williams (2015) present regression-based evidence showing the strong responsiveness of pharmaceutical development to the strength and length of patent protection.

6. DiMasi, Grabowski, and Hansen (2014) suggest that this cost now exceeds \$2 billion.

a disproportionate share of the world's drug development costs has limits that are visible in the context of election-year politics. Yet the benefits of new drugs are greater than ever in a world whose population is both growing and aging.

It is in this larger context that one needs to evaluate the push in the TPP and other recent trade agreements to strengthen IP protection for pharmaceuticals outside the United States. A trade agreement provides a forum in which groups of countries can agree to redistribute more equitably the burden of investing in tomorrow's miracle cures. As the leading developing countries have enjoyed sustained periods of economic growth, which have led them to account for an ever-increasing fraction of the world's GDP and consumer purchasing power, the argument that at least some of these countries can and should make a contribution toward the continued progress of humanity's pharmaceutical arsenal has strengthened.

## KEY INTELLECTUAL PROPERTY PROVISIONS IN THE TPP

### Data Protection

The TPP requires member states to grant newly approved drugs a monopoly right loosely referred to as data exclusivity or data protection; for convenience this chapter uses the term data protection. This protection is separate from and runs concurrently with patent protection.<sup>7</sup> The data at issue refer to the data branded drug companies submit to regulatory agencies that demonstrate the safety and efficacy of a drug. While drugs are under data protection, no other firm is allowed to market a competing product that relies on the same data to demonstrate safety and efficacy. Data protection thus prevents any generic competitor from competing with the original drug as long as it is in force.<sup>8</sup> Once the data protection period ends, drugs are protected only by their patents. Patent protection ends when patents expire, when patents are demonstrated to be invalid, or when a method is found to produce a version of the drug that does not infringe on the patent.

Data protection is not a new concept. All recent US free trade agreements (FTAs) have required it, and virtually all TPP member states already provide some degree of data protection for new drugs. The TPP requires that all current and future member states provide this protection, and it sets the minimum period of data protection at five years for chemically synthesized drugs (known in the industry as "small molecule" drugs) and eight years for drugs based on biotechnology (known in the industry as biologics).<sup>9</sup> This extended period of data protection for biologics is a first for a US trade agreement; it was easily the single most controversial provision of the entire agreement. Member states are allowed to exceed these minimums. The United States grants 12 years of data protection for biologics.<sup>10</sup> Western European markets grant 10 years of data protection

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7. The debate, as reported in the popular press, tends to use the terms data protection and data exclusivity interchangeably. Technically, data protection refers to a period during which generic firms are forbidden from using data submitted by a branded firm's original drug to obtain regulatory approval for a competing product, whereas data exclusivity refers to the period during which generic companies are forbidden from marketing a product based on that data. The TPP largely focuses on the latter concept. Article 39.3 of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) endorses the principle of protection for data submitted to regulatory authorities but does not stipulate minimum periods of protection in the way the TPP does.

8. In principle, the generic drug company could enter by conducting its own clinical trials to demonstrate safety and effectiveness, but that would be extremely expensive and time consuming, and generic companies do not pursue that pathway.

9. Member states are given the option of providing either eight years of data protection or five years of data protection plus other regulations that, together, ensure a comparable period of effective market protection against generic entry.

10. The US pharmaceutical industry balked when a 2014 budget proposal from the Department of Health and Human Services provided a calculation of the potential cost savings from reducing the period of data protection from 12 to 7 years. A recommendation to reduce the data protection period to seven years reappeared in the most recent budget proposal for the department, but President Obama has not emphasized this issue in his public statements or speeches, and there has been no significant effort on the part of the administration to lobby for a shorter data protection period (see [www.biopharma-reporter.com/Markets-Regulations/Seven-year-market-exclusivity-Industry-hits-out-at-Obama-s-pro-biosimilar-Budget](http://www.biopharma-reporter.com/Markets-Regulations/Seven-year-market-exclusivity-Industry-hits-out-at-Obama-s-pro-biosimilar-Budget)).

to both small molecule drugs and biologics. The minimum durations required by the TPP are thus not extreme by international standards.

Proponents of data protection assert that it provides a minimum period of monopoly protection to reward firms for the time, expense, and uncertainty involved in drug development. “Old” drugs—even ones for which the patents have expired—sometimes prove to be effective cures for diseases other than the ones they were originally developed to fight. Data protection compensates firms for the expense and risk of putting this old drug through an expensive and risky set of clinical trials to verify its effectiveness in fighting this different disease. Furthermore, patents are not perfect protectors of new ideas: Inventive chemists can sometimes find ways around the patents that protect a new drug, ending a legal monopoly without actually creating a new product.<sup>11</sup> These concerns about the adequacy of patent protection are heightened in the context of biologics. Drugs based on biotechnology are highly complex. Because generic versions of biologics, known in the industry as “biosimilars,” are not exact copies, there is some uncertainty about whether patents provide sufficient protection. NGOs and patient advocacy groups argue that by strengthening the (temporary) monopoly power of a drug innovator, data protection raises drug prices and limits drug access.

## Patent Linkage

The TPP contains obligations regarding the resolution of pharmaceutical patent disputes—a domain often loosely referred to in the wider debate as “patent linkage.” The TPP requires that members provide for (1) notification to patent holders of any request to market a generic drug that may infringe on their patent and (2) time and opportunity prior to the marketing of that generic drug for the patent holder to seek remedies if the patent has been infringed. The relevance of these provisions can be seen by contrasting US law with the current situation in many developing countries.

Under the US Hatch-Waxman Act ([box 2.1](#)), drug companies are required to identify the patents that protect the small molecule drugs for which they are requesting regulatory approval; those patents become part of an official government data record. If a producer of a generic wishes to enter the market while these patents are still in force, it has to inform the drug inventor of its intent and certify its belief that the original patents are invalid or that its own preparation of the medicine does not infringe these patents. If the incumbent patent holder believes its patent(s) to be valid and/or infringed, the US Food and Drug Administration (FDA) places an automatic 30-month stay on any generic entry pending legal resolution of the questions of patent validity and/or infringement. Upon the first court ruling in favor of the generic entrant, the FDA allows the generic product onto the market. The entry of biosimilars is governed under a separate law, the Biologics Price Competition and Innovation Act (BPCIA), which was enacted as part of the Affordable Care Act in 2010. That law also requires that generic entrants notify the incumbent patent holder and provides for the resolution of patent disputes before entry is approved. The idea of “patent linkage”—promotion of resolution of patent disputes before the entry of a generic product on the market—is thus deeply embedded in US law and regulatory practice (see the forthcoming article by Branstetter, Chatterjee, and Higgins). Similar provisions exist in Japan, Canada, Singapore, and other developed countries.

In some developing countries, generic producers can enter a market and compete unimpeded with patent-protected products until a court finds the generic producer liable for patent infringement. Drug regulators approve the generic entrants without delay, there is no requirement that the owners of the patents protecting existing drugs even be notified of the approval, and the local government leaves it to the (often dysfunctional) courts to determine if any infringement has taken place. If legal proceedings take years, the damage to the revenues of the innovator can be substantial.

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11. Branstetter, Chatterjee, and Higgins (forthcoming) explore the effects of generic entry while patents are still in force.



### **Box 2.1 The Hatch-Waxman Act**

In a far-reaching act of bipartisan legislating that is all too rare today, former liberal California Democratic Congressman Henry Waxman and conservative Utah Republican Senator Orrin Hatch joined forces in 1984 to create the landmark Hatch-Waxman Act. It sought to expand access to generic drugs while preserving adequate incentives for continued pharmaceutical innovation.

The Hatch-Waxman Act codified some of the same legal mechanisms—including data protection, patent linkage, patent term extensions, and limited protection for incremental innovation—that have been widely denounced by opponents of the TPP. Under the Hatch-Waxman regime, generic penetration in the US market rose steadily. It now exceeds 84 percent of prescription drug sales by volume, making the United States the biggest market for generic drugs in the world. Since 1984 waves of breakthrough therapies, including the antiretrovirals used to treat AIDS, have emerged that could not have been dreamed of when the law was passed.

In its purest form, patent linkage makes regulatory approval contingent on a legal resolution of any patent dispute. The TPP does not explicitly require patent disputes to be fully resolved before a health ministry is allowed to permit the introduction of a generic competitor to a branded drug, but it does require advance notification by any prospective generic manufacturer of intent to enter the market, and it requires that member states provide procedures for the expeditious resolution of patent disputes.

One way member states could comply with this requirement would be through the creation of an administrative procedure that could issue a judgment on claims of patent infringement before generic entry. A judgment against the generic entrant would stay entry; a judgment that no infringement occurred would allow entry. Either party would have the option of pursuing its position in the courts if it were not satisfied with the administrative judgment, but generic entry would not have to wait for a formal court resolution—a time-consuming prospect in many countries.

### **Patent Term Extensions**

The development of new drugs is not only extraordinarily expensive but also extremely time-consuming. The process, from the earliest phases of research (prediscovery) to final approval of a new product, can take a dozen years or more. The challenge for drug companies is that patents are typically taken out early on the research process, often before the true therapeutic value of the new prospective medicine is known. Under international law patents expire 20 years after the initial filing date. Companies can spend five to seven years guiding their prospective medicines through clinical trials. By the time regulatory approval is finally granted, they may have very little time left on their patent clocks in which to recoup the expenses of drug development.

The 1984 Hatch-Waxman Act in the United States provides drug innovators the opportunity to add up to five years to their patent clocks, in order to compensate them for time lost due to regulatory delays.<sup>12</sup> Japan, Australia, and a number of other developed countries already have provisions in their patent laws that provide a broadly similar degree of de jure or de facto patent term extension. The TPP seeks to make this compensation available in all TPP member states by requiring patent term extensions in the event of unreasonable regulatory delays. It provides for patent term extensions in response to both patent office delays in granting a patent and drug regulatory agency delays in granting product approval. It does not specify a minimum period of patent term extension. Instead, the language in the agreement stresses the principle of “compensation”—the notion that the extensions should be proportional to the delays.

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12. Branstetter, Chatterjee, and Higgins (forthcoming) review the major features of the Hatch-Waxman Act and quantify the consumer welfare gains that have arisen as a consequence of Paragraph-IV generic entry into the US market.

## Protection for Incremental Pharmaceutical Innovation

The TPP recognizes and rewards incremental pharmaceutical innovation by providing for five years of data protection for “combination” products that contain at least one new chemical entity or three years of data protection when previously approved products are proved to have efficacy in fighting diseases other than the one they were originally approved to treat. In addition, TPP member states are required to provide patent protection for at least one of the following: new uses, new methods of use, or new processes of existing products. Together these provisions ensure both patent protection and data protection for new medicines that build on or use previously discovered compounds.

