# 1NC v. Aadit Greenhill R3

## 1

### DA

#### Infrastructure passes now due to Biden and Pelosi involvement – Biden PC and tight timetables makes the margin for error literally ZERO

Elliott 9-16 (Philip Elliott is a Washington Correspondent for TIME. Before joining TIME in early 2015, he spent almost a decade at The Associated Press, where he covered politics, campaign finance, education and the White House. He is a graduate of the E.W. Scripps School of Journalism at Ohio University, September 16, 2021, accessed on 9-17-2021, Time, "Democrats Face a Grueling Two Weeks as Infighting Erupts Over Infrastructure", https://time.com/6098810/house-democrats-reconciliation/)//babcii

House Democrats yesterday finished penning a 2,600-page bill that **finally outlines the specifics** of their ambitious “soft” infrastructure plan that won’t attract a single Republican vote. But no one was really rushing to Schneider’s for bottles of bubbly. For a party ready to spend $3.5 trillion to fund its social policy agenda, there were plenty of glum faces on Capitol Hill. In fact, one key piece of the legislation—a deal that would finally let Medicare negotiate lower prices with drug companies—fell apart in the Energy and Commerce Committee when three Democrats voted against it. It found resurrection a short time later when Leadership aides literally plucked it from the Energy and Commerce team and delivered it to the Ways and Means Committee for its approval instead. Even there, though, one Democrat voted against it, saying the threat it posed to pharmaceutical companies’ profits would doom it in the Senate. “Every moment we spend debating provisions that will never become law is a moment wasted and will delay much-needed assistance to the American people,” Rep. Stephanie Murphy of Florida later argued. Put another way? Brace **for some nasty politics** over the next two weeks as House Speaker Nancy Pelosi tries to get this bill to a vote before the budget year ends on Sept. 30. And those 2,600 pages had better be recyclable. Democrats can **only afford three defectors** if they want to usher this bill into law, **and they’re perilously close to failure**. So far, five centrist Democrats in the House have said they prefer a scaled-back version of the Medicare component. But if Pelosi gives the five centrists that win, she risks losing the support of progressives who are already sour that things like a punitive wealth tax and the end to tax loopholes aren’t present in the current version of the bill. As it stands now, letting Medicare negotiate drug prices would save the government about $500 billion over the next decade. The scaled-back version doesn’t have an official cost, but a very similar version got its score in the Senate last year: roughly $100 billion in savings. Because Democrats are using a budgeting loophole to help them avoid a filibuster and pass this with bare majorities, that $400 billion gap matters a lot more than on most bills. Scaling back the Medicare savings means they would also have to scale back their overall spending on the bill—a big line in the sand for progressives who say they’ve already compromised too much. All of this, of course, comes as President Joe Biden and his top aides in the White House have been trying to get Senate **centrists onboard**. Just yesterday, he **met separately with Sens. Kyrsten Sinema and Joe Manchin**, fellow Democrats who have expressed worries about the $3.5 trillion price tag but have been vague about what exactly they want to cut back on. With the Senate evenly divided at 50-50, and Vice President Kamala Harris in position to break the ties to Democrats’ victories, any shenanigans from those two independent thinkers scrambles the whole package. Oh, and that other bipartisan infrastructure plan that carries $550 billion in new spending? It’s still sitting on the shelf in the House. Pelosi said she’d bring it to the floor only when the bigger—and entirely partisan—bill was ready. And there’s plenty of grumbling about that package, too. If this is all beginning to sound like a scratched record that keeps repeating, it’s because this has become something of a pattern here in Washington. Things look pretty grim for legislation in town these days, despite Democrats controlling the House, the Senate and the White House. Their margin for error **is literally zero**, and so hiccups from a half-dozen centrists can forewarn a doomed agenda. So far, Pelosi has been a master of holding the line on crucial votes and has managed to maneuver her team to victories, including on an earlier pandemic relief package that passed with only Democratic votes. Now she’s trying again, but the clock is ticking, and $3.5 trillion is an eye-popping sum of money that rivals the spending the United States unleashed to close out World War II.

#### Attacks on Pharmaceutical Profits triggers Mod Dem Backlash – it disrupts unity.

Cohen 9-6 Joshua Cohen 9-6-2021 "Democrats’ Plans To Introduce Prescription Drug Pricing Reform Face Formidable Obstacles" <https://www.forbes.com/sites/joshuacohen/2021/09/06/democrats-plans-to-introduce-prescription-drug-pricing-reform-face-obstacles/?sh=37a269917395> (independent healthcare analyst with over 22 years of experience analyzing healthcare and pharmaceuticals.)//Elmer

There’s considerable uncertainty regarding passage with a simple majority of the 2021 massive budget reconciliation bill. Last week, Senator Joe Manchin called on Democrats to pause pushing forward the budget reconciliation bill. If Manchin winds up saying no to the bill, this would scuttle it as the Democrats can’t afford to lose a single Senator. And, there’s speculation that provisions to reduce prescription drug prices may be watered down and not incorporate international price referencing. Additionally, reduced prices derived through Medicare negotiation may not be able to be applied to those with employer-based coverage. While the progressive wing of the Democratic Party supports drug pricing reform, **several key centrist Democrats** in both the House and Senate appear to be **uncomfortable** **with** particular aspects of the budget reconciliation bill, including a potential deal-breaker, namely the potential **negative impact of drug price controls on the domestic pharmaceutical industry**, as well as long-term patient access to new drugs. A paper released in 2019 by the nonpartisan Congressional Budget Office found that the proposed legislation, H.R. 3, would reduce global revenue for new drugs by 19%, leading to 8 fewer drugs approved in the U.S. between 2020 and 2029, and 30 fewer drugs over the next decade. And, a new report from the CBO reinforces the message that drug pricing legislation under consideration in Congress could lead to fewer new drugs being developed and launched. **Intense lobbying efforts from biopharmaceutical industry groups** **are underway**, **warning of** what they deem are **harms from price controls in** the form of diminished patient **access to new innovations**. The argument, based in part on assumptions and modeling included in the CBO reports, asserts that price controls would dampen investment critical to the biopharmaceutical industry’s pipeline of drugs and biologics. **This** won’t sway most Democrats, but has been a traditional talking point in the Republican Party for decades, and **may convince some centrist Democrats to withdraw backing** of provisions **that** in their eyes **stymie pharmaceutical innovation.** If the budget reconciliation bill would fail to garner a majority, a pared down version of H.R. 3, or perhaps a new bill altogether, with Senator Wyden spearheading the effort, could eventually land in the Senate. But, a similar set of provisos would apply, as majority support in both chambers would be far from a sure thing. In brief, Democrats’ plans at both the executive and legislative branch levels to introduce prescription **drug pricing reform** **encounter challenges** which may prevent impactful modifications from taking place.

#### Sinema specifically jumps Ship.

Hancock and Lucas 20 Jay Hancock and Elizabeth Lucas 5-29-2020 "A Senator From Arizona Emerges As A Pharma Favorite" <https://khn.org/news/a-senator-from-arizona-emerges-as-a-pharma-favorite/> (Senior Correspondent, joined KHN in 2012 from The Baltimore Sun, where he wrote a column on business and finance. Previously he covered the State Department and the economics beat for The Sun and health care for The Virginian-Pilot of Norfolk and the Daily Press of Newport News. He has a bachelor’s degree from Colgate University and a master’s in journalism from Northwestern University.)//Elmer

Sen. Kyrsten **Sinema formed** a **congressional caucus to raise** “**awareness of the benefits of personalized medicine**” in February. Soon after that, employees of **pharmaceutical companies** **donated** $35,000 to her campaign committee. Amgen gave $5,000. So did Genentech and Merck. Sanofi, Pfizer and Eli Lilly all gave $2,500. Each of those companies has invested heavily in personalized medicine, which promises individually tailored drugs that can cost a patient hundreds of thousands of dollars. **Sinema** is a first-term Democrat from Arizona but has nonetheless **emerged as a pharma favorite in Congress** as the industry steers through a new political and economic landscape formed by the coronavirus. She is a **leading recipient of pharma campaign cash** even though she’s not up for reelection until 2024 and lacks major committee or subcommittee leadership posts. For the 2019-20 election cycle through March, political action committees run by employees of drug companies and their trade groups gave her $98,500 in campaign funds, Kaiser Health News’ Pharma Cash to Congress database shows. That stands out in a Congress in which a third of the members got no pharma cash for the period and half of those who did got $10,000 or less. The contributions give companies a chance to cultivate Sinema as she restocks from a brutal 2018 election victory that cost nearly $25 million. Altogether, pharma PACs have so far given $9.2 million to congressional campaign chests in this cycle, compared with $9.4 million at this point in the 2017-18 period, a sustained surge as the industry has responded to complaints about soaring prices. Sinema’s pharma haul was twice that of Sen. Susan Collins of Maine, considered one of the most vulnerable Republicans in November, and approached that of fellow Democrat Steny Hoyer, the powerful House majority leader from Maryland. It all adds up to **a bet by drug companies that** the 43-year-old **Sinema**, first elected to the Senate in 2018, **will** gain influence in coming years and **serve as an industry ally** in a party that also includes many lawmakers harshly critical of high drug prices and the companies that set them.

#### Pharma backlash independently turns Case.

Huetteman 19 Emmarie Huetteman 2-26-2019 “Senators Who Led Pharma-Friendly Patent Reform Also Prime Targets For Pharma Cash” <https://khn.org/news/senators-who-led-pharma-friendly-patent-reform-also-prime-targets-for-pharma-cash/> (former NYT Congressional correspondent with an MA in public affairs reporting from Northwestern University’s Medill School)//Elmer

Early last year, as lawmakers vowed to curb rising drug prices, Sen. Thom Tillis was named chairman of the Senate Judiciary Committee’s subcommittee on intellectual property rights, a committee that had not met since 2007. As the new gatekeeper for laws and oversight of the nation’s patent system, the North Carolina Republican signaled he was determined to make it easier for American businesses to benefit from it — a welcome message to the drugmakers who already leverage patents to block competitors and keep prices high. Less than three weeks after introducing a bill that would make it harder for generic drugmakers to compete with patent-holding drugmakers, Tillis opened the subcommittee’s first meeting on Feb. 26, 2019, with his own vow. “From the United States Patent and Trademark Office to the State Department’s Office of Intellectual Property Enforcement, no department or bureau is too big or too small for this subcommittee to take interest,” he said. “And we will.” In the months that followed, tens of thousands of dollars flowed from pharmaceutical companies toward his campaign, as well as to the campaigns of other subcommittee members — including some who promised to stop drugmakers from playing money-making games with the patent system, like Sen. John Cornyn (R-Texas). Tillis received more than $156,000 from political action committees tied to drug manufacturers in 2019, more than any other member of Congress, a new analysis of KHN’s Pharma Cash to Congress database shows. Sen. Chris Coons (D-Del.), the top Democrat on the subcommittee who worked side by side with Tillis, received more than $124,000 in drugmaker contributions last year, making him the No. 3 recipient in Congress. No. 2 was Sen. Mitch McConnell (R-Ky.), who took in about $139,000. As the Senate majority leader, he controls what legislation gets voted on by the Senate. Neither Tillis nor Coons sits on the Senate committees that introduced legislation last year to lower drug prices through methods like capping price increases to the rate of inflation. Of the four senators who drafted those bills, none received more than $76,000 from drug manufacturers in 2019. Tillis and Coons spent much of last year working on significant legislation that would expand the range of items eligible to be patented — a change that some experts say would make it easier for companies developing medical tests and treatments to own things that aren’t traditionally inventions, like genetic code. They have not yet officially introduced a bill. As obscure as patents might seem in an era of public **outrage** **over** drug prices, the fact that **drugmakers** gave most **to** the **lawmakers working to change the patent system** belies how important securing **the exclusive right to market a drug, and keep competitors at bay, is to their bottom line**. “**Pharma will fight to the death to preserve patent rights**,” said Robin Feldman, a professor at the UC Hastings College of the Law in San Francisco who is an expert in intellectual property rights and drug pricing. “Strong patent rights are central to the games drug companies play to extend their monopolies and keep prices high.” Campaign contributions, closely tracked by the Federal Election Commission, are among the few windows into how much money flows from the political groups of drugmakers and other companies to the lawmakers and their campaigns. Private companies generally give money to members of Congress to encourage them to listen to the companies, typically through lobbyists, whose activities are difficult to track. They may also communicate through so-called dark money groups, which are not required to report who gives them money. Over the past 10 years, the **pharmaceutical industry** has **spent** about $**233 million per year on lobbying**, according to a new study published in JAMA Internal Medicine. That is more than any other industry, including the oil and gas industry. Why Patents Matter Developing and testing a new drug, and gaining approval from the Food and Drug Administration, can take years and cost hundreds of millions of dollars. Drugmakers are generally granted a six- or seven-year exclusivity period to recoup their investments. But drugmakers have found ways to extend that period of exclusivity, sometimes accumulating hundreds of patents on the same drug and blocking competition for decades. One method is to patent many inventions beyond a drug’s active ingredient, such as patenting the injection device that administers the drug. Keeping that arrangement intact, or expanding what can be patented, is where lawmakers come in. Lawmakers Dig In Tillis’ home state of North Carolina is also home to three major research universities and, not coincidentally, multiple drugmakers’ headquarters, factories and other facilities. From his swearing-in in 2015 to the end of 2018, Tillis received about $160,000 from drugmakers based there or beyond. He almost matched that four-year total in 2019 alone, in the midst of a difficult reelection campaign to be decided this fall. He has raised nearly $10 million for his campaign, with lobbyists among his biggest contributors, according to OpenSecrets. Daniel Keylin, a spokesperson for Tillis, said Tillis and Coons, the subcommittee’s top Democrat, are working to overhaul the country’s “antiquated intellectual property laws.” Keylin said the bipartisan effort protects the development and access to affordable, lifesaving medication for patients,” adding: “No contribution has any impact on how [Tillis] votes or legislates.” Tillis signaled his openness to the drug industry early on. The day before being named chairman, he reintroduced a bill that would limit the options generic drugmakers have to challenge allegedly invalid patents, effectively helping brand-name drugmakers protect their monopolies. Former Sen. Orrin Hatch (R-Utah), whose warm relationship with the drug industry was well-known, had introduced the legislation, the Hatch-Waxman Integrity Act, just days before his retirement in 2018. At his subcommittee’s first hearing, Tillis said the members would rely on testimony from private businesses to guide them. He promised to hold hearings on patent eligibility standards and “reforms to the Patent Trial and Appeal Board.” In practice, the Hatch-Waxman Integrity Act would require generics makers challenging another drugmaker’s patent to either take their claim to the Patent Trial and Appeal Board, which acts as a sort of cheaper, faster quality check to catch bad patents, or file a lawsuit. A study released last year found that, since Congress created the Patent Trial and Appeal Board in 2011, it has narrowed or overturned about 51% of the drugmaker patents that generics makers have challenged. Feldman said the drug industry “went berserk” over the number of patents the board changed and has been eager to limit use of the board as much as possible. Patent reviewers are often stretched thin and sometimes make mistakes, said Aaron Kesselheim, a Harvard Medical School professor who is an expert in intellectual property rights and drug development. Limiting the ways to challenge patents, as Tillis’ bill would, does not strengthen the patent system, he said. “You want overlapping oversight for a system that is as important and fundamental as this system is,” he said. As promised, Tillis and Coons also spent much of the year working on so-called Section 101 reform regarding what is eligible to be patented — “a very major change” that “would overturn more than a century of Supreme Court law,” Feldman said. Sean Coit, Coons’ spokesperson, said lowering drug prices is one of the senator’s top priorities and pointed to Coon’s support for legislation the pharmaceutical industry opposes. “One of the reasons Senator Coons is leading efforts in Congress to fix our broken patent system is so that life-saving medicines can actually be developed and produced at affordable prices for every American,” Coit wrote in an email, adding that “his work on Section 101 reform has brought together advocates from across the spectrum, including academics and health experts.” In August, when much of Capitol Hill had emptied for summer recess, Tillis and Coons held closed-door meetings to preview their legislation to stakeholders, including the Pharmaceutical Research and Manufacturers of America, or PhRMA, the brand-name drug industry’s lobbying group. “We regularly engage with members of Congress in both parties to advance practical policy solutions that will lower medicine costs for patients,” said Holly Campbell, a PhRMA spokesperson. Neither proposal has received a public hearing. In the 30 days before Tillis and Coons were named leaders of the revived subcommittee, drug manufacturers gave them $21,000 from their political action committees. In the 30 days following that first hearing, Tillis and Coons received $60,000. Among their donors were PhRMA; the Biotechnology Innovation Organization, the biotech lobbying group; and five of the seven drugmakers whose executives — as Tillis laid out a pharma-friendly agenda for his new subcommittee — were getting chewed out by senators in a different hearing room over patent abuse. Cornyn Goes After Patent Abuse Richard Gonzalez, chief executive of AbbVie Inc., the company known for its top-selling drug, Humira, had spent the morning sitting stone-faced before the Senate Finance Committee as, one after another, senators excoriated him and six other executives of brand-name drug manufacturers over how they price their products. Cornyn brought up AbbVie’s more than 130 patents on Humira. Hadn’t the company blocked its competition? Cornyn asked Gonzalez, who carefully explained how AbbVie’s lawsuit against a generics competitor and subsequent licensing deal was not what he would describe as anti-competitive behavior. “I realize it may not be popular,” Gonzalez said. “But I think it is a reasonable balance.” A minute later, Cornyn turned to Sen. Chuck Grassley (R-Iowa), who, like Cornyn, was also a member of the revived intellectual property subcommittee. This is worth looking into with “our Judiciary Committee authorities as well,” Cornyn said, effectively threatening legislation on patent abuse. The next day, Mylan, one of the largest producers of generic drugs, gave Cornyn $5,000, FEC records show. The company had not donated to Cornyn in years. By midsummer, every drug company that sent an executive to that hearing had given money to Cornyn, including AbbVie. Cornyn, who faces perhaps the most difficult reelection fight of his career this fall, ranks No. 6 among members of Congress in drugmaker PAC contributions last year, KHN’s analysis shows. He received about $104,000. Cornyn has received about $708,500 from drugmakers since 2007, KHN’s database shows. According to OpenSecrets, he has raised more than $17 million for this year’s reelection campaign. Cornyn’s office declined to comment. On May 9, Cornyn and Sen. Richard Blumenthal (D-Conn.) introduced the **Affordable Prescriptions for Patients Act,** which proposed to define two tactics used by drug companies to make it easier for the Federal Trade Commission to **prosecute** them: “**product-hopping**,” when drugmakers withdraw older versions of their drugs from the market to push patients toward newer, more expensive ones, and “**patent-thicketing**,” when drugmakers amass a series of patents to drag out their exclusivity and slow rival generics makers, who must challenge those patents to enter the market once the initial exclusivity ends. **PhRMA opposed the bill.** **The next day, it gave Cornyn $1,000**. Cornyn and Blumenthal’s bill would have been “very tough on the techniques that pharmaceutical companies use to extend patent protections and to keep prices high,” Feldman said. “The **pharmaceutical industry lobbied tooth and nail against it**,” she said. “And **when the bill finally came** out of committee, the strongest provisions — the **patent-thicketing provisions — had been stripped**.” In the months after the bill cleared committee and waited to be taken up by the Senate, Cornyn blamed Senate Democrats for blocking the bill while trying to secure votes on legislation with more direct controls on drug prices. The Senate has not voted on the bill.

#### Infrastructure reform solves Existential Climate Change – it results in spill-over.

USA Today 7-20 7-20-2021 "Climate change is at 'code red' status for the planet, and inaction is no longer an option" <https://www.usatoday.com/story/opinion/todaysdebate/2021/07/20/climate-change-biden-infrastructure-bill-good-start/7877118002/> //Elmer

**Not long ago**, **climate change** for many Americans **was** like **a distant bell**. News of starving polar bears or melting glaciers was tragic and disturbing, but other worldly. Not any more. **Top climate scientists** from around the world **warned of a "code red for humanity**" in a report issued Monday that says severe, human-caused global warming is become unassailable. Proof of the findings by the United Nations' Intergovernmental Panel on Climate Change is a now a factor of daily life. Due to **intense heat waves and drought**, 107 wildfires – including the largest ever in California – are now raging across the West, consuming 2.3 million acres. Earlier this summer, hundreds of people died in unprecedented triple-digit heat in Oregon, Washington and western Canada, when a "heat dome" of enormous proportions settled over the region for days. Some victims brought by stretcher into crowded hospital wards had body temperatures so high, their nervous systems had shut down. People collapsed trying to make their way to cooling shelters. Heat-trapping greenhouse gases Scientists say the event was almost **certainly made worse and more intransigent by human-caused climate change**. They attribute it to a combination of warming Arctic temperatures and a growing accumulation of heat-trapping greenhouse gases caused by the burning of fossil fuels. The **consequences of** what mankind has done to the atmo**sphere are now inescapable**. Periods of **extreme heat** are projected to **double** in the lower 48 states by 2100. **Heat deaths** are far **outpacing every other form of weather killer** in a 30-year average. A **persistent megadrought** in America's West continues to create tinder-dry conditions that augur another devastating wildfire season. And scientists say **warming oceans** are **fueling** ever **more powerful storms**, evidenced by Elsa and the early arrival of hurricane season this year. Increasingly severe weather is causing an estimated $100 billion in damage to the United States every year. "It is honestly surreal to see your projections manifesting themselves in real time, with all the suffering that accompanies them. It is heartbreaking," said climate scientist Katharine Hayhoe. **Rising seas** from global warming Investigators are still trying to determine what led to the collapse of a Miami-area condominium that left more than 100 dead or missing. But one concerning factor is the corrosive effect on reinforced steel structures of encroaching saltwater, made worse in Florida by a foot of rising seas from global warming since the 1900s. The clock is ticking for planet Earth. While the U.N. report concludes some level of severe climate change is now unavoidable, there is still a window of time when far more catastrophic events can be mitigated. But mankind must act soon to curb the release of heat-trapping gases. Global **temperature** has **risen** nearly **2 degrees** Fahrenheit since the pre-industrial era of the late 19th century. Scientists warn that in a decade, it could surpass a **2.7**-degree increase. That's **enough** warming **to cause catastrophic climate changes**. After a brief decline in global greenhouse gas emissions during the pandemic, pollution is on the rise. Years that could have been devoted to addressing the crisis were wasted during a feckless period of inaction by the Trump administration. Congress must act Joe Biden won the presidency promising broad new policies to cut America's greenhouse gas emissions. But Congress needs to act on those ideas this year. Democrats cannot risk losing narrow control of one or both chambers of Congress in the 2022 elections to a Republican Party too long resistant to meaningful action on the climate. So what's at issue? A trillion dollar **infrastructure bill** negotiated between Biden and a group of centrist senators (including 10 Republicans) is a start. In addition to repairing bridges, roads and rails, it would **improve access** by the nation's power infrastructure **to renewable energy sources,** **cap millions of abandoned oil and gas wells spewing greenhouse gases**, **and harden structures against climate change**. It also **offers tax credits for** the **purchase of electric vehicles** and funds the construction of charging stations. (**The nation's largest source of climate pollution are gas-powered vehicles**.) Senate approval could come very soon. Much **more is needed** if the nation is going to reach Biden's necessary goal of cutting U.S. climate pollution in half from 2005 levels by 2030. His ideas worth considering include a federal clean electricity standard for utilities, federal investments and tax credits to promote renewable energy, and tens of billions of dollars in clean energy research and development, including into ways of extracting greenhouse gases from the skies. Another idea worth considering is a fully refundable carbon tax. **The vehicle** for these additional proposals **would be a second infrastructure bill**. And if Republicans balk at the cost of such vital investment, Biden is rightly proposing to pass this package through a process known as budget reconciliation, which allows bills to clear the Senate with a simple majority vote. These are drastic legislative steps. But drastic times call for them. And when Biden attends a U.N. climate conference in November, he can use American progress on climate change as a mean of persuading others to follow our lead. Further delay is not an option.

## 2

### CP

#### CP text: States should add more stringent requirements for filing patents for medicines.

Newsome 17, A [(JD candidate George Washington School of Law). (2017). Side effects of evergreening may include decreased competition & increased prices in the pharmaceutical industry. AIPLA Quarterly Journal, 45(4), 791-822] Justin

The current framework for evaluating a patent application, particularly the requirements of utility and nonobviousness, is insufficient for evaluating whether a secondary patent should be issued for a drug. Given that courts are tied to the low bar for utility and inconsistent with their application of nonobviousness,1 04 it is necessary to pass legislation creating a new utility requirement tailored to secondary pharmaceutical patents. This Note's Author proposes legislation language as follows: 35 U.S.C. § 106: Patentable Pharmaceutical Inventions

(a) Utility requirement for secondary patent: In the case of a pharmaceutical invention claiming an improvement on a patented invention, the applicant shall demonstrate through clear and convincing evidence in the written description that such invention has increased efficacy as compared to the original.

(b) Increased efficacy defined: As used in part (a), "increased efficacy" refers to a proven improvement in the mechanism of action, as disclosed in the patent claims. 0 5

(c) Mechanism of action defined: As used in part (b), "mechanism of action" refers to the process by which a drug functions to produce a therapeutic effect, as disclosed in the patent claims. 06

Under this legislation, the USPTO could grant a secondary patent only if the new formula's mechanism of action, or production of the intended pharmacological effect, in fact improves upon the patented drug's mechanism of action. For example, because VidaDrug is a chemotherapy drug, the new formula must include a change in the mechanism of action which causes an improvement in the efficacy of the drug's tumor-shrinking abilities to be eligible for a secondary patent. A formula tweak that reduces side effects is insufficient, because the underlying purpose of the drug - to treat cancer - remains unaffected.

#### Solves best.

Newsome 17, A [(JD candidate George Washington School of Law). (2017). Side effects of evergreening may include decreased competition & increased prices in the pharmaceutical industry. AIPLA Quarterly Journal, 45(4), 791-822] Justin

Pharmaceutical patents are inherently different from software or manufacturing patents. 144 Pharmaceutical companies create life-saving drugs that carry a very serious benefit for a vulnerable group of consumers - patients. Because of this, the pharmaceutical industry should be held to a higher standard if its companies seek to prohibit affordable generic drugs from coming to the marketplace.

1. An Efficacy-Focused Standard Will Motivate Pharmaceutical Companies to Channel Resources to Creating Real Innovation Pharmaceutical companies argue that patent-life-cycle-management strategies (their preferred name for those tactics described herein as evergreening) are essential to ensuring they recoup R&D costs. 145 However, creation of a standard such as the one proposed here would ensure that pharmaceutical companies are properly incentivized to channel R&D resources to creating measurable change in the drugs, rather than creating minor changes that prolong the time they can profit off of monopolies at the expense of patients. For those industries in which R&D is more productive, like the pharmaceutical industry, "patent procedures should be refined to tighten the relationship between patents and the underlying inventions."14 6

2. A Higher Standard for Secondary Pharmaceutical Patents Will Increase Competition & Lead to Lower Prices The patent system enables pharmaceutical companies to retain market exclusivity for their drugs, allowing them to set high prices without an eye toward competition.1 47 The companies cite the need to recoup R&D costs as the driving factor for their pricing decisions,148 but critics say their main motivation is making a profit.'49 While the pharmaceutical companies' argument may hold weight, high prices for drugs have a negative impact on those patients who need those drugs, but cannot afford them.150 Tightening patent laws to prevent pharmaceutical companies from retaining patent protection for minor changes in their patented drugs will allow other companies to enter the marketplace sooner and drive prices down through competition. 5

## Case

### 1NC – AT: Underview

#### Reject 1AR theory- A] 7-6 time skew means it’s endlessly aff biased B] I don’t have a 3nr which allows for endless extrapolation C] 1AR theory is skewed to the aff because they have a 2ar judge psychology warrant.

#### Reasonability on 1AR shells –it checks 2AR sandbagging by preventing really abusive 1NCs while still giving the 2N a chance.

#### DTA on 1AR shells - They can blow up a blippy 20 second shell to 3 min of the 2AR while I have to split my time and can’t preempt 2AR spin which necessitates judge intervention

### 1NC – AT: Case

#### Feldman [\*\*and Wang\*\*] is a joke.

Risch 17 [Michael; “Data for the Evergreening Debate,” Written Description; 11/21/17; <https://writtendescription.blogspot.com/2017/11/data-for-evergreening-debate.html>] Justin

**Feldman and Wang** argue that the Orange Book has been used by companies to "evergreen" their drugs - that is, to extend exclusivity beyond patent expiration. The paper is on SSRN and the abstract is here:

Why do drug prices remain so high? Even in sub-optimally competitive markets such as health care, one might expect to see some measure of competition, at least in certain circumstances. Although anecdotal evidence has identified instances of evergreening, which can be defined as artificially extending the protection cliff, just how pervasive is such behavior? Is it simply a matter of certain bad actors, to whom everyone points repeatedly, or is the problem endemic to the industry?