## Other Provisions Related to Drugs

The TPP goes beyond patents and data protection to strengthen trade secrets. It is the first US FTA to require criminal penalties and procedures for misappropriation of trade secrets, including by cyber means. Trade secrets are important in many industries, including pharmaceuticals. They play a particularly significant role in the biologics industry, where the exact procedures used to manufacture the drug are often a valuable and important determinant of its safety and efficacy. The TPP also provides civil, border, and criminal enforcement proceedings against trademark counterfeiting, seeks to expedite patent examination and marketing approval processes, and provides for a 12-month patent grace period during which inventors can disclose research findings or present results at academic conferences without forfeiting the ability to obtain patent protection. This measure is significant for biotechnology firms, whose products are often based on recent science and the work of academic scientists. The grace period provides freedom to publish, which already exists under US patent law but not international patent law.

## General Enforcement Provisions

The TPP contains a wide range of provisions designed to strengthen the legal force and legal enforcement of IP protection across the board. It requires the creation of civil procedures to protect all the IP rights it enumerates, and it requires the establishment of criminal sanctions and procedures for trademark counterfeiting on a commercial scale. It also requires that judicial authorities possess the authority to adjudicate disputes and enforce judgments. The TPP requires injunctive relief, civil penalties in accordance with the economic losses incurred when IP is infringed (which directly addresses the problem of inadequate civil penalties), and payment of profits earned by infringers of copyrights and trademarks. It requires courts to have the power to collect evidence from alleged infringers and requires sanctions when parties to a legal dispute disclose confidential information being considered by the court.

## DOES THE TPP FAIL TO INCREASE INCENTIVES FOR INNOVATION?

The pharmaceutical industry has criticized the TPP as offering insufficient protection for drug innovation. These complaints stem from the period of data protection for biologics. The industry wanted to incorporate the United States’ 12-year standard of protection. Instead, it got eight years of protection. Is the industry right to claim that anything less than 12 years will bring an innovation apocalypse?

Biologics are complex and costly to create. But complexity cuts both ways: Clinical trials are generally required to determine whether a generic version of the drug will have the same therapeutic impact as the original drug. Small molecule generic drugs almost never require such trials. Generic entry is, therefore, cheap and rapid and quickly leads to sharp price declines and huge revenue losses for the innovator. Because biosimilars require the time and expense of clinical trials, generic competitors will enter the biologics market later, less

frequently, and at a smaller price discount than for chemically synthesized drugs, even after patents and data protection expire—as has been the case so far in Western Europe, which has more experience with biosimilars than any other major market. The European experience suggests that the complexity of biologics will limit the intensity of generic competition in this space long after data protection (and patents) expire.<sup>13</sup>

The dispute over data protection for biologics obscures the reality that the TPP does more to promote pharmaceutical innovation than any trade agreement in US history. The agreement meaningfully enhances data protection within the current TPP region. All but two of the United States' TPP partners will have to guarantee an extended period of protection for biologics in order to conform to the new standards. Indonesia currently has no data protection. If it joins the TPP—and its current leader has expressed interest in the agreement—Southeast Asia's most populous nation, like every country that wants to join the agreement, will have to implement the TPP's strong standards.

Adoption of these standards is important. When innovative drugs are protected only by patents, the return to innovators hinges exclusively on the quality and effectiveness of the institutions enforcing patent rights. In many developing countries, these institutions are imperfect at best. Patent infringement can take a long time to detect, and winning an infringement judgment against a politically connected local firm can be very difficult and take more years than firms have on their patent clocks. Even when a judgment favors the incumbent patent holder, the infringer may simply ignore the ruling because it is not effectively enforced. Data protection is a much simpler form of monopoly protection to adjudicate and enforce.

As countries develop, they strengthen patent protection. The TPP will encourage that process by requiring health ministries to expedite resolution of patent disputes before allowing new drugs into the market. The agreement extends patent terms when drug companies encounter unreasonable regulatory delays. It requires all member states to provide measures to address the theft of trade secrets. The United States' TPP partners were willing to scupper the entire agreement rather than grant 12 years of data protection to biologics. If the US drug industry fails to support the TPP, it will have committed the classic error of letting the (unattainable) perfect be the enemy of the good.

## **WILL THE AGREEMENT THREATEN PUBLIC HEALTH BY REDUCING ACCESS TO ESSENTIAL MEDICINES?**

NGOs and patient advocates have taken the opposite position of the pharmaceutical industry, arguing that the agreement will strengthen IP rights for new drugs too much, harming patient welfare in the process. Will the TPP create a public health disaster by destroying access to affordable medicines?

The impact of the TPP on drug prices and availability will be far more modest than the sweeping denunciations of its critics suggest, because it retains important safeguards to ensure access to life-saving medicines, especially in poor countries. Most drugs available for the treatment of disease around the world are already off patent. Even in the United States, generics account for more than 84 percent of all prescriptions. The TPP will have no impact on access to the vast majority of drugs for which patents have already expired. For drugs that are still protected by patents, member states will retain a far-reaching ability to influence the prices at which these drugs are sold within their jurisdictions. In Australia, New Zealand, and Japan, all of which have signed the TPP agreement, public agencies operating the national health insurance systems negotiate with international drug companies to lower the prices of patent-protected drugs sold locally. Nothing in the TPP will prevent these agencies from continuing to do so, and nothing in the TPP would prevent any other member state at any level of development from adopting similar policies.

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13. Branstetter, Chatterjee, and Higgins (2014) explore the implications for innovation of the very different dynamics of past and future generic competition in biologics and small molecule drugs.

The provisions in the TPP will modestly extend the term of regulatory protection enjoyed by innovative new medicines, thereby delaying generic entry. But current international law allows patent rights to be overridden in the event of a public health emergency, and the TPP does nothing to limit that possibility. If an epidemic breaks out in any TPP member state and no effective generic treatment exists, any TPP member state would have broad leeway under international laws explicitly endorsed by the TPP to ensure access to a life-saving medication by invoking its right to force any patent holder, foreign or domestic, to license the technology to low-cost producers, ensuring broad access at reasonable prices. For the poorest countries that are party to the agreement, the TPP allows delays of up to 10 years to come into full compliance, and these countries have the option of requesting additional delays under certain circumstances.

Finally, the TPP text reflects a compromise that omits a number of controversial provisions opposed by NGOs and patient advocate groups. The final draft does not require patents for surgical procedures or prohibit the establishment or restrict the use of a pre-grant opposition process. A pre-grant opposition process is an administrative procedure that allows parties opposed to the grant of a patent to submit to the patent office evidence contesting the validity of a patent application. Industry favored a prohibition on the grounds that such procedures can introduce delays and uncertainty into the patent application process, but member governments retain the freedom to employ such procedures in the final agreement.

Most of the provisions criticized by TPP opponents have been incorporated into earlier US FTAs, going back all the way to the US-Jordan FTA, in force since 2001.<sup>14</sup> Each of these agreements was denounced by the same groups that are denouncing the TPP, and each time the same stark warnings were voiced: Accession would be a disaster for public health in the developing countries joining the agreements. In his testimony on the TPP to the US International Trade Commission, Peru's ambassador to the United States, Luis Miguel Castilla, addressed these concerns, noting that opponents of Peru's TRIPS-Plus FTA warned of sharp price increases and loss of access to drugs. Instead, after implementation, the price of drugs in Peru grew by less than the rate of inflation, while total drug consumption expanded by more than a third between 2010 and 2014.<sup>15</sup>

My own empirical analysis shows that Peru's experience is not unique. Ph.D. student Rahul Ladhani, of Carnegie Mellon's Heinz College, and I analyzed the impact of these TRIPS-Plus FTAs on the average price of imported drugs. We found that their adoption had no statistically significant effect on overall drug prices. This result was not unexpected; it stems from the fact that US FTAs affect only a small fraction of the drug portfolio available in the typical partner country, namely, drugs introduced after the FTAs go into effect that are still protected by patents or data protection. Within a few years, these patents and data protections expire, and these drugs go generic.

It is theoretically possible that increases in the price of even a small fraction of drugs for a brief period of time could hurt public health. But the same kind of statistical analysis reveals that TRIPS-Plus FTAs have had no statistically significant impact on health expenditure as a share of GDP, life expectancy, or infant mortality. The TRIPS-Plus provisions in the TPP did not lead to a devastating collapse of drug access or a precipitous decline in public health in the United States' FTA partner countries before, and they will not do so now.

Like their counterparts in the drug industry, NGOs and patient advocates have fulminated against the eight-year compromise on data protection for biologics—for completely different reasons. These groups claim that the additional three years of data protection will deny consumers access to a large number of drugs at very

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14. US FTAs, beginning with the US-Jordan FTA, generally required IP protections over and above those enumerated in the 1995 TRIPS Agreement and are, therefore, referred to as TRIPS-Plus FTAs.

15. See "Remarks by the Ambassador of Peru to the United States, His Excellency Luis Miguel Castilla, on occasion of the International Trade Commission Public Hearing on the Trans-Pacific Partnership," January 13, 2016. Ambassador Castilla cites IMS Health data in supporting his claims about the growth in the size of the Peruvian drug market after implementation of the US-Peru FTA.

low prices. The claim presumes that the market for biosimilars will evolve like the market for small molecule generics—a premise the European experience suggests is false. Even after data protection expires, the typical biologic will have a portfolio of patents defending it, which the TPP member state will have a legal obligation to honor. And even after patents expire, the complexity of biologics will motivate most health regulatory agencies that care about drug safety to require clinical trials somewhere in the world that demonstrate the safety and efficacy of the biosimilar.<sup>16</sup> Such action will be a significant barrier to generic entry, ensuring that generic competition will be less frequent, arrive later in the life cycle, and involve a much less significant price discount relative to the innovator drug than has been typical in the small-molecule world. Furthermore, there just are not that many new biologic drugs approved in major markets. The year 2015 was a banner year for new biologic approvals, with the FDA approving 12 drugs in that category—the most in US history. Even so, the number represented only slightly more than a quarter of all new drug approvals for the year, and it may represent a high water mark that is not exceeded for some time. NGOs have likely exaggerated the negative impact of the eight-year compromise on patient welfare at least as much as the drug companies have exaggerated its negative impact on innovation.

## **CONCLUSION: THE TPP'S IP PROVISIONS REPRESENT A REASONABLE COMPROMISE**

Nobel Laureate Joseph Stiglitz is among the most prominent academic critics of the TPP. He has reserved particular ire for its pharma IP provisions. At the same time that he has bitterly criticized the TPP, he has praised the US Hatch-Waxman Act for the balance it strikes between creating incentives for new drug innovation and ensuring access to drugs.<sup>17</sup> Careful study of the TPP text shows that its IP chapter is, in essence, exporting the Hatch-Waxman model to a much broader Asia-Pacific context. It invites all 12 member states to enter into the same kind of bargain Hatch and Waxman struck decades ago. By entering into this agreement, member states are agreeing to pay a little more for new drugs for a brief period in return for new therapies that can be handed off, in generic form, to the next generation. This balance has worked for the United States. With the flexibilities built into the agreement, it will also work for the other TPP member states.