This study examines all drugs on the market between 2005 and 2015, identifying and analyzing every instance in which the company added new patents or exclusivities. The results show a startling departure from the classic conceptualization of intellectual property protection for pharmaceuticals. Key results include: 1) Rather than creating new medicines, pharmaceutical companies are recycling and repurposing old ones. Every year, at least 74% of the drugs associated with new patents in the FDA’s records were not new drugs coming on the market, but existing drugs; 2) Adding new patents and exclusivities to extend the protection cliff is particularly pronounced among blockbuster drugs. Of the roughly 100 best-selling drugs, almost 80% extended their protection at least once, with almost 50% extending the protection cliff more than once; 3) Once a company starts down this road, there is a tendency to keep returning to the well. Looking at the full group, 80% of those who added protections added more than one, with some becoming serial offenders; 4) The problem is growing across time.

I think the data the authors have gathered is extremely important, and I think that their study sheds important light on what happens in the pharmaceutical industry. That said, as I explain below, my takeaways from this paper are much different from theirs.

My concerns are fourfold. First, even assuming that every one of the efforts listed by the the study were an attempt to evergreen, I have no sense for whether evergreening actually happened. This study doesn't provide any data about generic entry or pricing. For example, the study describes 13 listings for OxyContin, but I'd bet dollars to donuts that there was plenty of generic oxycodone available. Similarly, many of the new listings are changes from Drug 1.0 to "new and improved!" Drug 2.0. This, of course, has been criticized as anti-competitive (since generics rely on auto-substitution laws), but the study presents no data about whether insurers refuse to pay for Drug 2.0 and instead require the generic, nor does it explain why generics can't do their own advertisements to get doctors to prescribe Drug 1.0.

Second, many of these listings and the new patents that go with them are for advances, like extended release and dissolvables. These can be critically important advances, and they are preferred by consumers. Thus, one person's "evergreening" is another person's innovation. I take extended release drugs (and expensive generic) to avoid side effects and I gave my son dissolvable Prevacid when he wouldn't stop crying with GERD (and was glad for it). Without consumer data or patent data, it is impossible to tell just how much evergreening is going on (or how harmful it is). Now, if these patents are obvious because making them dissolvable or extended is easy, I'm all for stripping protection - but that's a different issue.

Third, the article speaks of orphan drug approvals as if they are a bad thing. This made me bristle, quite frankly. My mother has an extremely rare autoimmune disease that is very painful. I often wondered, isn't there some incentive to develop drugs to treat it? Turns out there is, and though she got no relief, apparently a bunch of other rare diseases did, and that's the whole point behind orphan drug exclusivity. Concern about this exclusivity seems misguided anyway. If it turns out that drug companies are gaming it and nobody actually needs the drug, then the the loss is not too large, because it's a small population and nobody needs the generic anyway. And if it turns out that they do need it, the Orange Book only limits labeling, and doctors are free to prescribe a generic for off-label use. Without evidence that doctors refuse to do so, there's no real evidence that Orphan exclusivity does much harm. In another personal story, my wife was prescribed a generic drug in a different formulation than the patented tablet for off-label use.

Fourth, and most generally, the article speaks of new patents as if there is no innovation. New use discoveries are important. Many of our most important drugs are not for their original uses. As far as I know, generics are not barred from finding new uses and patenting them, either, though admittedly their hands are tied for patient use. So, where the authors see evergreening, I see innovation. Maybe. Maybe it's obvious. But we can't tell that from this high level, and I'm not ready to write it all off as evergreening. It is telling that I was able to provide four personal stories about how supposed evergreening efforts benefited, would have benefited, or did not increase costs for my family or me (and thankfully none of them involved oxycodone).

#### Companies will just obtain a patent in a different sector.

Thomas 15 [John R; Visiting Scholar, CRS; “Tailoring the Patent System for Specific Industries, Congressional Research Service,” CRS; 2015; <https://crsreports.congress.gov/product/pdf/R/R43264/7>] Justin

In view of the concerns noted above, commentators have gone so far to say that “it has become increasingly difficult to believe that a one-size-fits-all approach to patent law can survive.”75 To the extent the current patent system creates a blanket set of rules that apply comparably to distinct industries, it likely over-encourages innovation in some contexts and under-incentivizes it in others.76 Further, some observers have asserted that the need of firms to identify and access the patented inventions of others may differ among industries.77 As a result, the case can be made that distinct industrial, technological, and market characteristics that exist across the breadth of the U.S. economy compel industry-specific patent statutes. However, others have questioned the wisdom and practicality of such line-drawing.78 The following concerns, among others, have been identified:

• Over its long history, the U.S. patent system has flexibly adapted to new technologies such as biotechnology and computer software. Legislative adoption of technology-specific categories may leave unanticipated, cutting-edge technologies outside the patent system.79

• Defining a specific industry or category of technologies may prove to be a contested proposition.

80 • Over time, new industries may emerge and old industries may consolidate. The dynamic nature of the U.S. economy suggests greater need for legislative oversight within a differentiated patent regime.

81 • Even if an industry or technology remains relatively stable, the innovation environment within it might change. For example, technological or scientific advances might open new possibilities for research and development within hidebound industries—but also increase expense and risk for those firms.

82 • Distinct patent rights among industries or technologies may lead to strategic behavior on behalf of patent applicants. For example, a computer program that controls a fuel injector within an automobile could possibly be identified as either an automobile-related or a computer-related invention.

83 •The legislative effort to enact sector-specific patent laws may provide an opportunity for politically savvy firms to exert more lobbying and political power, at the possible expense of less sophisticated firms.

#### Prefer legal studies.

Parker and Mooney 7 [Scott and Kevin; “Is ‘evergreening’ a cause for concern? A legal perspective,” Journal of Commercial Biotechnology; 2007; <https://link.springer.com/article/10.1057/palgrave.jcb.3050066>] Justin

THE LEGAL BACKGROUND The patent system provides an incentive for companies to incur the cost and risk of research by providing the time-limited exclusive right to commercialise a patented product. At the heart of the patent system in the UK (and all other fully TRIPs compliant countries) is the requirement that to qualify for the monopoly right that the patent confers (20 years from the date of filing the patent application) the invention covered by the patent must be novel, non-obvious (ie it involves an inventive step) and capable of industrial application (‘utility’ or ‘usefulness’ in the US). The novelty and inventiveness of the patent is evaluated against the ‘state of the art’, which consists in general of every item of information which has ever been made available to the public by any kind of publication, or by use, anywhere in the world, at any point in time before the first filing date of the patent. It is a basic principle of patent law that once details of a product have entered the public domain (by being published anywhere without patent protection, or when any patents for the product or proposal expire or lapse), then everyone has freedom to use that information and any obvious developments of it. So before assuming that any new development relating to a known compound can be patented, we have to ask: 1 Is this new? Any previous publication or use, no matter how obscure, of the same invention destroys novelty and prevents a patent being issued or, if issued in ignorance of such a publication, this will subsequently cause the patent to be declared invalid if sought to be enforced. 2 Is there an inventive step? A patent cannot be granted for anything which is simply an obvious development or variant on any individual piece of information which is part of the state of the art. It is no answer that the piece of information in question may never have come to the attention of the fictitious ‘person skilled in the art’ who is central to any determination of ‘obviousness’. 3 Is there a proposed industrial application for the invention (in the broad sense of having some useful purpose)? The invention does not have to demonstrate an improvement on what is already known, but it cannot be speculative. It must have a use. For example, a DNA sequence for a recombinant gene fragment with a well-defined function is a patentable invention whereas a DNA sequence alone without any indication of function or of its useful attributes is not. 4 Does the patent describe how to put the invention into effect? The patent must be ‘enabling’; it must add to public knowledge, and contribute in its own right to the state of the art. In this way each new patent moves the frontier of the state of the art forward and makes it more difficult to find improvements which are neither old nor obvious. This disclosure enables third parties to implement the invention once the patent has expired and, is the consideration (in the legal sense) for the monopoly right granted by a patent. HOW THE PATENT SYSTEM DEALS WITH ‘EVERGREENING’ The criteria of patentability set out above apply equally to all inventions from the most basic mechanical patent to the most complex microelectronic or biotechnological invention. Similarly patent law does not distinguish between the invention of a wholly new product and inventions relating to improvements upon an existing product. The same criteria for patentability apply. ‘Double patenting’ is prohibited. That is to say the same invention cannot be covered by more than one patent. Thus for an improvement upon an existing pharmaceutical product to be patentable in its own right it will need to satisfy the criteria of novelty and non-obviousness taking into account the earlier product and all that is known about it in the public domain at the time that the second patent is applied for. If a patent is granted in respect of this improvement it will only cover the improvement to which it relates and will not extend to the originator product. That is to say a patent for a new product in a class will always be broader than any subsequent patent covering an improvement, modification or derivative of that product and so the exclusivity granted is in broad terms commensurate with the scope of the scientific advance that it reflects. An important corollary to the prohibition on ‘double patenting’ is that a patent covering an improved version of a pharmaceutical (or any other) product does not preclude a generic company from copying all forms of the originator product once the patents protecting these forms have expired. For example, if a company selling a patented pharmaceutical reformulates that product as a syrup for paediatric administration and then patents the new formulation, generic competition to the original adult formulation will be possible once the patents covering it expire or are invalidated. The existence of the patent on the paediatric formulation will not delay or prevent generic competition on the original formulation. The innovator company will, however, continue to have the exclusive right to sell the paediatric formulation for the remainder of the life of the patent covering this specific improvement. If in the above example the improvement made is not a paediatric formulation but a slow release formulation that allows once daily dosing and so improves patient compliance as a result of increased convenience, doctors and patients will have a choice between generic versions of the original formulation or the new once-daily product once any patent on the original formulation expires. The patents on the slow release formulation will not delay or prevent marketing of the original formulation. The market will then decide whether the benefits offered by the improved formulation make it worth paying for in the face of cheaper versions of the original product. The answer to this question will inevitably vary from market to market and between different patient populations. Either way the patient would appear to benefit from the increased choice available. A simple and further example of this is ibuprofen. The supermarket shelf carries premium-priced ibuprofen formulations which typically are quicker acting or easier to take than the traditional tablet. These formulations may be patent protected. Customers can, however, decide for themselves whether the added benefit is worth the extra cost. The patents do not prevent anybody from buying the ordinary, cheapest kind of tablet. Reference to patents covering the colour and scoring of tablets has been made in several articles criticising the pharmaceutical industry (without the specific patents that are complained of being identified).4 It is informative to consider how the patent system would apply to such ‘developments’. To the best of the authors’ knowledge no patents have ever been granted for the colour of pharmaceutical products. In fact, since UK patent law (and most others) expressly excludes the patenting of ‘aesthetic creations’ the colour of a pharmaceutical product could only ever be patentable if either: (a) it could be established that the colour itself produces a technical effect, such as a therapeutic benefit caused by increased compliance, that is novel and not obvious; or (b) that the means of obtaining that colour, the manufacturing process of colouring the tablet, is itself novel and not obvious. It goes without saying that for a ‘pink pill’ patent application the technical effect, novelty and inventiveness would be scrutinised carefully. Nevertheless, the application would be looked at on its own facts and applying the patentability criteria described above. Similarly, as regards the scoring of tablets, the same standard of patentability and scrutiny must be satisfied. It would need to be established that tablets had never been scored in this way before and that to do so was not an obvious departure from what has gone before. Without further investigation it should not be assumed that such an invention would be of no value to patients (eg it could be that compliance among children would be improved if the tablet is more cleanly cut as a result of the means of scoring employed). There are plenty of examples of developments (reformulations, new salts, combinations and the like) that have real therapeutic benefit but which at first blush may seem trivial. Again, the more minor that a variation is (eg a pink tablet or means of scoring the tablet) the more narrow the relevant patent protection will be and the easier it should be for a competitor to design around the patent without needing to seek to invalidate it. For example, if a patent is (or has been) granted that covers a particular colour of tablet or a particular means of scoring such tablet then such a patent would not stop a competitor from marketing (respectively) a different colour tablet or a tablet that is not scored or that is scored in a different way. In summary, therefore, the patent system is inherently adapted to reflect how much innovation in fact takes place (by way of improvements to existing technology) and to prevent ‘evergreening’. It allows the use of ‘old’ technology while protecting (and thus providing incentives for) improvements to that technology. Another factor to be taken into account in any debate on the patenting of ‘minor variations’ is that it is not only the company that owns the patents covering the originator product that can patent improvements thereto. Other companies (including generics) can (and do) do this, with the consequence that there may be a number of companies having similar products (some of which may for a variety of reasons be better suited to particular patients) and healthy competition in the marketplace. ‘STRATEGIC PATENTING’ A related charge that is sometimes made against innovator companies is that they file numerous patents on multiple attributes of a single product so as to create a ‘patent thicket’ that so complicates third-party research that it strangles innovation, or that they are guilty of what is sometimes referred to as ‘strategic patenting’.5 Implicit in these charges is that the only reason for filing these patents is maintenance of market share for as long as possible after the expiry of the patents covering the originator product itself. This is a serious charge that deserves to be looked at in more detail. Of course, pharmaceutical and biotechnology companies (like companies in all other R&D-based industries) have patenting strategies. In no other industry is there any suggestion that companies should restrict themselves to patenting inventions that meet some higher standard over and above the basic criteria for patentability or that companies should not seek protection for certain types of technological advance or that exceeding a certain number of patents in a technical area is per se reprehensible. When one considers that intellectual property rights are the life-blood that propels pharmaceutical advances in the private sector (and to an increasing extent in the public sector as well) and takes into account the sums that are typically spent on a new product during the 10–15-year-period from discovery through pre-clinical and clinical trials to regulatory approval and market launch, any company that did not do all that it could to protect its inventions would be acting negligently towards its shareholders. On the subject of patenting strategies in the pharmaceutical industry the UK Patents Court judge Mr Justice Jacob (now Lord Justice Jacob) said in the case of Synthon v SmithKline Beecham ‘I ask myself whether SB have done anything blameworthy…and I cannot see that they have. On the contrary, so far as I can see, they have employed competent and careful patent agents to obtain for them the best patent position which they think they can get. It may be good, it may be bad, but they are doing their job and I see no criticism whatever in the conduct of SB’.6 If one accepts that the nature of pharmaceutical and biotechnological innovation (as with other R&D based industries) is most often incremental and cumulative then it follows that the patent system should reflect this reality. This is indeed the case. As we have seen above, the patent system does not distinguish between ‘breakthroughs’ and ‘incremental improvements’ in terms of the patentability requirements that apply. At the same time a greater reward (a broader patent) is granted in respect of the ground breaking research than for inventions directed at solving further technical hurdles and optimisation of the initial invention. In the experience of the authors most of the patents that have been challenged by generic companies wishing to enter the market were applied for during the development of the originator product rather than once it has been established as a commercial success. This reflects the organic process of drug discovery and development and the time lag between drug discovery development, clinical testing and regulatory approval (ie that inventions are made in overcoming the various technical challenges faced during drug development). Nevertheless, some innovations are made at a later stage. For example, it may be that it is only after the product has been prescribed to a population of patients post-launch that it will become evident that further improvements need to be made to improve efficacy, deal with a compliance (or other) problem or expand the target patient population or disease indications. Such improvements may stem from greater experience of the product, problems unexpectedly encountered in particular patient populations or other advances made in the field. Given that the purpose of the patent system is to encourage innovation and (in the pharmaceutical sector) to lead to better medicines, it would be strange indeed if this incentive was removed or diminished once the first product of a particular type has been launched.

#### Evergreening is good---your authors misunderstand it.

Banana 19 [BananaIP; “DEMYSTIFYING THE EVERGREEN MYTH,” Executive Office of the President of the United States; 7/19/19—originally appeared 5/19/14; [https://www.bananaip.com/ip-news-center/chapter-iii-demystifying-evergreen-myth-comprehending-apprehension-apprehending-comprehension/]](https://www.bananaip.com/ip-news-center/chapter-iii-demystifying-evergreen-myth-comprehending-apprehension-apprehending-comprehension/%5d) Justin

Evergreening is like any other business strategy that market players would adopt to seek a competitive edge in the market. It doesn’t stop anyone from making the product claimed in the expired patent, but only makes sure that they can differentiate themselves from the other generic products through incremental inventions. More often than not, the R&D efforts and investments that go into the making of these incremental inventions can be very high and their results invaluable for treatment.

One of the rationales of the patent system is to incentivize innovation which is believed to lead to the progress in technology. A patent application is published 18 months after it is filed so as to ensure that the knowledge in the patent is made public for aspiring inventors to design around and build on it. Anyone, including the owner of an existing patent and their competitors, is free to invest in research in this direction as early as 18 months from the filing of such a patent. If a competitor files for an incremental patent, it is branded as innovation, but when a patent holder files for an incremental patent, it is looked upon as innovation leading to life cycle management or Evergreening.

In most parts of the world, life cycle management is considered as positive development. However, to the frustration of many pharmaceutical companies, symbolically represented by Bayer, life cycle management is quite a tricky business in India, thanks to the infamous Section 3(d) of the Indian Patent Act, often alluded to as the anti-evergreening law, which bears the burden of keeping a check on incremental pharmaceutical inventions that add no therapeutic value. Section 3(d) states that “the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance, or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus, unless such known process results in a new product or employs at least one new reactant” is not patentable.

#### Pharma drug innovation is high now – eliminating patent protections collapses incentives.

The Economist 20 5-23-2020 "Drug innovation is back in fashion" <https://www.economist.com/leaders/2020/05/23/drug-innovation-is-back-in-fashion> (The Economist is an international weekly newspaper printed in magazine-format and published digitally that focuses on current affairs, international business, politics, and technology.)//Elmer

For much of the past two decades big pharma has been a lost cause. Despised by the public, it became notorious for price-gouging, secretiveness and its neglect of global health problems. Big pharma also lost its lustre with investors, despite its bumper profits. They worried that a business model that relied too much on rent-seeking and too little on innovation was unsustainable, and that citizens would eventually revolt and demand more regulation—or even rip up the patent system that gives drugs firms a temporary monopoly over new medicines. As a result, in the five years before the covid crisis the pharmaceutical sector lagged behind America’s s&p 500 index. The pandemic has reminded the world of the industry’s strengths—its capacity to **innovate and provide drugs on a vast scale**. Many of the big firms, such as Johnson & Johnson and Sanofi, are working on covid-19 vaccines and therapies. Scores of smaller companies are at work, too. On May 18th Moderna, an American biotech firm, said that its much-anticipated vaccine has shown positive early results (although some analysts questioned the validity of its tests). AstraZeneca, a big British firm that invests heavily in research and development (r&d), is working on a vaccine with scientists at Oxford University, helped by $1bn of new funding from America’s government. Even before the virus, the industry had started to **invest more heavily**. In the most recent quarter America’s 30 biggest firms boosted their r&d by a median of **6%** year on year. Now medical **innovation is back in fashion.** It looks like big pharma’s moment to shine. However, the pandemic has also created new ethical and political dilemmas. Vaccine nationalism is spreading as governments panic that others may get their hands on crucial drugs first. France’s Sanofi has found itself embroiled in a transatlantic row over who will be first to get any covid-19 vaccine it develops. Paul Hudson, the firm’s boss, stated last week that because the American government invested in his firm’s risky scientific efforts, the United States would have early access. This led to a political explosion in France and a dressing-down from Emmanuel Macron, France’s president. And there is mounting pressure to suspend elements of the patent system. A gathering of the World Health Organisation this week passed a resolution urging drugs firms to pool patent rights. Several dozen current and former world leaders released an open letter demanding that any successful covid-19 vaccine should be made available patent-free. There is an alternative to beggar-thy-neighbour nationalism and taking a sledgehammer to the intellectual-property regime. First, a global agreement is needed to govern the manufacture and distribution of a potential vaccine. It could take several years to vaccinate the world’s population; global co-operation will mean that the vaccine is deployed first where it brings most benefit. Second, the patent system should be preserved because, correctly designed, it **incentivises investment in new treatments**. The big drugs firms have already said they will make any **vaccine available at cost-plus prices**. Arrangements exist for tiered pricing of medicines and free vaccinations for diseases afflicting the world’s poor that should be extended to covid-19 treatments. If a smaller drugs firm tried to price-gouge, governments in the West and elsewhere have the powers to pass compulsory licensing orders in an emergency. When the pandemic passes, there must be no going back to the bad old days. Governments should seek to authorise new drug patents faster, as the best way to balance innovation and lower prices. And big pharma needs to keep investing. That will help shareholders and global public health, too.

#### Strong IP protection are the only incentive for drug innovation.

* Answers Evergreening/Me-Too Drugs

Stevens and Ezell 20 Philip Stevens and Stephen Ezell 2-3-2020 "Delinkage Debunked: Why Replacing Patents With Prizes for Drug Development Won’t Work" <https://itif.org/publications/2020/02/03/delinkage-debunked-why-replacing-patents-prizes-drug-development-wont-work> (Philip founded Geneva Network in 2015. His main research interests are the intersection of intellectual property, trade, and health policy. Formerly he was an official at the World Intellectual Property Organization (WIPO) in Geneva, where he worked in its Global Challenges Division on a range of IP and health issues. Prior to his time with WIPO, Philip worked as director of policy for International Policy Network, a UK-based think tank, as well as holding research positions with the Adam Smith Institute and Reform, both in London. He has also worked as a political risk consultant and a management consultant. He is a regular columnist in a wide range of international newspapers and has published a number of academic studies. He holds degrees from the London School of Economics and Durham University (UK).)//Elmer

The **Current System** Has **Produced a Tremendous Amount of Life-Sciences Innovation** The frontier for biomedical innovation is seemingly limitless, and the challenges remain numerous—whether it comes to diseases that afflict millions, such as cancer or malaria, or the estimated 7,000 rare diseases that afflict fewer than 200,000 patients.24 And while certainly citizens in developed and developing nations confront differing health challenges, those challenges are increasingly converging. For instance, as of this year, analysts expect that **noncommunicable** diseases such as cardiovascular disease and diabetes will account for 70 percent of natural fatalities **in developing countries**.25 Citizens of low- and middle-income countries bear 80 percent of the world’s death burden from cardiovascular disease.26 Forty-six percent of Africans over 25 suffer from hypertension, more than anywhere else in the world. Similarly, 85 percent of the disease burden of cervical cancer is borne by individuals living in low- and middle-income countries.27 To develop treatments or cures for these conditions, novel biomedical innovation **will be needed from everywhere**. Yet tremendous progress has been made in recent decades. To tackle these challenges, the global pharmaceutical industry invested over **$1.36 trillion in R&D** in the decade from 2007 to 2016—and it’s expected that annual R&D investment by the global pharmaceutical industry will reach $181 billion by 2022.28 In no small part due to that investment, **943 new active substances have been introduced** globally over the prior 25 years.29 The U.S. Food and Drug Administration (FDA) has approved more than **500 new medicines since 2000** alone. And these medicines are getting to more individuals: Global medicine use **in 2020 will reach 4.5 trillion doses**, up 24 percent from 2015.30 Moreover, there are an estimated 7,000 new medicines under development globally (about half of them in the United States), with 74 percent being potentially first in class, meaning they use a new and unique mechanism of action for treating a medical condition.31 In the United States, over 85 percent of all drugs sold are generics (only 10 percent of U.S. prescriptions are filled by brand-name drugs).32 And while some assert that biotechnology companies focus too often on “me-too” drugs that compete with other treatments already on the market, the reality is many drugs currently under development are meant to tackle some of the **world’s most intractable diseases**, **including cancer and Alzheimer’s**.33 Moreover, such arguments miss that many of the drugs developed in recent years have in fact been first of their kind. For instance, in 2014, the FDA approved **41 new medicines** (at that point, the most since 1996) many of which were first-in-class medicines.34 In that year, 28 of the 41 drugs approved were considered biologic or specialty agents, and 41 percent of medicines approved were intended to treat rare diseases.35 Yet even when a new drug isn’t first of its kind, it can still produce benefits for patients, both through **enhanced clinical efficacy** (for instance, taking the treatment as a pill rather than an injection, with a superior dosing regimen, **or better treatment** for some individuals who don’t respond well to the original drug) and by generating competition that exerts downward price pressures. For example, a patient needing a cholesterol drug has a host of statins from which to choose, which is important because some statins produce harmful side effects for some patients. Similarly, patients with osteoporosis can choose from Actonel, Boniva, or Fosomax. Or take for example Hepatitis C, which until recently was an incurable disease eventually requiring a liver transplant for many patients. In 2013, a revolutionary new treatment called Solvadi was released that boosted cure rates to 90 percent. This was followed in 2014 by an improved treatment called Harvoni, which cures the Hepatitis C variant left untouched by Solvadi. Since then, an astonishing six new treatments for the disease have received FDA approval, opening up a wide range of treatment options that take into account patients’ liver and kidney status, co-infections, potential drug interactions, previous treatment failures, and the genotype of HCV virus.36 “If you have to have Hepatitis C, now is the time to have it,” as Douglas Dieterich, a liver specialist at the Icahn School of Medicine at Mount Sinai Hospital in New York, told the Financial Times. “We have these marvellous drugs we can treat you with right now, without side effects,” he added. “And this time next year, we’ll have another round of drugs available.”37 Moreover, the financial potential of this new product category has led to multiple competing products entering the market in quick succession, in turn placing downward pressure on prices.38 As Geoffrey Dusheiko and Charles Gore write in The Lancet, “The market has done its work for HCV treatments: after competing antiviral regimens entered the market, competition and innovative price negotiations have driven costs down from the initially high list prices in developed countries.”39 As noted previously, opponents of the current market- and IP-based system contend patents enable their holders to exploit a (temporary) market monopoly by inflating prices many multiples beyond the marginal cost of production. But rather than a conventional neoclassical analysis, an analysis based on “innovation economics” finds it is exactly this “distortion” that is required for innovation to progress. As William Baumol has pointed out, “Prices above marginal costs and price discrimination become the norm rather than the exception because … without such deviations from behaviour in the perfectly competitive model, innovation outlays and other unavoidable and repeated sunk outlays cannot be recouped.”40 Or, as the U.S. Congressional Office of Technology Assessment found, “Pharmaceutical R&D is a risky investment; therefore, high financial returns are necessary **to induce companies to invest** in researching new chemical entities.”41 This is also why, in 2018, the U.S. Congressional Budget Office estimated that because of high failure rates, biopharmaceutical **companies would need to earn a 61.8 percent rate of return on their successful new drug R&D projects in order to match a 4.8 percent after-tax rate of return on their investment**s.42 Indeed, **it’s the ability to recoup fixed costs, not just marginal** costs, through mechanisms such as patent protection that lies at the heart of all innovation-based industries and indeed all innovation and related economic progress. If companies could not find a way to pay for their R&D costs, and could only charge for the costs of producing the compound, **there would be no new drugs developed**, just as there would be no new products developed in any industry. Innovating in the life sciences remains expensive, risky, difficult, and uncertain. Just 1 in 5,000 drug candidates make it all the way from discovery to market.43 A 2018 study by the Deloitte Center for Health Solutions, “Unlocking R&D productivity: Measuring the return from pharmaceutical innovation 2018,” found that “the average cost to develop an asset [an innovative life-sciences drug] including the cost of failure, has increased in six out of eight years,” and that the average cost to create a new drug has risen to $2.8 billion.44 Related research has found the development of new drugs requires years of painstaking, risky, and expensive research that, for a new pharmaceutical compound, takes an average of 11.5 to 15 years of research, development, and clinical trials, at a cost of $1.7 billion to $**3.2 billion**.45 IP rights—including patents, copyrights, and data exclusivity protections—give innovators, whether in the life sciences or other sectors, the **confidence** to undertake the risky and expensive process of innovation, secure in the knowledge they’ll be able to capture a share of the gains from their efforts. And these gains are often only a small fraction of the true value created. For instance, Yale University economist William Nordhaus estimated inventors capture just 4 percent of the total social gains from their innovations; the rest spill over to other companies and society as a whole.46 Without adequate IP protection, private investors would never find it viable to fund advanced research because lower-cost copiers would be in a position to undercut the legitimate prices (and profits) of innovators, even while still generating substantial profits on their own.47 As the report “Wealth, Health and International Trade in the 21st Century” concludes, “Conferring robust intellectual property rights is, in the pharmaceutical and other technological-development contexts, **in the global public’s long-term interests.** Without adequate mechanisms for directly and indirectly securing the private and public funding of medicines and vaccines, research and development communities across the world will lose future benefits that would far outweigh the development costs involved.”48 Put simply, the current market- and IP-based life-sciences innovation system is producing life-changing biomedical innovation. As Jack Scannell, a senior fellow at Oxford University’s Center for the Advancement of Sustainable Medical Innovation has explained, “I would guess that one can buy today, at rock bottom generic prices, a set of small-molecule drugs that has greater medical utility than the entire set available to anyone, anywhere, at any price in 1995.” He continued, “Nearly all the generic medicine chest was created by firms who invested in R&D to win future profits that they tried pretty hard to maximize; short-term financial gain building a long-term common good.”49 For example, on September 14, 2017, the FDA approved Mvasi, the first biosimilar for Roche’s Avastin, a breakthrough anticancer drug when it came out in the mid-1990s for lung, cervical, and colorectal cancer.50 In other words, a medicine to treat forms of cancer that barely existed 20 years ago is now available as a generic drug today. It’s this dynamic that enables us to imagine a situation wherein drugs to treat diseases that aren’t available anywhere at any price today (for instance, treatments for Alzheimer’s or Parkinson’s) might be available as generics in 20 years. But that will only be the case if we preserve (and improve where possible) a life-sciences innovation system that is generally working. The current system does not require wholesale replacement by a prize-based system that—notwithstanding a meaningful success here or there—has produced nowhere near a similar level of novel biomedical innovation.