Beyond the contentious domain of pharmaceuticals, the IP provisions of the TPP offer a reasonable compromise. Copyright owners will get somewhat stronger protection, but with important exemptions, exceptions, and limitations on enforcement.<sup>18</sup> Member states will be held to a higher standard in terms of enforcement, but the agreement still retains considerable leeway for differences in legal practice at the national level. Legal remedies—civil and criminal—will be required to protect trade secrets, but the agreement does not spell out or mandate specific penalties.

Given the differences in interests of the negotiating parties, this agreement represents a useful compromise. As in the critical realm of new medicines, it strikes an intelligent balance between access and incentives for innovation.

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16. Some developing countries may rely on the biosimilar approval processes in more advanced nations, only approving a biosimilar for domestic consumption after the biosimilar has gone through the demanding approval process in Western Europe or the United States.

17. Stiglitz has made these points in many public statements, including in an interview with Democracy Now!, November 12, 2015, [www.democracynow.org/2015/11/12/a\\_very\\_big\\_mistake\\_joseph\\_stiglitz](http://www.democracynow.org/2015/11/12/a_very_big_mistake_joseph_stiglitz).

18. The internet creates special challenges for copyright-protected products that can be expressed in digital form. Legal mechanisms that could strengthen copyright protections on the Internet have been challenged as restrictions of free speech or free expression. Some of these issues are discussed in [chapter 6](#) of this volume, on the TPP and digital trade.

## APPENDIX 2A INNOVATION, INTELLECTUAL PROPERTY, AND THE US ECONOMY IN THE 21ST CENTURY

### INNOVATION, GROWTH, AND PATENTS

Most economists believe that innovation, broadly defined, is the primary driver of long-run economic growth. Governments promote innovation by subsidizing advanced technical education, providing tax credits to firms that invest in research and development (R&D), underwriting basic research in universities and other public science institutes, and offering inventors a temporary, government-guaranteed monopoly right over the use of their new ideas known as a patent.

The United States lost its status as the world's leading exporter of goods years ago, but it remains the world's leading exporter of ideas—a reality captured, albeit imperfectly, in official trade statistics. The licensing revenue generated by the United States' IP overseas exceeded \$130 billion in 2014, the most recent year for which aggregate data are available. Its surplus in trade in ideas was an astounding \$88 billion—a larger surplus than generated by aircraft, agricultural products, or any other category of goods trade.<sup>19</sup> Moreover, expert assessments of the quality of these data suggest that these figures almost certainly underestimate the true level of IP exports, perhaps by tens of billions of dollars.<sup>20</sup>

The official numbers also reflect the reality of a world in which there are widespread weaknesses in IP enforcement outside the United States. Estimates by the bipartisan Commission on the Theft of American Intellectual Property suggest that the losses from worldwide theft of US IP could run as high as \$300 billion a year, a number on par with total US exports to Asia.<sup>21</sup> Although these numbers are necessarily speculative, given the United States' clear revealed comparative advantage in innovation, there is little doubt that stronger IP in the rest of the world would benefit US producers of goods and services. The numbers also clearly show that TPP critics like Paul Krugman are simply wrong when they suggest that IP is a second-order issue for America's trade with the rest of the world.

### PATENTS, NEW DRUGS, AND HUMAN HEALTH

New drugs have had a disproportionate impact on human well-being, and patents are especially critical to pharmaceutical innovation. In 1998 Yale University economist William Nordhaus circulated a remarkable essay called "The Health of Nations." Drawing on economic theory and publicly available data, he concluded that improvements in health in the second half of the 20th century had a greater impact on human well-being than all other sources of consumption increases put together. The most important source of improvement in health care was the steadily expanding arsenal of effective medicines (Fuchs 1982). Although it is challenging to determine exactly how much of the improvement in human health is attributable to new drugs (because the expansion in their number came at the same time as declines in pollution, improvements in nutrition, and changes in health-affecting habits, such as smoking), every effort to determine a social rate of return on investment in new drugs yields very high numbers.<sup>22</sup>

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19. See Bureau of Economic Analysis, table 2.1 at [www.bea.gov/iTable/iTable.cfm?ReqID=62&step=1#reqid=62&step=6&isuri=1&6210=4&6200=160](http://www.bea.gov/iTable/iTable.cfm?ReqID=62&step=1#reqid=62&step=6&isuri=1&6210=4&6200=160).

20. See Feenstra et al. (2010), a report to the Committee on Economic Statistics commissioned by the American Economic Association.

21. See Commission on the Theft of American Intellectual Property (2013). These numbers include sales lost to counterfeit merchandise and are not directly comparable to the IP licensing numbers.

22. For example, Lichtenberg (2007) finds that an increase in the stock of "priority-review" drugs increases the mean age

Medical innovation is not only uniquely valuable but also uniquely dependent on patent protection. This proposition might seem like common sense: Once the compound of a chemical drug is known, it can be easily mass produced at close to marginal cost by a large number of generic drug companies, including many based in low-cost developing countries. When patents expire, the innovating drug companies typically experience a massive loss of revenue and profit.

A vast array of empirical evidence shows that this is indeed the case. Cohen et al. (2002) surveyed inventing firms across a range of industries and found that pharmaceutical companies (and manufacturers of industrial chemicals) value patents more than inventors in any other industry. The inconvenient truth is that our life-saving drugs do not fall like manna from heaven. They require long-term, expensive, risky investments and the engagement of large teams of very talented researchers and clinicians, not to mention patients willing to gamble with unproven remedies.

## THE END OF THE US PHARMACEUTICAL MARSHALL PLAN

Many economists and other policy analysts accept the rationale for reasonably strong patent protection in general—and drug patent protection in particular—in rich countries. The consensus among economists regarding the imposition of stronger patent rights in poor developing countries is much weaker. The idea that the rich should pay for innovation but that its fruits should be shared at very low cost with the global poor sounds particularly appealing in the context of medical innovation, where access can mean the difference between life and death. It is also appealing because a free pass for developing countries seems to have worked fairly well so far.

The world has long relied disproportionately on the US drug consumer to underwrite the cost of new drug development. Even today unofficial industry estimates suggest that the industry earns 60 percent of its profits in the United States. The United States has long provided strong IP protection for new drugs and refrained from imposing de facto price controls on patent-protected drugs. These efforts have kept US drug prices much higher than almost anywhere else in the developed world.

At the beginning of the postwar era, it probably made sense for the United States to offer up a kind of unofficial pharmaceutical Marshall Plan to the rest of the world. Incomes in the United States were higher than elsewhere, and expenditures on health care were a small fraction of GDP and household income. Because the science-based pharmaceutical industry was still at a relatively early stage of development, there was much low-hanging fruit for this industry to harvest. Hundreds of new drugs were developed in these years. At any reasonable value of a statistical life-year, the benefits reaped by the rest of the world from consuming drugs at a small fraction of the prices US consumers paid were staggering. These benefits exceeded those of the original Marshall Plan by orders of magnitude, and they extended to every part of the globe.

As appealing as this model may have been to activists, NGOs, and even some academic economists, it was not sustainable. The costs of R&D for new drugs rose as the low-hanging fruit was harvested and the industry shifted to more complex diseases. Health care costs rose at a faster pace, even as US wages stagnated, creating increasingly strong incentives for Americans to switch to generic drugs when they were available and putting strong pressures on large private insurers to use their market size to bargain for significant discounts on patent-protected drugs. An unusually productive era of pharmaceutical innovation partly insulated drug

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at death of Americans by nearly five months. Longevity effects alone imply a rate of return to pharmaceutical R&D on the order of 18 percent, without taking into account the positive effects on quality of life, reductions in the costs of surgeries and nonpharmaceutical medical care, and benefits to patients outside the United States.

companies from the financial consequences of these shifts until the mid-1990s; the lower rate of successful product introduction since then has left drug companies increasingly vulnerable to the double challenges of increasingly aggressive generic competition and skyrocketing drug development costs. The larger, publicly traded drug companies have responded by cutting back their R&D.

As the US population ages, Medicare and Medicaid programs will come under increasing pressure to use their large size and market power to negotiate the same kinds of discounts on patent-protected drugs that their counterparts around the world have done routinely for decades. The profitability of the US market will almost certainly erode further. Now that the rest of the world has grown richer and healthier, thanks in part to US innovations, it is neither fair nor realistic for the world to expect that US consumers will continue to foot the bill. The large industrial nations other than the United States generally suffer from even greater fiscal and demographic challenges. No one expects slow-growing Western Europe or an increasingly indebted Japan to dramatically raise the prices they pay for the medicines of their aging populations. It is in this context that one needs to evaluate the push in the TPP and other recent trade agreements to strengthen IP protection for pharmaceuticals outside the United States.

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# BioCentury

WEEK OF DECEMBER 21, 2015

**5 STRATEGY:  
PREFERENTIAL PRACTICES**  
BIO and PPMD's collaboration on patient preference studies could allow stakeholders to hit the ground running with studies of their own.

**8 EMERGING COMPANY PROFILE:  
NEW PURPOSE IN FLU**  
Atriva's repurposed MEK inhibitors may provide broader efficacy and a better resistance profile than Tamiflu in influenza.

**9 POLITICS, POLICY & LAW:  
RELIEVING PACIRA'S PAIN**  
Pacira's settlement with FDA suggests the controversy was the result of a management failure, not unconstitutional overreach.

**11 EBB & FLOW:  
BLOOD MONEY**  
Flagship's modality spree continues with Rubius. Plus: Kallyope's stomach for white space.

## HAPPY HOLIDAYS

BioCentury will be closed Dec. 24-25 and Jan. 1 and will not publish the week of Dec. 28. BioCentury will begin its 24th year of service the week of Jan. 4 with the 2016 Financial Markets Preview.

## TRANS-PACIFIC DREAMS

BY STEVE USDIN, WASHINGTON EDITOR

If Republicans in Congress move past their disappointment with biologics exclusivity provisions and ratify the Trans-Pacific Partnership trade treaty, the stage will be set for a significant strengthening of global IP protections for pharmaceuticals.

The agreement extends key U.S. pharmaceutical IP practices to countries that account for 40% of world trade and sets precedents that could be applied in future trade treaties around the world. It is likely to be expanded by the addition of Indonesia and other Asia-Pacific countries. Korea, the Philippines and Taiwan are considering joining TPP, and China and India would have to take it into consideration when negotiating treaties with other Pacific countries.

Apart from a shorter biologics exclusivity period than PhRMA wanted, the TPP's IP provisions read like a wish list from the trade group's Special 301 annual letter to the Office of the U.S. Trade Representative (USTR). The letter outlines steps the industry believes should be taken to level the international playing field for trade in new drugs.

Protections that innovator pharmaceutical companies have been demanding for decades and that TPP countries have agreed to include criteria for patentability of medicines, extension of drug patents for regulatory and patenting delays and data protection principles (see "TPP IP Provisions," page 3).

While conservative free-trade supporters are concerned that TPP provides insufficient protection to biologics, the deal is being attacked by progressive Democrats as a giveaway to big pharma.