#### Secondary and Follow-on patents are key to innovation.

IP Watch 18 9-21-2018 "Inside Views: Why Follow-On Pharmaceutical Innovations Should Be Eligible For Patent Protection" <https://www.ip-watch.org/2018/09/21/follow-pharmaceutical-innovations-eligible-patent-protection/> (a non-profit independent news service that provides professional coverage of global policymaking on intellectual property and innovation.)//Elmer

Why Protect Follow-On Innovation? The **attack on secondary** pharmaceutical **patents is based** in part **on** the **flawed premise** that **follow-on innovation is of marginal value** at best, and thus less deserving of protection than the primary inventive act of identifying and validating a new drug active ingredient. In fact, **follow-on innovation** **can play** a **critical role in transforming** **an interesting drug candidate into a safe and effective treatment option** for patients. A good example can be seen in the case of **AZT** (zidovudine), a drug ironically described in the Guidelines as the “first breakthrough in AIDS therapy.” AZT **began** its life **as a** failed attempt at a **cancer drug**, and it was **only years later** that its potential **application in the fight against AIDS** was realized. Follow-on research resulted in a method-of-use patent directed towards the use of AZT in the treatment of AIDS, and it was this patent that incentivized the investment necessary to bridge the gap between a promising drug candidate and a safe, effective, and FDA-approved pharmaceutical. Significantly, because of the long lag time between the first public disclosure of AZT and the discovery of its use in the treatment of AIDS, patent protection for the molecule per se was unavailable. In a world where follow-on innovation is unpatentable, there would have been no patent incentive to invest in the development of the drug, and without that incentive AZT might have languished on the shelf as simply one more failed drug candidate. Other examples of important drugs that likely never would have been made available to patients without the availability of a “secondary” patent include **Evista** (raloxifene, used in the treatment of osteoporosis and to reduce the risk of invasive breast cancer), **Zyprexa** (olanzapine, used in the treatment of schizophrenia), and an orally-administrable formulation of the antibiotic cefuroxime. **Pharmaceutical development** **is prolonged and unpredictable**, and frequently **a safe and effective drug** **occurs only as a result of** **follow-on innovation** occurring **long** **after the initial synthesis** and characterization of a pharmaceutically interesting chemical compound. The inventions protected by secondary patents can be just as critical to the development of drugs as a patent on the active ingredient itself. The Benefits of Follow-On Innovation The criticism of patents on follow-on pharmaceutical innovation rests on an assumption that follow-on innovation provides little if any benefit to patients, and merely serves as a pretense for extending patent protection on an existing drug. In fact, there are many examples of follow-on products that represent significant improvements in the safety-efficacy profile. For example, the original formulation of Lumigan (used to treat glaucoma) had an unfortunate tendency to cause severe hyperemia (i.e., redeye), and this adverse event often lead patients to stop using the drug, at times resulting in blindness. Subsequent research led to a new formulation which largely alleviated the problem of hyperemia, an example of the type of follow-on innovation that significantly benefits patients but that which would be discouraged by a patent regime that does not reward follow-on innovation. Follow-on pharmaceutical innovation can come in the form of an extended-release formulation that permits the drug to be administered at less frequent intervals than the original formulation. Critics of secondary patents downplay the significance of extended-release formulations, claiming that they represent nothing more than a ploy to extend patent protection without providing any real benefit to patients. In fact, the availability of a drug that can be taken once a day has been shown to improve patient compliance, a significant issue with many drugs, particularly in the case of drugs taken by patients with dementia or other cognitive impairments. Extended-release formulations can also provide a more consistent dosing throughout the day, avoiding the peaks and valleys in blood levels experienced by patients forced to take an immediate-release drug multiple times a day. Other examples of improved formulations that provide real benefits to patients are orally administrable formulations of drugs that could previously only be administered by more invasive intravenous or intramuscular injection, combination products that combine two or more active pharmaceutical agents in a single formulation (resulting in improved patient compliance), and a heat-stable formulation of a lifesaving drug used to treat HIV infection and AIDS (an important characteristic for use in developing countries with a hot climate).

### 1NC – AT: Feldman

#### 1] Indict their Feldman evidence – the underlying research ignores key factors

Risch 17

[Michael; “Data for the Evergreening Debate,” Written Description; 11/21/17; <https://writtendescription.blogspot.com/2017/11/data-for-evergreening-debate.html>] Justin -recut CAT

The Orange Book is a list of drugs and pharmaceuticals that the U.S. Food and Drug Administration ([FDA](https://www.investopedia.com/terms/f/fda.asp)) has approved as both safe and effective. Although it is commonly called the Orange Book, its formal name is Approved Drug Products with Therapeutic Equivalence Evaluations.

**Feldman and Wang** argue that the Orange Book has been used by companies to "evergreen" their drugs - that is, to extend exclusivity beyond patent expiration. The paper is on SSRN and the abstract is here:

Why do drug prices remain so high? Even in sub-optimally competitive markets such as health care, one might expect to see some measure of competition, at least in certain circumstances. Although anecdotal evidence has identified instances of evergreening, which can be defined as artificially extending the protection cliff, just how pervasive is such behavior? Is it simply a matter of certain bad actors, to whom everyone points repeatedly, or is the problem endemic to the industry?

This study examines all drugs on the market between 2005 and 2015, identifying and analyzing every instance in which the company added new patents or exclusivities. The results show a startling departure from the classic conceptualization of intellectual property protection for pharmaceuticals. Key results include: 1) Rather than creating new medicines, pharmaceutical companies are recycling and repurposing old ones. Every year, at least 74% of the drugs associated with new patents in the FDA’s records were not new drugs coming on the market, but existing drugs; 2) Adding new patents and exclusivities to extend the protection cliff is particularly pronounced among blockbuster drugs. Of the roughly 100 best-selling drugs, almost 80% extended their protection at least once, with almost 50% extending the protection cliff more than once; 3) Once a company starts down this road, there is a tendency to keep returning to the well. Looking at the full group, 80% of those who added protections added more than one, with some becoming serial offenders; 4) The problem is growing across time.

I think the data the authors have gathered is extremely important, and I think that their study sheds important light on what happens in the pharmaceutical industry. That said, as I explain below, my takeaways from this paper are much different from theirs. My concerns are fourfold. First, even assuming that every one of the efforts listed by the the study were an attempt to evergreen, I have no sense for whether evergreening actually happened. This study doesn't provide any data about generic entry or pricing. For example, the study describes 13 listings for OxyContin, but I'd bet dollars to donuts that there was plenty of generic oxycodone available. Similarly, many of the new listings are changes from Drug 1.0 to "new and improved!" Drug 2.0. This, of course, has been criticized as anti-competitive (since generics rely on auto-substitution laws), but the study presents no data about whether insurers refuse to pay for Drug 2.0 and instead require the generic, nor does it explain why generics can't do their own advertisements to get doctors to prescribe Drug 1.0. Second, many of these listings and the new patents that go with them are for advances, like extended release and dissolvables. These can be critically important advances, and they are preferred by consumers. Thus, one person's "evergreening" is another person's innovation. I take extended release drugs (and expensive generic) to avoid side effects and I gave my son dissolvable Prevacid when he wouldn't stop crying with GERD (and was glad for it). Without consumer data or patent data, it is impossible to tell just how much evergreening is going on (or how harmful it is). Now, if these patents are obvious because making them dissolvable or extended is easy, I'm all for stripping protection - but that's a different issue. Third, the article speaks of orphan drug approvals as if they are a bad thing. This made me bristle, quite frankly. My mother has an extremely rare autoimmune disease that is very painful. I often wondered, isn't there some incentive to develop drugs to treat it? Turns out there is, and though she got no relief, apparently a bunch of other rare diseases did, and that's the whole point behind orphan drug exclusivity. Concern about this exclusivity seems misguided anyway. If it turns out that drug companies are gaming it and nobody actually needs the drug, then the the loss is not too large, because it's a small population and nobody needs the generic anyway. And if it turns out that they do need it, the Orange Book only limits labeling, and doctors are free to prescribe a generic for off-label use. Without evidence that doctors refuse to do so, there's no real evidence that Orphan exclusivity does much harm. In another personal story, my wife was prescribed a generic drug in a different formulation than the patented tablet for off-label use. Fourth, and most generally, the article speaks of new patents as if there is no innovation. New use discoveries are important. Many of our most important drugs are not for their original uses. As far as I know, generics are not barred from finding new uses and patenting them, either, though admittedly their hands are tied for patient use. So, where the authors see evergreening, I see innovation. Maybe. Maybe it's obvious. But we can't tell that from this high level, and I'm not ready to write it all off as evergreening. It is telling that I was able to provide four personal stories about how supposed evergreening efforts benefited, would have benefited, or did not increase costs for my family or me (and thankfully none of them involved oxycodone).

#### 2] Turn the link – Secondary patents are key to innovation – that means the 1AC is taking a sledgehammer to 80% of all innovation

IP Watch 18 9-21-2018 "Inside Views: Why Follow-On Pharmaceutical Innovations Should Be Eligible For Patent Protection" <https://www.ip-watch.org/2018/09/21/follow-pharmaceutical-innovations-eligible-patent-protection/> (a non-profit independent news service that provides professional coverage of global policymaking on intellectual property and innovation.)//Elmer -recut CAT

Why Protect Follow-On Innovation? The attack on secondary pharmaceutical patents is based in part on the flawed premise that follow-on innovation is of marginal value at best, and thus less deserving of protection than the primary inventive act of identifying and validating a new drug active ingredient. In fact, follow-on innovation can play a critical role in transforming an interesting drug candidate into a safe and effective treatment option for patients. A good example can be seen in the case of AZT (zidovudine), a drug ironically described in the Guidelines as the “first breakthrough in AIDS therapy.” AZT began its life as a failed attempt at a cancer drug, and it was only years later that its potential application in the fight against AIDS was realized. Follow-on research resulted in a method-of-use patent directed towards the use of AZT in the treatment of AIDS, and it was this patent that incentivized the investment necessary to bridge the gap between a promising drug candidate and a safe, effective, and FDA-approved pharmaceutical. Significantly, because of the long lag time between the first public disclosure of AZT and the discovery of its use in the treatment of AIDS, patent protection for the molecule per se was unavailable. In a world where follow-on innovation is unpatentable, there would have been no patent incentive to invest in the development of the drug, and without that incentive AZT might have languished on the shelf as simply one more failed drug candidate. Other examples of important drugs that likely never would have been made available to patients without the availability of a “secondary” patent include **Evista** (raloxifene, used in the treatment of osteoporosis and to reduce the risk of invasive breast cancer), **Zyprexa** (olanzapine, used in the treatment of schizophrenia), and an orally-administrable formulation of the antibiotic cefuroxime. **Pharmaceutical development** **is prolonged and unpredictable**, and frequently **a safe and effective drug** **occurs only as a result of** **follow-on innovation** occurring **long** **after the initial synthesis** and characterization of a pharmaceutically interesting chemical compound. The inventions protected by secondary patents can be just as critical to the development of drugs as a patent on the active ingredient itself. The Benefits of Follow-On Innovation The criticism of patents on follow-on pharmaceutical innovation rests on an assumption that follow-on innovation provides little if any benefit to patients, and merely serves as a pretense for extending patent protection on an existing drug. In fact, there are many examples of follow-on products that represent significant improvements in the safety-efficacy profile. For example, the original formulation of Lumigan (used to treat glaucoma) had an unfortunate tendency to cause severe hyperemia (i.e., redeye), and this adverse event often lead patients to stop using the drug, at times resulting in blindness. Subsequent research led to a new formulation which largely alleviated the problem of hyperemia, an example of the type of follow-on innovation that significantly benefits patients but that which would be discouraged by a patent regime that does not reward follow-on innovation. Follow-on pharmaceutical innovation can come in the form of an extended-release formulation that permits the drug to be administered at less frequent intervals than the original formulation. Critics of secondary patents downplay the significance of extended-release formulations, claiming that they represent nothing more than a ploy to extend patent protection without providing any real benefit to patients. In fact, the availability of a drug that can be taken once a day has been shown to improve patient compliance, a significant issue with many drugs, particularly in the case of drugs taken by patients with dementia or other cognitive impairments. Extended-release formulations can also provide a more consistent dosing throughout the day, avoiding the peaks and valleys in blood levels experienced by patients forced to take an immediate-release drug multiple times a day. Other examples of improved formulations that provide real benefits to patients are orally administrable formulations of drugs that could previously only be administered by more invasive intravenous or intramuscular injection, combination products that combine two or more active pharmaceutical agents in a single formulation (resulting in improved patient compliance), and a heat-stable formulation of a lifesaving drug used to treat HIV infection and AIDS (an important characteristic for use in developing countries with a hot climate).

### 1NC – AT: Arnold Ventures

#### 1] Calling this the “only major study” ev is power-tagged. It’s a case study of one drug, and it’s not the only one—there are tons of examples of valuable incremental innovations critical to healthcare accessibility

Jones 6

Nigel Jones (International Chamber of Commerce; Barrister for Gatehouse Chambers). “The importance of incremental innovation for development.” Submission to the World Health Organization’s Commission on Intellectual Property Rights, Innovation and Public Health. March 2006. JDN. <https://www.lesi.org/publications/les-nouvelles/les-nouvelles-online/2006-2015/2006/march-2006/2011/08/08/the-importance-of-incremental-innovation-for-development>

Wyeth is a research-based pharmaceutical company that funnels a significant percentage of its revenue each year to research and develop new drugs and new therapies for treating diseases. In the 1980s, Wyeth researchers developed venlafaxine as an **unprecedented antidepressant** that works by selectively inhibiting the neuronal reuptake of serotonin and norepinephrine, two naturally occurring neurotransmitters that have been implicated in depression and other mental disorders. Wyeth scientists recognized venlafaxine’s promise as an important antidepressant medication and pressed forward with its development. Wyeth launched venlafaxine for the treatment of depression in the United States in early 1994 under the trade name Effexor®. As originally launched, Effexor® was an immediate release dosage form. Although effective, it was not used in a wide-spread manner, primarily due to the side effects of nausea and vomiting. Patients who could benefit from this unique drug were deprived of an effective therapy due to these side effects. Wyeth researchers worked to develop an extended-release formulation that could provide adequate blood plasma levels of venlafaxine such that it could be taken once a day. **This was a significant advance involving a sufficient inventive step to warrant a patent**, since it was unknown if a once-a-day formulation would be therapeutically effective. Not only did Wyeth’s research result in a formulation that could be administered once-a-day while maintaining efficacy, thereby making it more convenient for patients and improving compliance, but it also unexpectedly reduced side effects, such as nausea and emesis, as compared to the immediate release formulation. Venlafaxine is now widely prescribed because patients are able to adhere to the dosing regimen and tolerate therapeutic blood levels without lengthy and severe nausea. The ability of patients to benefit from the power of venlafaxine is to a large extent attributable to the efforts of Wyeth’s work on the extended release formulation. Had Wyeth stopped its research efforts after discovering venlafaxine and launching Effexor®, **the true potential** of this drug **would never have been realized.**

#### 2] Here’s an empirical example – in 2021 we just patented a combined anthrax and smallpox vaccine based on incremental changes from a prior vaccine.

Park et al 21

Deok Bum Park, Bo-Eun Ahn, Hosun Son, Young-Ran Lee, Yu-Ri Kim, Su Kyoung Jo, Jeong-Hoon Chun, Jae-Yon Yu, Myung-Min Choi & Gi-eun Rhie Construction of a bivalent vaccine against anthrax and smallpox using the attenuated vaccinia virus KVAC103 BMC Microbiology volume 21, Article number: 76 (2021) <https://bmcmicrobiol.biomedcentral.com/articles/10.1186/s12866-021-02121-5> -CAT

Anthrax and smallpox are high-risk infectious diseases, and considered as potential agents for bioterrorism. To develop an effective countermeasure for these diseases, we constructed a bivalent vaccine against **both anthrax and smallpox** by integrating a gene encoding protective antigen (PA) of Bacillus anthracis to the genome of the attenuated vaccinia virus strain, KVAC103. Results Immunization with this bivalent vaccine induced antibodies against both PA and vaccinia virus in a mouse model. We also observed that the efficacy of this vaccine can be enhanced by combined immunization with immunoadjuvant-expressing KVAC103. Mouse groups co-immunized with PA-expressing KVAC103 and either interleukin-15 (IL-15) or cholera toxin subunit A (CTA1)-expressing KVAC103 showed increased anti-PA IgG titer and survival rate against B. anthracis spore challenge compared to the group immunized with PA-expressing KVAC103 alone. Conclusions We demonstrated that the attenuated smallpox vaccine KVAC103 is an available platform for a multivalent vaccine and co-immunization of immunoadjuvants can improve vaccine performance. Background Bacillus anthracis and Variola virus are causative agents of anthrax and smallpox, respectively, and representative pathogens that can be possibly utilized as bioterrorism or biological weapons. Development of effective medical countermeasures against these pathogens is a national task of high priority [1, 2]. The biological attack in 2001 by B. anthracis spores via the US postal system has prompted the need to develop vaccines and therapeutics against anthrax [1]. Protective antigen (PA) is one of the major component of anthrax toxin, and also a principal ingredient of two licensed anthrax vaccines, Anthrax Vaccine Adsorbed (AVA) and Anthrax Vaccine Precipitated (AVP) [3]. Recently, a recombinant PA protein vaccine is being developed by Korea Centers for Disease Control (KCDC), and clinical trials are in progress [4, 5]. Although endemic smallpox was declared eradicated since the last case observed in 1977, Variolar virus still remains a potential biological weapon [2], and smallpox vaccines have been stockpiled for strategic use in some nations. To reduce side effects of conventional smallpox vaccines, attenuated vaccinia virus strains have been investigated in various ways [6]. KVAC103 is an attenuated vaccinia virus developed by KCDC [7]. Interleukin-15 (IL-15) is a cytokine involved in the proliferation and maintenance of CD8+ memory T cells, and has been suggested as an effective vaccine adjuvant [8, 9]. Previous studies on HIV-1 vaccine demonstrated that co-immunization of IL-15 strongly increased antigen-specific memory T cells and long-term immunity [10, 11]. Smallpox vaccines with integrated IL-15, tested in a mouse model, showed increased and prolonged cellular and humoral immunity [12]. This IL-15-containing smallpox vaccine also has been applied in a multivalent influenza vaccine [13]. Co-administration of IL-15 with staphylococcal enterotoxin B vaccine increased the number of dendritic cells in a mouse model [14]. Cholera toxin (CT) also has long been investigated as an efficient immunoadjuvant. The toxin is composed of subunit A and B, and subunit A contains two fragments, A1 and A2 [15]. The ADP-ribosyltransferase activity of cholera toxin subunit A1 (CTA1) is known to be important for enhancing immune responses [16]. The effect of CTA1 as an immunoadjuvant has been demonstrated against numerous pathogens, such as influenza A virus, HIV, Helicobacter pylori, and Mycobacterium tuberculosis [17,18,19,20]. Vaccinia virus is a popular platform for gene transfer and multivalent vaccine against various diseases [21, 22]. In a previous study, a dual vaccine for smallpox and anthrax has been developed by inserting PA gene of B. anthracis into Wyeth or modified vaccinia Ankara (MVA) strain [23]. A viral vector system that utilizes KVAC103 as a gene delivery system and a multivalent vaccine has been previously invented [7, 24]. In this study, we constructed a bivalent vaccine candidate against both smallpox and anthrax, by integrating a recombinant anthrax PA-encoding gene into KVAC103, using a viral vector pVVT1-EGFP-C7L. We examined the protective efficacy of KVAC103-derived bivalent vaccine in a mouse model. In addition, we observed that the vaccine supplemented with immunoadjuvant-expressing vaccinia viruses can increase immune response against anthrax. Results A human codon-optimized PA was cloned into viral vector pVVT1 to generate smallpox/anthrax dual vaccine candidate. A signal peptide derived from the tissue plasminogen activator was attached to the N-terminal of PA (thPA). We also constructed viral vector clones encoding a human IL-15 (hIL15) or a human codon-optimized CTA1 (hCTA1) gene. The viral vectors were integrated into the KVAC103 genome by homologous recombination at the thymidine kinase (TK) gene site (Fig. 1). Fig. 1 figure1 A diagram of viral vector construction. Human codon-optimized genes encoding PA with a signal peptide (MDAMKRGLCCVLLLCGAVFVSP) derived from the tissue plasminogen activator polypeptide (thPA), IL-15 (hIL15), or CTA1 (hCTA1) were cloned into pVVT1-EGFP-C7L. The GeneBank sequence ID for PA, IL-15, and CTA1 are AAA22637.1, NP\_000576.1, and CAA24995.1, respectively. The expected molecular weight of integrated thPA, IL-15, and CTA1 are 81 kDa (757 aa), 18 kDa (162 aa), and 29 kDa (258 aa), respectively. Viral vector constructs are integrated into KVAC103 genome by homologous recombination at TK gene site Full size image Protein expression of PA and CTA1 in the dual vaccine candidate viruses were confirmed by immunoblot assay (Fig. 2)a. PA and CTA1 were detected in virus-infected cell lysates. This indicates that cells infected by KVAC-thPA-C7L or KVAC-hCTA1-C7L viruses properly express PA or CTA1, respectively. The IL-15 ELISA result shows that cells infected by KVAC-hIL15-C7L also secreted IL-15 in vitro (Fig. 2b). Fig. 2 figure2 Expression of integrated proteins in vitro. a The expression of PA and CTA1 was detected by immunoblot assay in cell lysates. Vero cells were infected with KVAC-thPA-C7L and KVAC-CTA1-C7L for 48 h, and 50 μg of cell lysates from the infected cells were analyzed. The molecular weights from a size marker are indicated on the left. b The expression level of IL-15 was detected by ELISA. The IL-15 expression levels of infected Vero cells with KVAC103 derivatives were determined by the IL-15 ELISA kit (Biolegend). The bars on the graph indicates means of IL-15 expression levels from duplicated results in the same experiments, and the error bars stand for the standard error of the mean (\*\*\*P < 0.001). NS, not significant. One-way ANOVA was applied for analysis Full size image In a preliminary experiment, we observed that repeated vaccination in 3 week interval increased the anti-PA antibody titer around 10-fold compared to single vaccination (data not shown). The in vivo efficacy of the dual vaccine candidate with or without adjuvant-expressing viruses was estimated in a mouse model (Fig. 3). We immunized A/J mice (n = 8) with our vaccine candidate KVAC-thPA-C7L with or without adjuvant expressing viruses 2 times with a 3-week interval. The anti-PA antibody levels of all groups immunized with KVAC-thPA-C7L were increased compared to the groups immunized with the adjuvant only (KVAC-hIL15-C7L or KVAC-hCTA1-C7L). Mouse groups vaccinated with KVAC-thPA-C7L plus an immunoadjuvant-containing strain (KVAC-hIL15-C7L or KVAC-CTA1-C7L) exhibited higher mean values of antibody titers compared to the group immunized with KVAC-thPA-C7L only (Fig. 3a). Except the two outliers which are extraordinarily high in the group immunized with KVAC-thPA-C7L only in Fig. 3a (29,800 and 30,600), the mean values of anti-PA antibody titer are significantly increased in the mouse groups immunized with both KVAC-tPA-C7L and adjuvant-expressing strains (One-way ANOVA, p value < 0.01). Fig. 3 figure3 Immunogenicity and protective efficacy of the bivalent vaccine with or without adjuvant-expressing viruses in a mouse model. a Anti-PA IgG titers of individual mice in 5 groups (n = 8 for each group) were determined by ELISA. The Y-axis represents EC50 values. The horizontal bars indicate mean of individual groups (for KVAC-thPA-C7L, the mean value calculated except the two outliers). The error bars represent standard error of the mean. The asterisks (\*\*) represent significant differences between indicated groups in statistical analysis (\*\*P < 0.01). NMS, normal mouse sera. b Anti-viral antibody titers were determined by PRNT assay. The Y-axis represents PRNT50, the reciprocal of the dilution factor of sera reducing plaque formation in half. The bars represent arithmetic means of results from two independent assays with pooled sera of individual groups (eight mice per group) and the error bars represent standard error of the mean (\*\*\*P < 0.001). NS, not significant. NMS, normal mouse sera. c Immunized mice were challenged with 50 × LD50 of B. anthracis Sterne spores by s.c. injections. Survival rates of 5 groups (n = 8 for each group) were observed for 14 days. The p-value between KVAC-thPA-C7L and KVAC-C7L with immunoadjuvant only (KVAC-hIL-C7L, KVAC-hCTA1-C7L) is lower than 0.001 and indicated as \*\*\*. The p-value between KVAC-thPA-C7L and both KVAC-C7L with PA and immunoadjuvant (KVAC-thPA-C7L + KVAC-hIL-C7L, KVAC-thPA-C7L + KVAC-hCTA1-C7L) is lower than 0.05 and indicated as \* Full size image Neutralizing antibodies against vaccinia virus in mouse sera were measured by PRNT assay. Unlike the anti-PA antibodies, production of neutralizing antibodies against vaccinia virus does not appear to be significantly affected by the presence of immunoadjuvant (Fig. 3b). In a previous study, IL-15 expressing vaccinia virus induced increased neutralizing antibodies compared to the control vaccinia virus in a mouse model [12]. In our experiment, the effect of adjuvants was not observed and all the sera immunized with the constructs induced similar level of neutralizing antibodies. Immunized mice were challenged with B. anthracis Sterne spores 3 weeks after the final vaccination. Survival rates were monitored for 2 weeks. Mice immunized with adjuvant only were all dead within a week. In the group immunized with KVAC-thPA-C7L only, 62.5% of mice survived, while groups immunized with both KVAC-thPA-C7L and immunoadjuvant expressing virus (KVAC-hIL15-C7L or KVAC-CTA1-C7L) were fully protected from the challenge (Fig. 3c). The result indicates that enhanced immunity achieved by co-expression of adjuvant can protect the mice more effectively against anthrax. Discussion Poxviruses have been often used as a vector system for vaccines because of their large DNA genome and convenience in manipulation [21, 22]. In a previous study, engineered vaccinia strains expressing both PA and IL-15 showed enhanced immunogenicity against B. anthracis compared to the conventional anthrax vaccine AVA in animal test [23]. Our result presented that the co-expression of IL-15 in KVAC103 also enhanced protective efficacy of our bivalent vaccine. Co-expression of CTA1 induced immune response against the PA-expressing vaccine in the similar level to IL-15. Our result demonstrated that co-immunization of CTA1, as well as IL-15, was effective enough to enhance the immune responses against PA and reconfirmed that CTA1 is a suitable adjuvant for multivalent vaccines derived from KVAC103. This result is the first observation of the effect of CTA1 as an immunoadjuvant in a viral vaccine system. Conclusion In summary, we explored the possibility of developing a bivalent vaccine using KVAC103, an attenuated vaccinia virus strain. Like other vaccinia virus strains previously utilized, it is confirmed that KVAC103 also can serve as a useful platform for multivalent vaccines. In addition, the vaccine can be further effective with the supplement of cytokines or adjuvants. Methods Cell and virus Vero cell (African green monkey kidney cell) was purchased from the American Type Culture Collection (ATCC, USA). Cells were grown in Opti-Eagle’s Minimum Essential Medium (Opti-MEM, Invitrogen) supplemented with 2% heat-inactivated fetal bovine serum (FBS, Invitrogen), incubated at 37 °C, and humidified with 5% CO2. The attenuated vaccinia virus strain KVAC103 and the viral vector pVVT1-EGFP-C7L were provided by Korea National Institute of Health (KNIH). This vector contains the vaccine virus C7L gene which encodes interferon antagonist, and this is one of the 26 genes defective in KVAC103 compared to its ancestor strain. This gene is required for enhanced viral reproduction [24]. Construction of anthrax/smallpox dual vaccine candidate vectors Viral vector constructs were generated using the pVVT1-EGFP-C7L vector [24] as a template (Fig. 1). Human IL-15 gene and human codon-optimized B. anthracis PA and CTA1 genes were synthesized (Bioneer). The synthesized genes were cloned into the vector using SfiI restriction enzyme site. The constructed vectors were mixed with Lipofectamine (Invitrogen) and transfected into KVAC103-infected Vero cells. Single plaques were isolated from the original infected cells and verified using PCR. The primer sequences used for verification were 5′-TTT GAA GCA TTG GAA GCA ACT-3′ and ‘5’-ACG TTG AAA TGT CCC ATC GAG T-3′. Virus preparation Viruses were infected to mono-layered Vero cells with 0.01 MOI. The virus-infected cell media were harvested when more than 80% of total cells showed cytopathic effect. From the harvested culture supernatant, viruses were collected by ultra-centrifugation. The pellet was resuspended in 1× PBS, pH 7.0 (Gibco). The concentration of viral particles was determined by the standard plaque assay. The viruses were infected the Vero cells overlaid on 6-well plates for 2 days. The plate were staining with crystal violet and the plaque numbers on each well were counted. Western blot analysis Virus-infected Vero cells or their culture supernatants were lysed in 1× RIPA buffer (G-Bioscience) containing 1% PMSF (Theromfisher Scientific) at 4 °C. Fifty μg of protein from each cell lysate was resolved on denaturing polyacrylamide gel electrophoresis (PAGE) and transferred to polyvinylidene difluoride (PVDF) membrane (Amersham). Expression levels of PA and CTA1 proteins were detected using mouse monoclonal antibodies against PA and cholera toxin, respectively (Abcam, 1:1000), and horse radish peroxide (HRP)-conjugated secondary antibodies (Abcam, 1:3000). Mouse immunization and serum collection Female A/J mice (5-week old) were purchased from SLC, Inc. (Japan) and housed in an animal biosafety level 2 (ABL2) facility in KCDC. Mice were immunized with the vaccine candidate virus (5 × 107 pfu/mouse) with or without the adjuvant-expressing virus (5 × 107 pfu/mouse) 2-times at 3-week intervals subcutaneously (s.c.) with 8 mice as a group. Mice sera were collected 20 days after final immunization to measure anti-PA IgG and vaccinia virus plaque reduction neutralizing antibody titers. The schematic view of mouse immunization and serum collection is in Fig. 4. Fig. 4 figure4 A Schematic view of the animal experiment. Mice were immunized two times with 3 weeks interval and sera were collected by bleeding 20 days after the last vaccination. One day after bleeding, mice were challenged with anthrax spores. Survival was observed for 14 days Full size image Enzyme-linked immunosorbent assay (ELISA) The anti-PA IgG titers of mice sera were determined by ELISA as previously described with some modifications [25]. Briefly, 96 well plates were coated with 1 μg/ml of recombinant PA (Green Cross, Korea). Mouse sera were diluted from 1:100 to 1:204800 and loaded to each well, incubated for 1 h at 37 °C. Horseradish peroxidase-conjugated anti-mouse IgG goat antibody (Invitrogen) and 3,3`,5,5`-tetramethylbenzidine (TMB) substrate were used for detection. The optical density of each well was measured at 450 nm and the half maximal effective concentration (EC50) was calculated by 4-parameter logistic equation regression using SoftMaxPro5.3 (Molecular Device, USA). The data were analyzed and visualized using GraphPad Prism 5. The IL-15 expression level of KVAC103 derivatives were determined by the IL-15 ELISA kit (Biolegend) according to the manufacturer’s protocol. Vero cells were infected with viruses of 0.01 MOI. Cell lysates were collected 2 days after infection and analyzed. Plaque reduction neutralization test (PRNT) Serial two-fold dilutions of heat-inactivated mouse sera were mixed with vaccinia virus Lister strain of approximately 50 plaque forming units (PFU). After 2 h incubation at 37 °C, the serum and virus mixtures were inoculated onto monolayered Vero cells. After two days incubation at 37 °C with 5% CO2, cells were fixed and stained using a mixture of crystal violet and formalin for 10 min. Stained plates were dried in air at room temperature and the plaque numbers were counted. The neutralizing antibody titer was defined as the reciprocal of dilution factor that reduced plaque numbers in half (50%) compared to a serum-free control (PRNT50). B. anthracis spore challenge Immunized mice were challenged with 50-fold of lethal dose 50 (LD50) of B. anthracis Sterne spore by s.c. injections. Survival of the mice was monitored for 14 days as described in Fig. 4. Spores were prepared according to a previous study [26]. The LD50 determined by Reed-Muench method [27] in A/J mice model via s.c. route was 1794 spores. Survived animals were euthanized using CO2 gas. Animal study protocols (KCDC-102-16-2A and KCDC-039-17-2A) were approved by the Institutional Animal Care and Use Committee (IACUC) of Korea Centers for Disease Control and Prevention (KCDC). All procedures involved in the housing and care of animal strictly followed guidelines and requirements of the IACUC. Statistical analysis The Statistical analysis was performed using GraphPad Prism 5. To analyze the anti-PA ELISA titer, One-way ANOVA followed by Tukey’s post hoc test were used to evaluate the difference between groups. To analyze the survival rate, Kaplan-Meier survival plots were evaluated with the log-rank test. Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. References 1. Russell PK. Project BioShield: What It Is, Why It Is Needed, and Its Accomplishments So Far. Clin Infect Dis. 2007;45(Supplement\_1):S68–72. Article Google Scholar 2. Cieslak TJ, Christopher GW, Kortepeter MG, Rowe JR, Pavlin JA, Culpepper RC, Eitzen EM Jr. Immunization against potential biological warfare agents. Clin Infect Dis. 2000;30(6):843–50. CAS Article Google Scholar 3. Cybulski RJ Jr, Sanz P, O'Brien AD. Anthrax vaccination strategies. Mol Asp Med. 2009;30(6):490–502. CAS Article Google Scholar 4. Rhie GE, Park YM, Chun JH, Yoo CK, Seong WK, Oh HB. Expression and secretion of the protective antigen of Bacillus anthracis in Bacillus brevis. FEMS Immunol Med Microbiol. 2005;45(2):331–9. CAS Article Google Scholar 5. Kang CK, Kim NH, Kim CJ, Rhie GE, Jo SK, Ahn M, Kang J, Choe PG, Park WB, Kim NJ, et al. Immunogenicity and safety of a novel recombinant protective antigen anthrax vaccine (GC1109), a randomized, single-blind, placebo controlled phase II clinical study. Vaccine. 2019;37:3820–4. CAS Article Google Scholar 6. Kennedy RB, Lane JM, Henderson DA, Poland GA. 54 - Smallpox and Vaccinia. In: Plotkin SA, Orenstein WA, Offit PA, Edwards KM, editors. Plotkin's Vaccines (Seventh Edition): Elsevier; 2018. p. 1001–30. e1012. https://doi.org/10.1016/B978-0-323-35761-6.00054-7. https://www.sciencedirect.com/science/article/pii/B9780323357616000547. 7. Lee YJ, Son HS, Yeo SG, Yoo JS, Lee SW. Development of viral vector using attenuated Vaccinia virus strain, KVAC103. Public Health Weekly Report, KCDC. 2016;9(38):755–9. Google Scholar 8. Tovey MG, Lallemand C. Adjuvant activity of cytokines. Methods Mol Biol. 2010;626:287–309. CAS Article Google Scholar 9. Perera PY, Lichy JH, Waldmann TA, Perera LP. The role of interleukin-15 in inflammation and immune responses to infection: implications for its therapeutic use. Microbes Infect. 2012;14(3):247–61. CAS Article Google Scholar 10. Calarota SA, Dai A, Trocio JN, Weiner DB, Lori F, Lisziewicz J. IL-15 as memory T-cell adjuvant for topical HIV-1 DermaVir vaccine. Vaccine. 2008;26(40):5188–95. CAS Article Google Scholar 11. Oh S, Berzofsky JA, Burke DS, Waldmann TA, Perera LP. Coadministration of HIV vaccine vectors with vaccinia viruses expressing IL-15 but not IL-2 induces long-lasting cellular immunity. Proc Natl Acad Sci U S A. 2003;100(6):3392–7. CAS Article Google Scholar 12. Perera LP, Waldmann TA, Mosca JD, Baldwin N, Berzofsky JA, Oh S. Development of smallpox vaccine candidates with integrated interleukin-15 that demonstrate superior immunogenicity, efficacy, and safety in mice. J Virol. 2007;81(16):8774–83. CAS Article Google Scholar 13. Valkenburg SA, Li OT, Mak PW, Mok CK, Nicholls JM, Guan Y, Waldmann TA, Peiris JS, Perera LP, Poon LL. IL-15 adjuvanted multivalent vaccinia-based universal influenza vaccine requires CD4+ T cells for heterosubtypic protection. Proc Natl Acad Sci U S A. 2014;111(15):5676–81. CAS Article Google Scholar 14. Saikh KU, Kissner TL, Nystrom S, Ruthel G, Ulrich RG. Interleukin-15 increases vaccine efficacy through a mechanism linked to dendritic cell maturation and enhanced antibody titers. Clin Vaccine Immunol. 2008;15(1):131–7. CAS Article Google Scholar 15. Agren L, Lowenadler B, Lycke N. A novel concept in mucosal adjuvanticity: the CTA1-DD adjuvant is a B cell-targeted fusion protein that incorporates the enzymatically active cholera toxin A1 subunit. Immunol Cell Biol. 1998;76(3):280–7. CAS Article Google Scholar 16. Agren LC, Ekman L, Lowenadler B, Nedrud JG, Lycke NY. Adjuvanticity of the cholera toxin A1-based gene fusion protein, CTA1-DD, is critically dependent on the ADP-ribosyltransferase and Ig-binding activity. J Immunol. 1999;162(4):2432–40. CAS PubMed Google Scholar 17. Eliasson DG, El Bakkouri K, Schon K, Ramne A, Festjens E, Lowenadler B, Fiers W, Saelens X, Lycke N. CTA1-M2e-DD: a novel mucosal adjuvant targeted influenza vaccine. Vaccine. 2008;26(9):1243–52. CAS Article Google Scholar 18. Sundling C, Schon K, Morner A, Forsell MNE, Wyatt RT, Thorstensson R, Hedestam GBK, Lycke NY. CTA1-DD adjuvant promotes strong immunity against human immunodeficiency virus type 1 envelope glycoproteins following mucosal immunization. J Gen Virol. 2008;89(Pt 12):2954–64. CAS Article Google Scholar 19. Akhiani AA, Stensson A, Schon K, Lycke N. The nontoxic CTA1-DD adjuvant enhances protective immunity against helicobacter pylori infection following mucosal immunization. Scand J Immunol. 2006;63(2):97–105. CAS Article Google Scholar 20. Andersen CS, Dietrich J, Agger EM, Lycke NY, Lovgren K, Andersen P. The combined CTA1-DD/ISCOMs vector is an effective intranasal adjuvant for boosting prior Mycobacterium bovis BCG immunity to Mycobacterium tuberculosis. Infect Immun. 2007;75(1):408–16. CAS Article Google Scholar 21. Altenburg AF, Kreijtz JH, de Vries RD, Song F, Fux R, Rimmelzwaan GF, Sutter G, Volz A. Modified vaccinia virus Ankara (MVA) as production platform for vaccines against influenza and other viral respiratory diseases. Viruses. 2014;6(7):2735–61. CAS Article Google Scholar 22. Gomez CE, Najera JL, Krupa M, Esteban M. The poxvirus vectors MVA and NYVAC as gene delivery systems for vaccination against infectious diseases and cancer. Curr Gene Ther. 2008;8(2):97–120. CAS Article Google Scholar 23. Merkel TJ, Perera PY, Kelly VK, Verma A, Llewellyn ZN, Waldmann TA, Mosca JD, Perera LP. Development of a highly efficacious vaccinia-based dual vaccine against smallpox and anthrax, two important bioterror entities. Proc Natl Acad Sci U S A. 2010;107(42):18091–6. CAS Article Google Scholar 24. Son HS, Yeo SG, Lee SW: Recombinant Vaccinia Virus Derived From Kvac103 Strain. In. US patent 9,879,281: Korea centers for disease control and prevention; 2016. 25. Chun JH, Choi OJ, Cho MH, Hong KJ, Seong WK, Oh HB, Rhie GE. Serological correlate of protection in Guinea pigs for a recombinant protective antigen Anthrax vaccine produced from Bacillus brevis. Osong Public Health Res Perspect. 2012;3(3):170–6. Article Google Scholar 26. Ivins B, Fellows P, Pitt L, Estep J, Farchaus J, Friedlander A, Gibbs P. Experimental anthrax vaccines: efficacy of adjuvants combined with protective antigen against an aerosol Bacillus anthracis spore challenge in Guinea pigs. Vaccine. 1995;13(18):1779–84. CAS Article Google Scholar 27. Reed LJ, Muench H. A simple method of estimating fifty per cent endpointS12. Am J Epidemiol. 1938;27(3):493–7.