Hillary Clinton has cited benefits to drug companies as her principal reason for opposing the treaty, and industry critics including Médecins Sans Frontières (MSF), Knowledge Ecology International and Public Citizen are urging Congress to block the deal because it strengthens IP protections.

“The TPP introduces far-reaching monopoly protections that lengthen, strengthen and broaden patents and other pharmaceutical monopolies,” said MSF’s Rohit Malpani at a Dec. 8 hearing organized by House Ways and Means Committee Democrats. “While the text has improved over initial U.S. government demands, mostly due to the widespread opposition of most TPP countries, the TPP will still go down in history as the worst-ever trade agreement for access to medicines.”

Malpani is director of policy and analysis at MSF’s Access Campaign.

PhRMA and BIO have not publicly discussed provisions of TPP other than biologics exclusivity. In testimony at the Ways and Means Committee hearing, BIO SVP for International Affairs Joseph Damond said the “most important and fundamental protection for BIO members is the term of data protection for biologic products.” He did not discuss other IP protections in the treaty.

## “THE TPP WILL STILL GO DOWN IN HISTORY AS THE WORST-EVER TRADE AGREEMENT FOR ACCESS TO MEDICINES.”

ROHIT MALPANI, MÉDECINS SANS FRONTIÈRES

U.S. Trade Representative Michael Froman told BioCentury the Obama administration cut the best deal possible for U.S. interests — including the pharmaceutical industry. He said that after five years of intense negotiations among a dozen countries at disparate levels of economic development, changing TPP or conjuring up a new deal would be impossible.

The alternative to TPP, said Froman, is living with weaker IP protections in the Asia-Pacific region.

### BIOPOLITICS

TPP highlights the importance of biopharmaceuticals to the global economy, and the potency of biopolitics. Tens of thousands of people took to the streets in New Zealand to protest against efforts to use TPP to lengthen biologics exclusivity, and the issue was a potential deal breaker for Australia and other countries.

Even though biologics represent a tiny fraction of the trade affected by the treaty, controversy over exclusivity came close to preventing an agreement that could produce annual global income gains of \$295 billion, including \$78 billion for the U.S., according to modeling conducted by researchers at the Peterson Institute for International Economics.

“Biologics was the last issue in the negotiation and it was the issue that posed a threat of bringing the whole negotiation to failure,” Froman told BioCentury.

American biopharmaceutical CEOs and lobbyists privately acknowledge they never expected to force the rest of the world to adopt the U.S.

exclusivity standard, and their lobbying has been intended primarily to shore up political support at home for retaining a dozen years of market freedom for biologics.

In the end, Froman said the closest he could get to the 12 years of exclusivity biologics receive in the U.S. was an artful fudge that gives parties to the TPP agreement a choice between granting eight years of exclusivity or five years plus unspecified “other measures” that “deliver a comparable outcome in the market.”

The language allowed trade ministers from Australia, New Zealand and other countries to honor pledges their governments made to withhold agreement on any treaty that forced their countries to legislate longer biologics exclusivity.

To sell the deal to the U.S. Congress, at a minimum Froman has to persuade Republicans that he has achieved a solid, enforceable eight years of biologics exclusivity, and square this assertion with statements from other governments.

“When Australia or Chile say they don’t have to change their laws, they might be right, but this is an obligation, and they have to provide other measures to deliver comparable results,” Froman told BioCentury.

PhRMA and BIO have publicly said the biologics exclusivity provisions in TPP are unacceptable, and a delegation of pharmaceutical company CEOs reiterated the point in a private meeting with President Obama. In the White House meeting they did not suggest any steps that the administration or Congress could take to mitigate their displeasure, a participant in the meeting told BioCentury.

Industry has not advocated that Congress withhold support for the treaty.

Drug company lobbyists told BioCentury that formal commitments from TPP parties to an eight-year floor on biologics exclusivity could help build support for the treaty. The lobbyists, who did not want to be identified, said the industry will take its cues on TPP ratification from Sen. Orrin Hatch (R-Utah), chair of the Finance Committee.

Hatch has publicly suggested that biologics terms of the treaty could be renegotiated, a suggestion the Obama administration rejects.

“Renegotiation isn’t possible,” Froman told BioCentury.

He and other Obama administration officials say that after five years of negotiations to weave together the most complex trade treaty in history, pulling out a single thread like the biologics provisions would unravel the entire deal.

### IP WISH LIST

Even with eight years of biologics exclusivity, the biopharma industry is far better off with TPP than without it because the agreement redefines pharmaceutical IP on terms that favor innovators, economist Lee Branstetter told BioCentury. Branstetter is a non-resident senior fellow at the Peterson Institute for International Economics and a professor of economics and public policy at Carnegie Mellon University.

Products that contain at least one NCE, including single-agent drugs and fixed-dose combinations, would be entitled to five years of data protection, or exclusivity, under TPP. That means regulators could not approve competing products that rely on an innovator’s data, including generic drugs, for a minimum of five years.

Critically, the five-year period starts with the date of approval in each market, not the first approval worldwide. Defining a new product this way creates an incentive for countries to approve drugs quickly to get the clock ticking.

“Most, but not all of the TPP countries have some kind of data protection, but most of the countries will have to strengthen data protection standards to come into compliance with TPP, and all future acceding countries will have to come into compliance with these standards,” Branstetter said.

Countries that ratify TPP must extend patent terms to compensate for “unreasonable” delays in the issuance of patents — defined as either more than five years from filing of a patent application, or three years from an examination request — and for delays in marketing approval.

Patent term extension, or restoration, is not currently available in all TPP countries. For example, in 1994 New Zealand eliminated patent term extensions for delays in issuing patents, and extensions are not provided in Brunei, Malaysia or Vietnam.

PhRMA’s 2015 Special 301 letter cites TPP countries Canada, Chile, Malaysia, New Zealand and Vietnam, plus Thailand and Turkey, as having “concerning patent backlogs and marketing approval delays.”

The TPP gives new teeth to drug IP enforcement, mandating the establishment of civil, administrative and criminal procedures, and remedies such as damages and injunctions, to protect against infringement.

In the Special 301 letter PhRMA said it was “deeply concerned about the failure of almost all the developing countries” discussed in the letter to “prevent unfair commercial use of undisclosed test data” as they are obligated to do under international trade treaties. PhRMA singled out several TPP parties for failing to protect data, including Australia, Canada, Chile, Malaysia, Mexico, Peru and Vietnam.

TPP’s data protection provisions are intended to reinforce these commitments and make them legally enforceable.

Countries that ratify TPP would commit to use scientific criteria for making drug approval decisions. The agreement states that marketing authorization is to be based on safety and efficacy data and manufacturing quality. It specifically precludes the use of pricing or other economic data for marketing approval decisions, and prohibits countries from making approval contingent on local manufacturing.

The agreement also requires countries to issue patents for new uses of a drug, as well as new methods of using a drug. Pharma industry critics and generic drug manufacturers fought these provisions, arguing that they facilitate evergreening.

The provisions could address concerns PhRMA raised in its 2015 Special 301 letter. For example, according to PhRMA, at least 20 patents on drugs it considers innovative have been invalidated in Canada as a result of standards for demonstrating patentable utility that PhRMA said are “inconsistent with international practice.”

PhRMA cited a dozen other U.S. trading partners, including TPP members Vietnam and Peru, and potential members such as the Philippines, Thailand and Costa Rica, as having “behavior of concern related to scope of patentability.”

In addition to issuing patents for new uses, countries that ratify TPP would be required to provide an additional three years of exclusivity when

## BIOPHARMA-FRIENDLY TPP PROVISIONS

The Trans-Pacific Partnership includes IP and other provisions that favor biopharmaceutical innovators. The IP protections resemble those provided in the U.S. and are stronger than IP protections in China and India. Twelve countries negotiated the TPP: Australia, Brunei, Canada, Chile, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, the U.S. and Vietnam. For the treaty to go into effect, it must be ratified by six of these countries, with ratifying countries representing 85% of the total GDP of the 12 original signatories. This means that TPP will go into effect only if both the U.S. and Japan ratify it. *Source: Trans-Pacific Partnership agreement text*

Biologics exclusivity	• Eight years of biologics exclusivity or five years plus measures to achieve “comparable outcome”
Data protection	• Five years of data protection for new drugs (including combinations with at least one new chemical entity) • Three years of data protection for new uses of an approved drug
Patent restoration	• Patent term extension for delays in issuance of patents • Patent term extension for regulatory delays
Supplemental indications	• Patents for new uses of approved drugs
Linkage	• “Linkage” between patents on innovator drugs and approval of generic competitors
Approval criteria	• Marketing approval of drugs must be based on scientific criteria, not economic considerations

it grants supplemental approval for a new use of a drug based on clinical data. This is a major win for pharma companies, as Canada and some other TPP countries do not now provide exclusivity for new uses.

### LINKAGE

TPP includes a commitment to providing “linkage” between approval of a generic drug and evidence that the generic does not infringe a patent on the original drug. Pharma critics and generic drug companies fought against linkage, arguing that drug companies routinely hold up generic competition by litigating in support of weak or invalid patents.

The treaty allows countries to choose between two linkage schemes. Under the first, patent holders must be notified prior to the marketing of a generic version of their drug and given an opportunity to assert that the generic should be blocked because it infringes a patent. The TPP agreement states that the challenge could be adjudicated by a court or through “administrative proceedings,” and the process must provide for “expeditious remedies, such as preliminary injunctions or equivalent effective provisional measures, for the timely resolution of disputes concerning the validity or infringement of an applicable patent.”

Alternatively, TPP allows countries to establish a system under which a generic can be marketed only with the consent of the new drug manufacturer.

New Zealand currently has no linkage requirement, and other TPP countries will have to strengthen their linkage systems, according to Branstetter.

The patent linkage requirements in TPP “are not nearly as strong as what we have in the U.S., but they are stronger than the status quo ante,”

Branstetter said. “Whenever a regulator allows a generic to enter the market, if there is a patent that is disputed, then a notification would be required and the patent owner would have some time to respond. USTR tried but didn’t succeed in putting in a Hatch-Waxman provision” that would have created automatic stays on generic entry.

PhRMA said in its 2015 Special 301 letter that linkage is important, because “legal mechanisms that allow for early resolution of patent disputes before an infringing product is launched on the market avoid the unnecessary costs and time of litigating damages claims in patent litigation and increase market predictability.”

**“BIOLOGICS WAS THE LAST ISSUE IN THE NEGOTIATION AND IT WAS THE ISSUE THAT POSED A THREAT OF BRINGING THE WHOLE NEGOTIATION TO FAILURE.”**

**MICHAEL FROMAN, U.S. TRADE REPRESENTATIVE**

#### A LAME DUCK DEAL?

The path to ratification of TPP is steep because the treaty’s natural allies — free-trade Republicans — are both strong supporters of the biopharmaceutical industry and among President Obama’s most ardent opponents.