#### 3] The 1AC also doesn’t do most of the Arnold Ventures plan – alt causes mean no solvency.

1AC Arnold Ventures, RECUT, CATONSVILLE READS GREEN

9-24-2020 "'Evergreening' Stunts Competition, Costs Consumers and Taxpayers" <https://www.arnoldventures.org/stories/evergreening-stunts-competition-costs-consumers-and-taxpayers/> (Arnold Ventures is focused on evidence-based giving in a wide range of categories including: criminal justice, education, health care, and public finance)//Elmer -recut CAT

What Can Be Done As the Evergreen Drug Patent Search makes clear, the positive impact of Hatch-Waxman has been steadily and severely eroded by a regulatory system vulnerable to increasingly sophisticated forms of manipulation. “You might say that the patent and regulatory system has been weaponized,” Feldman said. “When billions of dollars are at stake, there’s a lot of money available to look for ways to exploit the legal system. And companies have become adept at this, as our work has found.” There are several key steps that Congress could take to restore the balance between innovation and competition that is the key to a successful prescription drug regulatory process. These may include: Imposing restrictions on the number of patents that prescription drug manufacturers can defend in court to discourage the use of anticompetitive patent thickets. Limiting the patentability of so-called secondary patents — which don’t improve the safety or efficacy of a drug — through patent and exclusivity reform. Reforming the 180-day generic exclusivity, which can currently be abused to block other competitive therapies. “The Evergreen Drug Patent Search provides the publicly available, evidence-based foundation that defines the extent of the problem, and it can be used to develop policies that solve the problem of anti-competitive patent abuses,” said Kristi Martin, VP of Drug Pricing at Arnold Ventures. “Our incentives have gotten out of whack,” Martin said. “The luxury of monopoly protection should only be provided to innovations that provide meaningful benefits in saving lives, curing illnesses, or improving the quality of people’s lives. It should not be provided to those gaming the system. If we can change that, we can save consumers, employers, and taxpayers many billions of dollars while increasing the incentives for pharmaceutical companies to achieve breakthroughs."

#### And this card is literally from a foundation run by a billionaire so it’s kind of laughable that they accuse neg ev of being biased.

### 1NC – AT: Radhakrishnan

#### Their Radhakrishnan ev is circular. The only evidence of a “Big pharma” conspiracy is that Pharma files a lot of secondary patents, which entirely begs the question of whether those patents are bad. And it doesn’t make any of the sweeping epistemological indicts implied by the tagline. The CP better solves because we have an independent judicial check that the patent really is non-obvious.

### 1NC – AT: Plan

#### It’s easy to say “oh, don’t let pharma companies make small modifications and renew their patents,” but the real work is drawing the line and the 1AC just doesn’t do that.