TPP also contains another political tripwire, apart from biologics: limitations on the ability of tobacco companies to use dispute resolution procedures to diminish restrictions on their products. The issue is particularly important to Senate Majority Leader Mitch McConnell, a Republican from tobacco-growing Kentucky.

In a Nov. 18 television interview with *The Wall Street Journal*, House Speaker Paul Ryan (R-Wis.) said a vote on TPP during the current session of Congress is possible but not guaranteed. Asked if he will support ratification, Ryan said, “I haven’t made a decision. I’m concerned about biologics, quite frankly.”

The treaty will be ratified by the current Congress only if the Republican leadership is persuaded that it doesn’t undermine the pharmaceutical industry at home or abroad, and if the vote isn’t perceived as helping Democrats.

Having made their displeasure over the biologics exclusivity provisions abundantly clear, there are signs that pharma companies may adopt a neutral stance rather than actively seeking to scuttle TPP.

On Dec. 3, private sector members of the President’s Export Council, a national advisory committee on international trade, recommended to Obama that the administration “engage Congress to implement the Trans-Pacific Partnership as soon as possible.” Council members who joined the discussion include Kenneth Frazier, chairman and CEO of [Merck & Co. Inc.](#), and Ian Read, chairman and CEO of [Pfizer Inc.](#)

Frazier is currently serving as chairman of PhRMA.

Some influential supporters of the pharmaceutical industry are urging Congress to look past the biologics exclusivity issue.

Douglas Holtz-Eakin, president of American Action Forum, a conservative think tank, told BioCentury he favors ratification of TPP.

Holtz-Eakin, who has served as director of the Congressional Budget Office and chief economist of President George W. Bush’s Council of Economic Advisers, emphasized American strategic interests. TPP “is a good idea. It is not perfect. Its value is increased by the fact that it sets the rules for trade in a way that puts China on notice that it is not going to dictate them,” he said.

He added: “If I am BIO and PhRMA, I am disappointed [about biologics exclusivity] and don’t want this agreement. If I am Congress, I have to worry about not just this issue, but everything involved, and that’s a different calculation. On balance, Congress should ratify.”

If cigarettes and biologics make it impossible to pass TPP before the 2016 elections, members of Congress who believe its geopolitical benefits outweigh concerns about impacts on specific interests may take it up during the lame duck session.

Alternatively, TPP could be considered under the next president’s watch. The two leading Democratic candidates oppose the treaty, as do Sen. Ted Cruz (R-Texas) and Donald Trump, but Sen. Marco Rubio (R-Fla.) and Jeb Bush have expressed support for the treaty. [52](#)

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#### COMPANIES AND INSTITUTIONS MENTIONED

**American Action Forum**, Washington, D.C.  
**Biotechnology Industry Organization (BIO)**, Washington, D.C.  
**Carnegie Mellon University**, Pittsburgh, Pa.  
**Knowledge Ecology International**, Washington, D.C.  
**Médecins Sans Frontières (MSF)**, Geneva, Switzerland  
**Merck & Co. Inc.** (NYSE:MRK), Kenilworth, N.J.  
**Office of the U.S. Trade Representative (USTR)**, Washington, D.C.  
**Peterson Institute for International Economics**, Washington, D.C.  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**Pharmaceutical Research and Manufacturers of America (PhRMA)**, Washington, D.C.  
**Public Citizen**, Washington, D.C.

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**Usdin, S.** “Trans-Pacific politics.” *BioCentury* (2015)

STRATEGY

## PREFERENTIAL PRACTICES

BY ERIN MCCALLISTER, SENIOR EDITOR

Facing calls from its members and patient groups for a framework on how patient preference studies for drugs should be designed and executed, BIO enlisted [Parent Project Muscular Dystrophy](#) to help create a set of general guidelines and recommendations that stakeholders can use to design and execute disease-specific patient preference studies.

Patient preference research is grounded in the notion that patients have distinct preferences about the trade-offs and risks inherent in medical decisions, which are frequently different from the choices physicians would make.

The research methods are well-established and have been applied in healthcare settings for 25 years, but their use to inform medical product development and regulation is quite new.

Only one medical product has been approved based on data from patient preference studies. The Maestro Rechargeable System from [EnteroMedics Inc.](#) missed the primary endpoint in a trial to treat obesity. But FDA's Center for Devices and Radiological Health (CDRH) was able to approve the device after a preference study conducted by CDRH showed that a group of patients would accept the risks associated with the device for the amount of weight loss it was expected to provide.

CDRH later issued a draft patient preference guidance outlining qualities of patient preference studies, recommendations for collecting patient preference data, necessary steps to get patient preference data included on a device's label and hypothetical examples that illustrate how patient preference information may inform the center's regulatory decision making.

BIO and PPMD will draw upon the CDRH's work and other successful patient preference studies to identify what practices are exportable to drugs.

The group's recommendations are expected to be available in a white paper early next year, and there are already patient groups and companies eager to use the tools.

### ESTABLISHING PREFERENCE

Formal patient preference studies can provide hard data on the specific benefits, risks and harms patients care about and quantify both the relative importance of these factors, and the willingness of patients to make trade-offs among them.

Preference studies also can identify and characterize subpopulations that might benefit from a product — and populations for whom no amount of benefit would outweigh the risks.

The data can also help companies and regulators understand the clinical need, and the product characteristics and data benchmarks necessary for success.



SOURCE: BIOCENTURY AND THINKSTOCK

In the majority of preference studies, patients are offered a series of hypothetical choices to elucidate and quantify their trade-offs. For example, a study could offer patients a set of hypothetical product profiles that have varying levels of benefit and toxicity. Based on patient responses related to their preferred regimens, the study can elucidate how much toxicity patients are willing to tolerate for a given benefit.

The CDRH guidance notes that patient preference studies can be used throughout a device's life cycle (from discovery to launch and beyond) and outlines when such studies are most appropriate: when multiple treatment options exist but no one option is clearly superior for all preferences; when the evidence supporting one option over others is considerably uncertain or variable; and/or when patients' views about the most important benefits and acceptable risks of a technology vary considerably within a population.

There are some obvious differences between the ways devices and drugs are developed, which would be expected to translate into differences in

the ways preference research should be designed and used. But PPMD doesn't think it will be a "heavy lift" to translate the CDRH guidance into something that could also be applicable to drugs.

"There may be slight differences, but nothing substantial," said Ryan Fischer, SVP of community engagement at PPMD.

## EXPERIENCED PARTNER

PPMD designed and conducted patient preferences studies in Duchenne muscular dystrophy (DMD) that helped to inform draft guidance written by PPMD and eventually adopted, almost in its entirety, by FDA this year.

Based on input from a handful of caregivers, doctors, academics and drug companies, PPMD and academic collaborators designed a study to assess the six attributes of a drug most important to patients: effects on muscle function and life span, knowledge about the drug, nausea, risk of bleeds and risk of arrhythmia.

**"PPMD HAS PAVED A PATH TO ELEVATE THE PATIENT VOICE, AND WE BELIEVE OTHER STAKEHOLDERS CAN LEARN FROM THEIR INCREDIBLE EFFORTS."**

LAUREN NEFF, BIO

The study used a best-worst study design in which caregivers were asked to pick the "best" and "worst" attribute of a hypothetical treatment. The study found that the 124 participating caregivers ranked the ability of a drug to slow or stop disease progression as being the most important (28.7%) followed by the risk of arrhythmia (22.4%). Results were published in 2014 in *Clinical Therapeutics*.

"They prioritized slowing disease progression over adding years to life," said PPMD President and CEO Pat Furlong.

A subsequent study in adult patients with limited arm function found that the highest priority for these patients was resolution of cough. "This can lead to infection, and if your chest is full of secretions, you can't call out for help. So cough is a critical factor in terms of communication," Furlong said. The study results have yet to be published.

The DMD guidance FDA issued includes endpoints that are measures of disease progression like timed function tests and respiratory endpoints.

PPMD is now working with patients and caregivers to assess their preferences over the course of the patient's disease "to see if it changes with progressive disease," Furlong said.

"PPMD has paved a path to elevate the patient voice, and we believe other stakeholders can learn from their incredible efforts," said Lauren Neff, BIO's managing director for alliance development.

## PRACTICAL OUTLINE

Based on PPMD's preference studies and other examples, the patient group and BIO will assemble a list of considerations and processes stakeholders can use to design and execute patient preference studies.

"The idea is to provide best practices for studies that could be used by FDA in a consistent and rigorous way that is the same across divisions. So while it won't be the exact same as CDRH's guidance, because drugs and devices are different, we will take some learnings from what they have done and what is different in the devices and drugs area," Furlong said.

The best practices will include recommendations for how to include stakeholders in the design of studies and the validation of survey tools through an iterative process.

"You have to be sure that you're reflecting what is meaningful to the patients, so you have to have all of these checks and balances throughout the process," Furlong said.

The best practices also will address how to conduct scientifically rigorous analyses that can quantitatively assess things like risk tolerance.

"One of the things the best practices will explore is what methodologies to use to arrive at quantitative results. It is much different than market research, and we want to make sure that the best practices acknowledge this," Furlong said.

The document also will provide recommendations on how to identify social scientists who have the skills to conduct these analyses, and it will include questions companies or other stakeholders might consider before designing a preference study.

"The questions that will need to be asked are going to vary considerably depending on what the disease is," Neff said. "There is no one-size-fits-all model and that in some instances, a patient preference study may not be necessary."

BIO and PPMD will seek input into the best practices from FDA.

"Our intention is for this to be an iterative process with FDA, and they have been very receptive and encouraged by the development," Neff said.

Furlong added: "We can't develop these if FDA doesn't agree that these are the best practices. So we'll share what we know and are learning with FDA and get their input. We don't want to spend our time doing one-offs of everything and not meeting a standard that FDA can integrate into the review."

PPMD and BIO plan to meet with Center for Drug Evaluation and Research (CDER) Director Janet Woodcock next month.

The partners expect swift uptake of the recommendations among companies and patient groups.

"We're seeing a lot of patient groups that would like to replicate what PPMD has done," said National Health Council CEO Marc Boutin. "From the company perspective, the document will provide opportunities on the best ways to go and gather data that would be more specific to a product or disease area."

Boutin is a member of the initiative's expert review committee.



## COVER STORY

### A MEETING ABOUT A MEETING

The international summit on gene editing was enough of a kumbaya for organizers to declare success, but postponed hard decisions for another day.

## STRATEGY

### SAN DIEGO CEILING

With four high-profile hires in under 18 months to San Diego's academic powerhouses, the region is still trying to kick-start its ability to turn the strength of its science into new biotechs.

## TOOLS

### HEARTFELT CONVERSION

A China-U.S. collaboration has found a high efficiency way to convert skin cells into cardiac progenitors and is spinning out the tech to form Qurgen.

### RNA UPGRADES

How technologies are improving delivery and efficacy of RNA therapeutics: a graphical snapshot of the last three years.

## TRANSLATION IN BRIEF

### COMPOUND COLLABORATIONS

Sanofi and AstraZeneca are sharing segments of their compound libraries without restrictions.

### OH, THE PLACES YOU'LL GO

A pair of imaging studies suggests patient responses to cancer nanotherapies might be predicted by following nanoparticle distribution in vivo.

## DISTILLERY


### This week in therapeutics

This week in therapeutics includes important research findings on targets and compounds, grouped first by disease class and then alphabetically by indication.

### This week in techniques

This week in techniques includes findings about research tools, disease models and manufacturing processes that have the potential to enable or improve all stages of drug discovery and development.

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"We anticipate that there will be a series of guidances around preference studies — making them, how do you present them to FDA, whether they make it into the benefit-risk framework — and then there will also probably be guidance that will evolve on the methods used and in specific disease areas. All of which will be informed by BIO and PPMD's activities," said Boutin. 

## COMPANIES AND INSTITUTIONS MENTIONED

**Biotechnology Industry Organization (BIO)**, Washington, D.C.

**EnteroMedics Inc.** (NASDAQ:ETRM), St. Paul, Minn.

**National Health Council (NHC)**, Washington, D.C.

**Parent Project Muscular Dystrophy (PPMD)**, Hackensack, N.J.

**U.S. Food and Drug Administration (FDA)**, Silver Spring, Md.

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**FDA Center for Devices and Radiological Health.** "Patient preference information — submission, review in PMAs, HDE applications, and *de novo* requests, and inclusion in device labeling." (2015)

**Peay, H., et al.** "A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy." *Clinical Therapeutics* (2014)

**Unsigned commentary.** "Back to school: Changing the subject." *BioCentury* (2015)

**Usdin, S.** "Would you rather?" *BioCentury* (2015)



## EMERGING COMPANY PROFILE

# NEW PURPOSE IN FLU

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Atriva Therapeutics GmbH is repurposing MEK inhibitors to stop influenza viruses from hijacking host cellular pathways necessary for viral replication. The strategy may provide better efficacy than existing flu therapies by avoiding viral resistance.

Roche's Tamiflu oseltamivir is the market-leading antiviral for treating influenza. Yet use of the neuraminidase inhibitor is limited because of modest efficacy and a short treatment window of just 24–48 hours from symptom onset.

According to the label, Tamiflu reduced the median time to symptom improvement by 1.3 days in two placebo-controlled Phase III trials. In geriatric patients, who are at higher risk of serious complications from influenza, the reduction in time to improvement was only one day.

Tamiflu's label also lists numerous observed neuraminidase amino acid substitutions that convey resistance to treatment. According to Atriva co-founder and CBO Henrik Luessen, viral resistance reduces Tamiflu's efficacy. The company is therefore targeting host MEK.

During an infection, the influenza virus temporarily activates the MEK pathway in infected cells to gain access to the nucleus, where it replicates, proliferates and is excreted from the cell.

"With our MEK inhibitors, we cannot reproduce an alternative resistance mechanism and do not see any resistance," Luessen said.

Luessen said unpublished data from mice infected with five times the lethal dose of influenza showed that treatment with a MEK inhibitor 48 hours after infection led to a 60% survival rate at 14 days. Tamiflu-treated mice and untreated mice all died by day 8. He said additional data show MEK inhibitors are effective when treatment is begun as late as four days after infection.

### ATRIVA THERAPEUTICS GMBH

Tübingen, Germany

**Technology:** MEK inhibitors for influenza

**Disease focus:** Infectious

**Clinical status:** Preclinical

**Founded:** 2015 by Sebastian Canisius, Emilie Hofstetter, Rainer Lichtenberger, Henrik Luessen, Stephan Ludwig, Rolf Naumann, Oliver Planz, Stephan Pleschka

**University collaborators:** University of Tübingen, University of Münster, Justus-Liebig University of Giessen

**Corporate partners:** None

**Number of employees:** 8

**Funds raised:** Undisclosed

**Investors:** Undisclosed

**CEO:** Rainer Lichtenberger

**Patents:** 2 issued covering the use of MEK inhibitors to prevent or treat infections by negative strand RNA viruses

He added that because the replication mechanism is conserved across influenza strains, MEK inhibitors should work against both seasonal and pandemic strains. In 2011, Atriva's academic co-founders published data in *Antiviral Research* showing that in a mouse model, MEK inhibitors had broad activity against pandemic strains H1N1 and H5N1, as well as newly emergent strains such as H7N9.

The company's lead compound is ATR-001, an undisclosed MEK inhibitor that failed in Phase II for cancer because of poor bioavailability.

Co-founder and CEO Rainer Lichtenberger said that should not be a problem in influenza because lower concentrations are required for efficacy.

"The viral inhibition EC<sub>50</sub> is much, much lower than the EC<sub>50</sub> in tumor cells," he told BioCentury.

Luessen added that the side effects of marketed MEK inhibitors in cancer — including rash, diarrhea and vomiting, cardiomyopathy, retinal vein occlusion, skin toxicity and embryofetal toxicity — are unlikely to emerge with the low doses and short treatment period that will be tested in influenza.

He said the antiviral dose will likely be 5–10x lower than the dose for cancer, and the treatment period would be five days.

"If you talk to oncologists who use these compounds, they never observed side effects within the first few days," he said.

Lichtenberger declined to disclose whether or not the biotech has a license to ATR-001 from the originator, but he did say the composition of matter patent expires "in a few years." He said Atriva has IP covering the use of MEK inhibitors to treat and prevent influenza infection.

Atriva has raised less than €1 million (\$1.1 million) from undisclosed investors to finance the preclinical work. The company is looking to raise up to €15 million (\$16.1 million), which Luessen said would fund GMP manufacturing, a Phase I trial and a Phase IIb head-to-head study vs. Tamiflu.

He said Atriva would likely look for a partner after Phase II, but could seek to raise an additional €30 million (\$32.3 million) to fund Phase III development. [be](#)

### COMPANIES AND INSTITUTIONS MENTIONED

Atriva Therapeutics GmbH, Tübingen, Germany

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

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Dröebner, K., et al. "Antiviral activity of the MEK-inhibitor U0126 against pandemic H1N1v and highly pathogenic avian influenza virus *in vitro* and *in vivo*." *Antiviral Research* (2011)

## POLITICS, POLICY &amp; LAW

## RELIEVING PACIRA'S PAIN

BY STEVE USDIN, WASHINGTON EDITOR

In September, when [Pacira Pharmaceuticals Inc.](#) asked a federal court to force FDA to lift restrictions on the company's promotion of Exparel bupivacaine, it looked like yet another drug company was launching a First Amendment challenge to the agency's enforcement practices. Based on the settlement filed with the court last week, it now looks like the controversy stemmed from a more prosaic cause: a management failure at FDA's Center for Drug Evaluation and Research.

The story starts in 2011, when CDER's Division of Anesthesia, Analgesia and Addiction Products (DAAAP) reviewed Pacira's NDA for Exparel, a liposomal extended-release version of bupivacaine, a generic analgesic.

Pacira submitted an NDA under the 505(b)(2) pathway seeking a broad indication for "postsurgical analgesia." Consistent with FDA's draft guidance on developing drugs for analgesic indications, the NDA included data from two Phase III trials that studied Exparel's use to control pain from hemorrhoidectomy and bunionectomy surgeries.

According to the guidance, to obtain "an indication of the treatment of general acute pain, two successful trials in nociceptive pain, one in visceral pain and one in nonvisceral pain, generally will be considered to be adequate."

However, the medical reviewer assigned to the application, Arthur Simone, argued against a broad indication because of differences in the dose and method of administration in the two trials. He agreed that Pacira had demonstrated safety and efficacy, but he recommended that Exparel's proposed indication be narrowed to postoperative analgesia following hemorrhoidectomy or bunionectomy.

Simone's superiors, including DAAAP Director Bob Rappaport, apparently disagreed.

The Exparel approval letter, dated Oct. 28, 2011, and signed by Rappaport, noted that the approved indication was "for single-dose infiltration into the surgical site to produce postsurgical analgesia." The indication was not limited to hemorrhoidectomy or bunionectomy procedures. The dosage and administration section of the label described its use in the two types of surgery that had been conducted in Phase III trials.

Pacira developed a marketing campaign that included training surgeons on use of Exparel in a variety of surgical procedures. Although Exparel was criticized in the medical literature by physicians who said Exparel was no better than generic bupivacaine, the company's activities were not challenged by FDA for three years.

Then Pacira received an unexpected warning letter from FDA's Office of Prescription Drug Promotion (OPDP) stating that the company had been promoting Exparel for unapproved uses.

## UNEXPECTED WARNING

The Sept. 22, 2014, letter asserted that Exparel was not approved to treat pain from surgeries other than hemorrhoidectomy or bunionectomy.

"These violations are extremely concerning from a public health perspective because they provide evidence of the intended use of Exparel in surgical procedures other than those for which the drug has been shown to be safe and effective and they suggest that Exparel is more effective than has been demonstrated," the letter stated.

In addition to ceasing its promotion of uses other than treating pain from hemorrhoidectomy or bunionectomy, OPDP instructed Pacira to send corrective messages and threatened the company with criminal and civil penalties.

## "NOBODY HERE HAD ON THEIR BUCKET LIST TO SUE THE FDA."

DAVID STACK, PACIRA

The warning letter tripped up a three and a half year climb in Pacira's market valuation (see "Pacira's Peak," page 10).

Pacira CEO and Chairman David Stack told BioCentury the company "really doesn't know" why FDA tried to restrict its promotion of Exparel. "We've asked ourselves that a million times" and don't have an answer, he said.

After receiving the warning letter, Pacira wrote to FDA defending the company's promotion of Exparel as consistent with the product label, and requested meetings to make its case. According to legal documents Pacira submitted to the U.S. District Court for the Southern District of New York, FDA refused to meet and reiterated the demands made in its warning letter.

Pacira complied with FDA's demands, and sued the agency in the district court, a jurisdiction that has a long history of overturning FDA decisions. "Despite Pacira's requests that FDA explain why speech consistent with Exparel's general 'Indications and Usage' section could be criminal, FDA refused and continues to refuse to meet with Pacira or otherwise explain its position," the company told the court.

The complaint accused FDA of illegally imposing a retroactive modification to the Exparel label, and violating the First Amendment to the U.S. Constitution by seeking to prevent truthful and non-misleading speech.

FDA has experienced a string of defeats in First Amendment cases, including recent suits that successfully challenged the agency's ability to prohibit drug companies from communicating truthful, non-misleading information to physicians about off-label uses.

Pacira's lawsuit, and the prospect of losing another First Amendment case, got the attention of FDA's senior leadership.

"Once we started talking to folks at higher levels of FDA, they clearly understood an error had been made and the discussions very quickly became collaborative on how we could fix this," Stack told BioCentury.

FDA removed the warning letter from its website, an extremely unusual step, and entered into negotiations with Pacira's attorneys to settle the case. The settlement announced last week included confirmation from FDA that Exparel had been approved for postsurgical analgesia and that the indication was not limited to the surgical indications studied in Phase III trials.

In addition to formally rescinding the warning letter, FDA approved a new package insert with language noting that dosing should be adjusted based on the kind of surgery being performed. The new label includes several additions Pacira requested to boost its ability to market Exparel, including co-administration of the drug with bupivacaine in a single syringe.

"It is an absolute affirmation from FDA that what we thought we had, we did indeed have, including a broad label for all surgical indications," Stack said.

## STUCK IN THE MIDDLE?

Based on the review documents, it appears that Pacira was caught in a dispute between a medical reviewer who felt that Exparel should have a narrow label, and his superiors who had granted a broad indication.

In a letter to Pacira, CDER Director Janet Woodcock wrote: "Based on the plain language of the Indications and Usage section of the full prescribing information, as well as the clinical trial submitted in support of that approval, FDA determined that the indication approved in 2011, was not limited to bunionectomy and hemorrhoidectomy procedures."

The warning letter stated that OPDP had uncovered the violations as a result of its "routine monitoring and surveillance program," and that a journal ad had been submitted as part of the office's "Bad Ad" program, which asks the public to submit examples of potentially illegal promotional activities.

When Exparel appeared on OPDP's radar, the logical first step would have been to contact DAAAP, and it is possible that a case involving promotion of a 505(b)(2) drug would not have been brought to the attention of the division director.

The language and concepts in the warning letter echo Simone's review.

Whatever instigated the warning letter, Stack said he is happy to have resolved the issue without litigating the First Amendment issues. "Our objective was not to set a precedent. Nobody here had on their bucket list to sue the FDA."

Because FDA immediately agreed to Pacira's demands, the settlement did not touch on the First Amendment arguments, Stack said.

## PACIRA'S PEAK

Shares of **Pacira Pharmaceuticals Inc.** (NASDAQ:PCRX) gained more than 9x between FDA approval of Exparel bupivacaine in October 2011 and September 2014, when it received a warning letter from the agency objecting to the company's promotion of the pain drug. Since then, the stock has lost about a quarter of its value as of last Friday. Pacira rose 23% last week after announcing a resolution to its suit against FDA seeking to withdraw the warning letter. Selected events tracked against Pacira's daily share price below. Sources: *BCIQ: BioCentury Online Intelligence, Pacira*



- A. 2/3/11 — Pacira raises \$42M in IPO.
- B. 10/28/11 — FDA approves Exparel bupivacaine for postsurgical pain management.
- C. 4/9/12 — Pacira launches Exparel.
- D. 9/22/14 — FDA issues a warning letter objecting to the company's promotion of Exparel for indications other than treating pain associated with bunionectomy and hemorrhoidectomy surgeries.
- E. 3/2/15 — FDA issues a complete response letter to Pacira for an sNDA for Exparel as a nerve block to provide postsurgical analgesia. The company declines to disclose the nature of FDA's concerns.
- F. 9/8/15 — Pacira files suit in the U.S. District Court for the Southern District of New York seeking to have the warning letter withdrawn.
- G. 10/13/15 — FDA removes warning letter from website.
- H. 12/15/15 — Pacira announces resolution of its September lawsuit. Terms include labeling changes to reinforce the use of Exparel is not limited to any specific surgery type or site, and formal FDA rescission of 2014 warning letter.

FDA may find it more difficult to extricate itself from another First Amendment case pending in the U.S. District Court for the Southern District of New York. **Amarin Corp. plc** has already won a preliminary injunction against FDA's efforts to limit its promotion of Vascepa icosapent ethyl.

The U.S. government is scheduled to inform the court of the status of ongoing settlement discussions with Amarin in February 2016. [bc](#)

## COMPANIES AND INSTITUTIONS MENTIONED

- Amarin Corp. plc** (NASDAQ:AMRN), Dublin, Ireland
- Pacira Pharmaceuticals Inc.** (NASDAQ:PCRX), Parsippany, N.J.
- U.S. Food and Drug Administration (FDA)**, Silver Spring, Md.

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## EBB &amp; FLOW

## BLOOD MONEY

Flagship Ventures appears to have a thing for platform companies developing novel therapeutic modalities. The company debuted [Rubius Therapeutics Inc.](#) this month with a \$25 million series A round to develop a basket of engineered red blood cells for multiple indications.

It's the third start-up with a new therapeutic modality launched this quarter, and at least the seventh among 19 companies incubated within the VC's VentureLabs group.

Rubius genetically engineers hematopoietic progenitors to produce a therapeutic protein of interest when the progenitor differentiates into an RBC. Because RBCs lack nuclei, Rubius expects its products will not have safety concerns related to unwanted differentiation that can accompany other types of cell therapies. The company uses O-negative stem cells so that resulting products lack the A, B and Rh antigens that could cause immune rejection, CEO Avak Kahvejian told BioCentury.

"We can endow the blood cells with a variety of capabilities in metabolic diseases, cancer and autoimmune conditions," said Kahvejian. "It's basically a function of our imagination and where we think we can have the most therapeutic impact."

This year, Rubius expects to start clinical testing of an engineered RBC for phenylketonuria (PKU) that processes phenylalanine by an undisclosed mechanism. PKU is a rare inborn error of metabolism that renders patients unable to process phenylalanine, resulting in a toxic buildup of the metabolite.

The disease is managed by low-protein diet restrictions that can have debilitating consequences, such as developmental deficits in children. The lone drug for the condition, Kuvan sapropterin dihydrochloride from [BioMarin Pharmaceutical Inc.](#) (NASDAQ:BMRN), does not alleviate the dietary restrictions.

"We aim to liberalize patients from their protein-limited diets," said Kahvejian, who also is a partner at Flagship's VentureLabs unit.

BioMarin's pegvaliase, the only product in the clinic for PKU, includes keeping diet constant but does not specify a type of diet. Phase III data are expected in April 2016.

Kahvejian said Rubius is still deciding how many programs it wants to pursue in parallel. "We have dozens and dozens of prototypes for a variety of indications," he said.

VentureLabs incubated Rubius for about 18 months. The other two therapeutic modality plays that debuted this quarter are [Codiak BioSciences Inc.](#) and [Evelo Therapeutics Inc.](#) Codiak is using synthetic exosomes to diagnose and treat cancer (see [BioCentury, Nov. 23](#)).

Evelo is developing Oncobiotics, which are bacteria with antitumor mechanisms (see [BioCentury, Nov. 9](#)).

— Steve Edelson

## APPETITE FOR WHITE SPACE

Lux Capital has decided signaling between the gut and brain represents investable white space. The firm led a \$44 million series A round last week for [Kallyope Inc.](#), which plans to develop therapies that act on the gut-brain axis for metabolic and psychological conditions.

Other investors included Polaris Partners, The Column Group, [Illumina Inc.](#) (NASDAQ:ILMN), Tony Evnin and Alexandria Venture Investments. Evnin invested as an individual, not as a partner at Venrock.

"There are 300 million neurons in the gut, and the undeniable link between the gut and brain is totally unexplored. Right now there's unowned white space that we think is there for the taking," said Lux's Josh Wolfe, who sits on Kallyope's board.

**"WE AIM TO  
LIBERALIZE PATIENTS  
FROM THEIR PROTEIN-  
LIMITED DIETS."**

AVAK KAHVEJIAN, RUBIUS

The biotech is not discussing specific targets or therapeutic areas it plans to pursue, although Wolfe said programs will extend beyond diseases typically associated with the gut, like diabetes and obesity.

“This axis is important because it’s triggering the gut through the brain, and the inverse. Lots of companies are trying to cross the blood-brain barrier, but I think that people don’t realize there’s another highway to get into the brain. The axis plays roles in human psychology, behavior, cognition and taste,” he said.

Academic research has been elucidating communication along the gut-brain axis for some time. In 2006, for example, [Imperial College London](#) researchers described neural communication between the small intestine and the brain that acted to curb food intake.

Lux wanted to form a company focused on the gut-brain axis for a few years, but Wolfe said technologies for interrogating targets and pathways were not yet ripe. That has since changed with the availability of single-cell sequencing from Illumina, imaging technologies, circuit mapping and microbiome research, all of which can be used in combination.

“Five years ago these technologies weren’t accessible let alone combinatorial,” said Wolfe.

Kallyope says it is the first biotech working on the gut-brain axis. The newco is headquartered in New York City and its scientific founders are a trio of [Columbia University](#) professors: Charles Zuker, Tom Maniatis and Richard Axel.

CEO Nancy Thornberry said therapeutics are the main thrust of Kallyope, but added the company also may pursue undisclosed nutritional products.

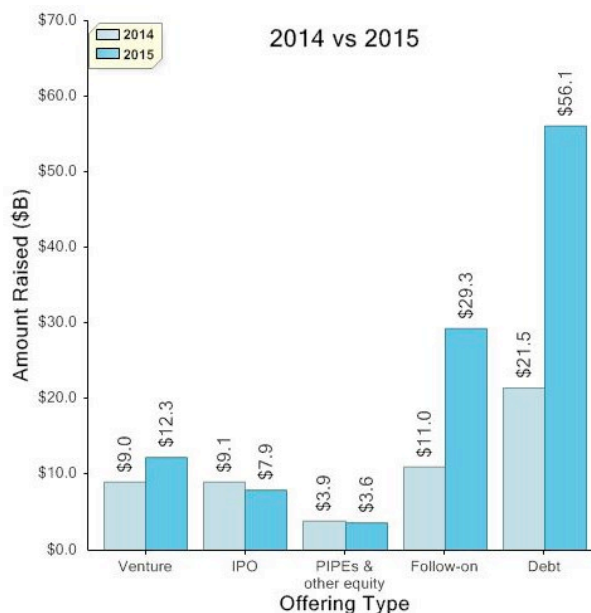
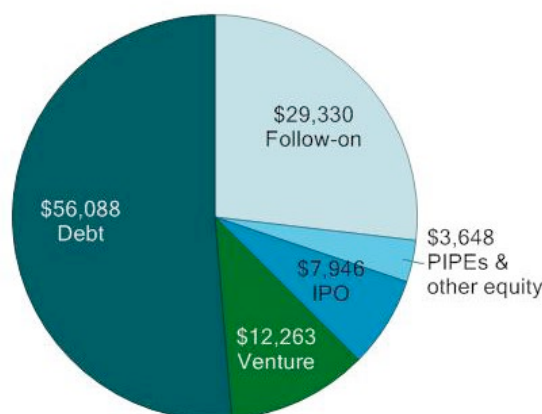
“The gut-brain axis is of high interest to nutrition companies, and we will fully explore interesting business development opportunities,” she said. <sup>bc</sup>

— Steve Edelson

## MONEY RAISED IN 2015

Last week, the biotech industry raised \$331 million, bringing to \$109.3 billion the total raised year-to-date. In 2014, a total of \$54.9 billion was raised, including \$21.6 billion in debt, \$11.1 billion in follow-ons, \$4 billion in PIPEs and other equity, \$9.1 billion in IPOs, and \$9.2 billion in venture capital. Totals include overallocments and warrants, and are rounded to the nearest millions.

Total YTD: \$109,276 (\$M)

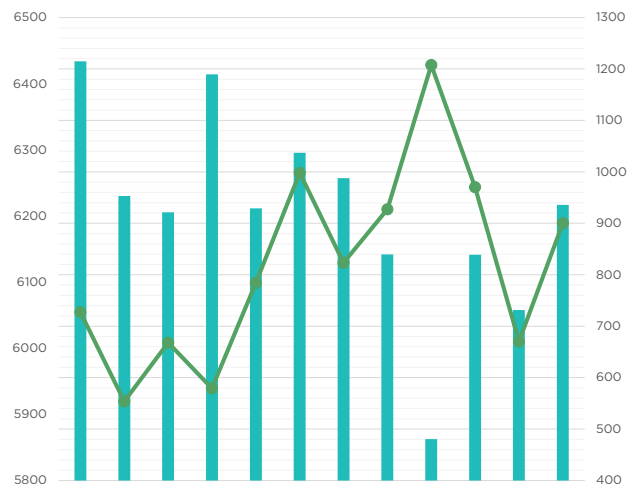


## Analyst picks & changes

Company	Bank	Analyst	Coverage	Opinion	Wk chg	12/18 cls
<b>Cerus Corp.</b> (NASDAQ:CERS)	Wedbush	Zarak Khurshid	Downgrade	Neutral (from outperform)	-8%	\$5.90
<p>Khurshid downgraded, noting the stock is up 25% in the past six months. His target is \$6.50. In late 2014, FDA approved Cerus' Intercept Blood System, which is used to neutralize pathogens in donated blood products. Khurshid maintained a conservative 2016 revenue estimate of \$44M vs. \$47M for consensus, noting Cerus' "heavy exposure to the Euro and further U.S. dollar strengthening plus low visibility into the U.S. revenue story."</p>						
<b>Relypsa Inc.</b> (NASDAQ:RLYP)	H.C. Wainwright	Ed Arce	New	Buy	4%	\$27.92
<p>Arce initiated coverage with a \$63 target ahead of an expected January U.S. launch of Relypsa's Veltassa patiomer, a high-capacity oral potassium binder, to treat hyperkalemia. Arce thinks Veltassa is likely to become a blockbuster drug in the U.S. by 2022 and models peak U.S. sales of \$1.6B in 2026.</p>						
<b>Valeant Pharmaceuticals International Inc.</b> (TSX:VRX; NYSE:VRX)	Mizuho	Irina Koffler	Downgrade	Neutral (from buy)	17%	\$108.52
<p>Koffler downgraded, saying she is less certain about Valeant "crushing the numbers" each quarter and is unable to identify a near-term catalyst that could take the stock beyond her \$130 target without additional M&amp;A or significant outperformance. While investors "cheered" the news of last week's product distribution deal with <b>Walgreens Boots Alliance Inc.</b> (NASDAQ:WBA), Koffler said she does not "understand how this partnership will improve filled prescriptions if payer restrictions persist."</p>						

## BIOCENTURY 100 PRICE & VOLUME TREND

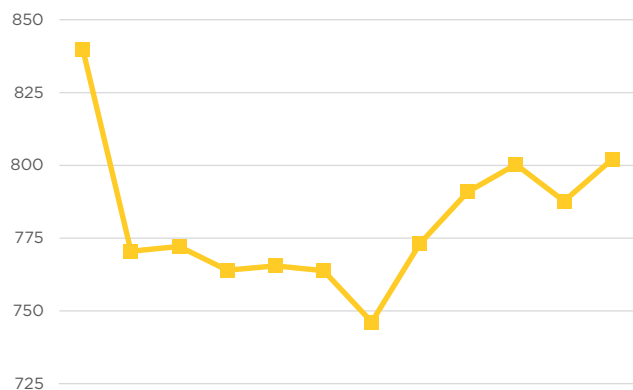
Cumulative weekly performance of 100 bioscience stocks. 12-week period. Line shows Price Level change (Left scale. Index base=1000 on May 10, 1996). Bars show cumulative volume in millions (right scale).



BioCentury tracks 806 issues that report prices and volume daily. The BioCentury 100 is a subset used to monitor price and volume trends

## BIOCENTURY LONDON INDEX

Weekly change in the combined market capitalization for 14 bioscience stocks listed on the LSE or AIM, 12-week period. Index base =1000 on May 10, 1996.



## BIOCENTURY 100 INDICATORS

Week ended 12/18/15



### PRICES

6189.21  
up 3%

### VOLUME

935.7M shrs  
up 28%

## PRICE GAINS

Stocks with greatest % price increase in the week ended 12/18. (Priced above \$2; 5,000 minimum share volume)

Company	Ticker	\$Close	\$Chg	% Chg	Vol(00)
ContraFect	CFRX	4.920	1.730	54%	8519
Relmada	RLMD	3.250	0.900	38%	1077
Poxel	POXEL	€10.200	€2.810	38%	5784
aTyr	LIFE	10.070	2.460	32%	21104
Aclaris	ACRS	28.680	6.630	30%	12477
Nicox	COX	€8.310	€1.910	30%	19186
Akebia	AKBA	12.350	2.600	27%	54274
Pacific Biosciences	PACB	12.200	2.520	26%	99825
Calithera Biosciences	CALA	7.500	1.520	25%	8688
Actinium	ATNM	2.270	0.460	25%	62157
Keryx	KERX	5.380	1.080	25%	188313
Marinus	MRNS	7.640	1.530	25%	6555
Sage Therapeutics	SAGE	60.950	12.200	25%	32086
Aptose Biosciences <sup>1</sup>	APTO	2.840	0.560	25%	1532

## PRICE DECLINES

Stocks with greatest % price decline (criteria as above).

Company	Ticker	\$Close	\$Chg	% Chg	Vol(00)
Great Basin <sup>2</sup>	GBSN	2.270	-3.412	-60%	100731
Atara Biotherapeutics	ATRA	24.080	-9.120	-27%	68653
Bind Therapeutics	BIND	2.590	-0.950	-27%	13079
Xtant Medical	XTNT	2.390	-0.810	-25%	1231
Midatech Pharma <sup>3</sup>	MTP	4.950	-1.340	-21%	3095
Viking Therapeutics	VKTX	2.020	-0.500	-20%	1495
Diadexus	DDXS	2.000	-0.400	-17%	283
Neovasc <sup>1</sup>	NVCN	3.550	-0.700	-16%	1296
AmpliPhi BioSciences	APHB	4.610	-0.890	-16%	1013
Stellar Biotechnologies <sup>4</sup>	SBOT	7.090	-1.360	-16%	1526
OncoSec	ONCS	2.230	-0.420	-16%	8673

## VOLUME GAINS

Greatest changes in volume above 5,000 shares.

Company	Ticker	Vol(00)	%Chg	\$Close	\$Chg
4D Pharma	DDDD	65	2809%	785p	-2.5p
Epistem	EHP	1413	2763%	120p	2.5p
Ergomed	ERGO	10535	1126%	169p	11.5p
aTyr	LIFE	21104	599%	10.070	2.460
Check-Cap	CHEK	1485	584%	2.105	0.075
ContraFect	CFRX	8519	564%	4.920	1.730
RaQualia	4579	93994	545%	¥359.000	-¥3.000
arGEN-X	ARGX	670	541%	€10.010	€0.260
Alimera Sciences	ALIM	49626	499%	2.840	-0.040
Mirna Therapeutics	MIRN	3709	446%	7.210	0.110

1 Includes volume from Toronto Stock Exchange (TSX).

2 1-for-60 reverse split: Great Basin on 12/14. Price and volume adjusted to reflect split.

3 Includes volume from London Stock Exchange.

4 Includes volume from TSX Venture Exchange.

## BIOCENTURY 100 ADVANCE-DECLINE TRENDS

Week ended	BC100 Price Level	BC100 Stocks gaining	Gaining vol. (00)	BC100 Stocks declining	Declining vol. (00)
Nov 20	6210.16	69	6459520	31	1934593
Nov 27	6428.09	88	10813197	12	2383981
Dec 04	6243.52	27	3165883	73	5031569
Dec 11	6010.29	12	717879	88	6088142
Dec 18	6189.21	78	7595026	21	1730953

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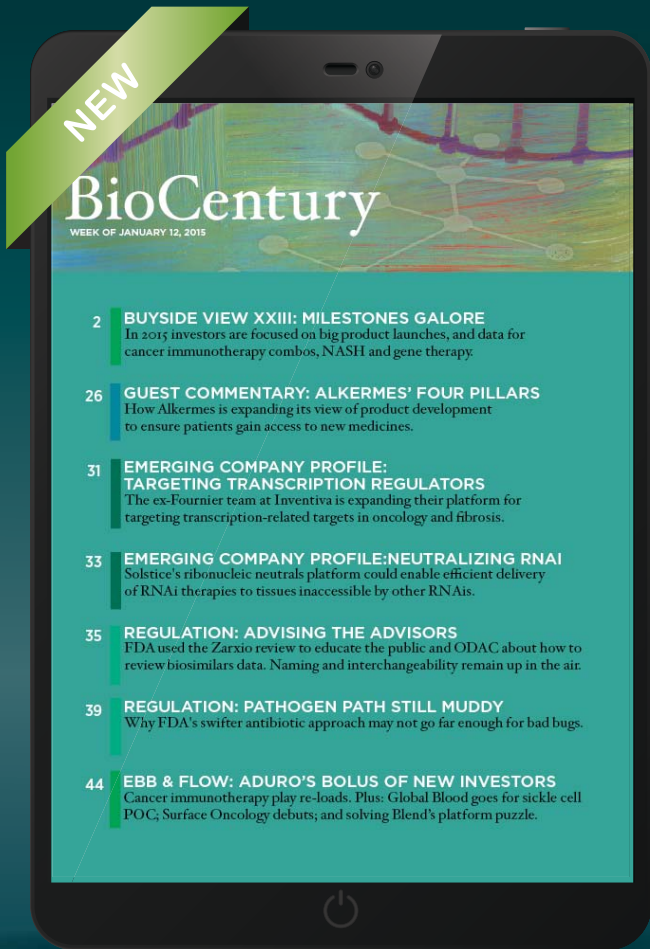
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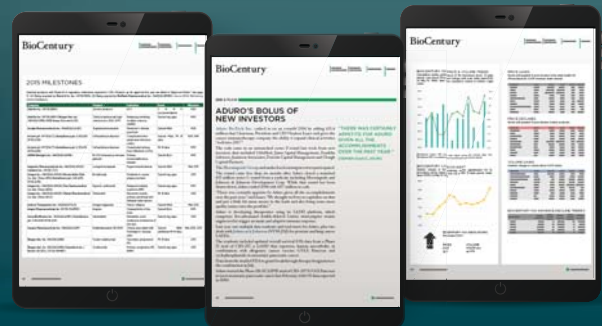
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