**That turns case – ambiguous legal standards shred solvency – encourage circumvention, abuse, and costly litigation**

**Halaijan 13**

Dina Halaijan (JD, Brooklyn Law School). “Inadequacy of TRIPS & the Compulsory License: Why Broad Compulsory Licensing is Not a Viable Solution to the Access Medicine Problem.” Brooklyn Journal of International Law. Volume 38, Issue 3, Article 7 (2013). JDN. <https://brooklynworks.brooklaw.edu/cgi/viewcontent.cgi?article=1050&context=bjil>

Ambiguities in the interpretation of TRIPS due to the lack of substantive guidelines or definitions also hinder its effective use by increasing the risk of litigation.111 The Doha Declaration merely stated that individual countries have “the right to determine what constitutes a national emergency or other circumstances of extreme urgency” in deciding to grant a compulsory license, and thus did little to ameliorate the different interpretive approaches of developed and developing countries.112 The flexible scope of compulsory licenses leads to abuse which further instills resistance and suspicion from pharmaceutical companies.113 For example, Egypt’s compulsory license for Pfizer’s Viagra tarnishes the reputation of compulsory licensing because erectile dysfunction is clearly a less dire situation and one likely not intended to be covered by the public health exception of TRIPS.114 Such excessive abuse and over-use of compulsory licensing likely encourages pharmaceutical companies to aggressively resist valid uses of compulsory licenses to prevent over-expansion of scope.115 In addition to ambiguity in the scope of intended diseases, conflicting interpretations exist in the type of pharmaceutical products intended for compulsory licensing.116 The scope of countries that should benefit from compulsory licensing remains another area of contention.117 Not limiting the scope of applicable nations may create a chilling effect on the types of drugs pharmaceutical companies choose to invest in and develop to avoid the potential for a compulsory license, which hurts developing nations most in need of help.118 Interpreting the morality exclusion in Article 27(2) also proves difficult, as there is no universally accepted definition.119 In addition to causing differing interpretations between countries, the lack of concrete definitions allows countries to alter their position to fit their self-interest and creates potential for abuse.120 For example, despite the United States’ narrow interpretation of TRIPS flexibilities, the United States contradicted itself during the 2001 anthrax scare by suggesting use of a compulsory license for Cipro, a drug that combats the effects of anthrax.121 On a related note, as India’s government and pharmaceutical industry’s capabilities grow, the future of India’s willingness to grant compulsory licenses and produce cheap generic drugs for export to other developing countries is questionable.122 Indian companies may opt to serve their self-interest and become “innovator companies” to compete globally with other large pharmaceutical companies.123 The vagueness of Article 30, which allowed a narrow interpretation to be given by the WTO dispute resolution panel, is a further impediment to increasing access to medicines.124 Calculating adequate remuneration for payment to the patent holder when a compulsory license is issued is another obstacle to successful use of TRIPS flexibilities and is further complicated by the requirement to take the economic value of the authorization into account, as TRIPS does not provide guidance to determine what is ‘adequate’ and what is the authorization’s ‘value.’125 The WTO members’ inability to reach a decision regarding parallel importation created a “fundamental flaw” of ambiguity.126 In regard to compulsory licensing under the Paragraph 6 Decision, drugs made for export must be distinguishable by special labels, colors, or shapes to prevent trade diversion.127 However, lack of monitoring guidelines and repercussions makes the re-exportation issue troubling.128

### 1NC – AT: Solvency

#### 1] Big pharma can easily circumvent the 1AC; that guts their solvency – CX proves

Song and Han 16

Chie Hoon Song and Jeung‑Whan Han\* Research Center for Epigenome Regulation, School of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea Patent cliff and strategic switch: exploring strategic design possibilities in the pharmaceutical industry Song and Han SpringerPlus (2016) 5:692 DOI 10.1186/s40064-016-2323-1 <https://springerplus.springeropen.com/track/pdf/10.1186/s40064-016-2323-1.pdf> -CAT

Prevention strategy The first generic strategic orientation to extend the patent protection is to temporarily prevent or distort competition. The basic principle of ‘prevention strategy’ is therefore to exploit possibilities for extension of market exclusivity mostly by means of legal measures. One commonly applied strategy is related to strategic patenting. Patents are the primary tools that the research-driven companies use to establish and maintain their brands in the marketplace and provide a window of opportunity to enforce the exclusivity of the inventions (Cantrell 2009). Pharmaceutical industry has adopted a strategy of filing multiple patents to protect its branded drug. This practice of forming a network surrounding the base patent, is called creating “patent clusters”.2 The acquisition of secondary patents, obtaining features other than the main active drug ingredient (such as crystalline forms of the original compound, methods of use or formulations), can create a solid portfolio covering different aspects of the drug (Burdon and Sloper 2003). For instance, if the manufacturing process is optimized after filing a patent application so that the new synthesis method did not have to be disclosed at the time of initial filing, the related process patent, such as enhancing of purity level, can be filed at a later stage of the product lifecycle. Additionally, the primary patent may be split into several patents. One patent may seek protection for a broad genus encompassing various compounds, while another patent may comprise a claim related to a specific compound. In some cases, if one isomer3 is found to be more active than the other or offers substantial and previously unpredicted therapeutic advantages over others, it may provide a basis for a separate patenting for the more beneficial isomer (Hutchins 2003). Accordingly, secondary patents encompass inventions directed to the incremental 2 Pharmaceutical products are usually protected by a large number of product and process patents. Instead of facing single patent expiration, there are several successive ones. In most cases, there is one main patent protecting the active compound and several secondary patents protecting aspects other than main patent. Upon patent expiry, if generic companies cannot find ways to bypass a patent protecting the supporting aspects, it can act as a competition limiting factor. 3 Chemical compounds often appear in different isomeric forms (i.e. having the same chemical structure, but differs in spatial arrangement), such as cis/trans-isomers or enantiomers. Isomers may demonstrate different biological activity. Choice of strategic pathway Prevention Innovation Extraction Adaption Fig. 2 Overview of the four generic strategic pathways [Source: modelled after Raasch (2006)] Song and Han SpringerPlus (2016) 5:692 Page 6 of 14 improvement of the primary patent and would permit the innovator-company to maintain the market share, even if the generic producers try to enter the market by contesting the validity of the primary patent. Amin and Kesselheim (2012) reported that a large cluster of secondary patents related to HIV medication (ritonavir) could delay generic competition 12 years after the expiration of the patents on the drug’s base compound. The Sector Inquiry by European Commission has revealed that there is a trend for companies to continuously file patent applications as the expiry date of the primary patent approaches, whereby the ratio of primary to secondary patents is 1:7. This kind of strategic patenting intends to build portfolios of patents for a defensive rather than for inventive purposes, placing the innovator-company in a more favorable position for the patent-related disputes concerning the launch of generics. Glasgow (2001) concludes: “[…] intellectual property protection is not being used to promote an incentive to create and innovate. Rather, intellectual property rights are being used to gain and maintain an exclusive market share for the most profitable, not necessarily the most beneficial, drug”. Consequently, the term “evergreening” indicates the strategic maneuver to intentionally extend the market monopoly beyond the known patent life through secondary patenting (Dwivedi et al. 2010). The consequent patent maze from secondary patents can result in difficulties for generic suppliers to determine when relevant patents will expire and when it is safe to enter the market without inadvertently running into patent infringement problems. Even if the generic suppliers have success in maintaining a clear view through the multiple layers of patent protection, they find themselves at a disadvantage in that they might be prohibited from using the compound produced by the most economical route or using the most stable forms of the drug (Hutchins 2003). However, more recently, patent-related legal challenges from generic suppliers have been more successful and the lead time for the market launch of generic products has become much shorter (European Commission 2009). The secondary patents may not cover the proposed generic product properly and are contestable (Glass 2004). At the same time, it is important to keep in mind that there is a tendency to restrict the patentability of secondary patents, especially in developing countries, leading to questionable patents on highly prolific medication to receive a strong second look. In brief, strategic patenting behavior can deter generic entry, as the costs to invent around or challenge the patent maze can be detrimental, but stricter patentability standards make the strategic patenting more vulnerable. Another possibility to extend the market exclusivity by pursuing legal avenues is provided through obtaining of supplementary protection certificates (SPCs). SPCs are an additional protective mechanism introduced by EU to serve as an extension to the patent right (Hitchcock and Tugal 2003). For the pharmaceutical sector, SPCs can be issued to compensate the efforts put into research and development and the elapsed period between the patent filing and obtaining market authorization to place the approved drug on the market. SPCs extend the effective protection of products already on the market by a maximum of 5 years upon patent expiry. However, the protection granted through SPC can be legally challenged and declared as invalid. A similar practice has been adopted by US and Japan under the name of “patent term restoration” in the 1980s. In US, the innovator-companies can apply for up to five additional years of patent protection for the new drug to make up for the time lost while the product was subject to the FDA’s regulatory review (Title II of the Hatch–Waxman Act) (Agrawal and Thakkar 1997). Building on this legislation, brand owners can file a patent infringement suit, after an ANDA with paragraph IV certification is filed by a generic manufacturer.4 The FDA cannot approve the ANDA until the court decision, thereby leading up to 30 months extension of market exclusivity (Bhat 2005). Another way of extending the market exclusivity is to apply for orphan drug status. In EU, orphan drug status is granted to drugs for treating rare (life-threatening or chronically debilitating) diseases affecting not more than 5 in 10,000 for which there is currently no adequate or possible treatment, while making them sufficiently profitable to bring to market (EMA 2015). Historically, a rare disease is not addressed by the pharmaceutical industry because of its small number of patients. The regulation encompassing the orphan drug designation in EU, which was laid down in early 2000, grants 10 years of market exclusivity, acceleration of the authorization procedure and reduction of administration fees (Haffner et al. 2008). In some cases, an already authorized medicinal product may seek accreditation for an as orphan drug designated indication. Due to the expanded range of application as well as the possibility to use the new indication as a distinguishing feature with respect to the generic competitors, the turnover of the patent-free product can be maintained. However, attaining the orphan-drug-status cannot completely prevent the generic manufacturers from competing in the same market segment, since the prescriber can administer the generics in the category of “off-label” use. In contrast, the Orphan Drug Act has been in force since 1983 in US. The law provides several similar economic and regulatory incentives, including 7 years of market exclusivity, fast-track approval and tax credit, to encourage the development of orphan drugs 4 Paragraph IV Certification contains the claim of a generic firm that the patent of brand owner is not infringed or is invalid. Song and Han SpringerPlus (2016) 5:692 Page 7 of 14 (Minghetti et al. 2000). However, it has been suggested that orphan drug regulations have not quite lived up to their expectations, thus the current regulations should be revised to provide improved incentives for industry and for better priority-setting of development (Tambuyzer 2010). Besides, companies can be granted a 6-month patent term extension for submitting pediatric clinical trials (Kvesic 2008). Generic entrants might challenge the validity of the patents enjoyed by the brand owner, either by entering the market at risk or taking the case to the court. In this context, the brand owner and generic companies are entitled to reach an out-of-court agreement and settle their patent litigation to avoid the costly expenses of pursuing legal action at court. In order to prevent generic entry, the brand owner agrees with generic competitors to not enter the market in return for substantial payment or conveniences, granting the equivalent of what they would have earned upon the market entry (Bulow 2004). This strategy is only applicable if the expected profit from the market dominance exceeds the payments. The generic competitors would stay out of the market for the duration of the agreements and the brand owner can enjoy an effect similar to successfully enforcing its patent right. However, out-of-court agreements between companies in relation to patent litigation are not immune from competition law scrutiny (OECD 2014). Although companies have a legitimate interest in finding a mutually acceptable compromise through settlements, some form of settlements may be problematic from a competition law perspective. In recent years, the anticompetitive practices such as the pay-for-delay agreements in the context of patent settlement are under intensified monitoring of competition authorities and should be coordinated with care, since they can entail the risk of high penalty payments and damage to company’s reputation and are detrimental to the interest of the communities (Table 2).

#### 2] The squo has already adjusted to evergreening – secondary patents get less protection, face more skepticism.

Song and Han 2

Chie Hoon Song and Jeung‑Whan Han\* Research Center for Epigenome Regulation, School of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea Patent cliff and strategic switch: exploring strategic design possibilities in the pharmaceutical industry Song and Han SpringerPlus (2016) 5:692 DOI 10.1186/s40064-016-2323-1 <https://springerplus.springeropen.com/track/pdf/10.1186/s40064-016-2323-1.pdf> -CAT

Consequently, the term “evergreening” indicates the strategic maneuver to intentionally extend the market monopoly beyond the known patent life through secondary patenting (Dwivedi et al. 2010). The consequent patent maze from secondary patents can result in difficulties for generic suppliers to determine when relevant patents will expire and when it is safe to enter the market without inadvertently running into patent infringement problems. Even if the generic suppliers have success in maintaining a clear view through the multiple layers of patent protection, they find themselves at a disadvantage in that they might be prohibited from using the compound produced by the most economical route or using the most stable forms of the drug (Hutchins 2003). However, more recently, patent-related legal challenges from generic suppliers have been more successful and the lead time for the market launch of generic products has become much shorter (European Commission 2009). The secondary patents may not cover the proposed generic product properly and are contestable (Glass 2004). At the same time, it is important to keep in mind that there is a tendency to restrict the patentability of secondary patents, especially in developing countries, leading to questionable patents on highly prolific medication to receive a strong second look. In brief, strategic patenting behavior can deter generic entry, as the costs to invent around or challenge the patent maze can be detrimental, but stricter patentability standards make the strategic patenting more vulnerable.

### 1NC – AT: AMR

#### 1] Low prices independently cause AMR.

Babu and Suma 6 Babu, Varsha, and C. Suma. "Antibiotic pricing: when cheaper may not be better." Clinical infectious diseases 43.8 (2006): 1085-1086. (Government Primary Health Center)//Elmer

To The Editor—Antibiotics in India have always been cheaper in absolute terms thanks to weak patent laws that have been in effect until recently. Because a direct translation of drug prices from US dollars to Indian rupees (INR) would have rendered most new antibiotics inaccessible to the vast majority of Indians, such patent violations were subtly encouraged. Even despite this, we were caught unaware when pharmaceutical representatives approached our primary care center in rural India, claiming that a 5-day course of levofloxacin would henceforth cost the patient ∼INR 20 (<$0.50). Reluctant to accept such a statement at face value, we consulted the CIMS Updated Prescriber's Handbook [1], a popular index of pharmaceutical drugs available in India. Here, we discovered that a 5-day course of oral levofloxacin (500 mg once daily) cost anywhere from INR 19.5 to INR 475 ($0.50–$10.50), with most companies pricing their brand at <$1 for a full course. The same course in the United States would cost >$100. Intrigued, we did some more research and came up with the following results. The cheapest 5-day courses of first-line antibiotics, such as oral amoxicillin (500 mg thrice daily) or oral erythromycin (500 mg 4 times daily), cost INR 45 ($1) and INR 90 ($2), respectively. On the other hand, the cost of a 3-day course of oral azithromycin (500 mg daily) was one-half that of a course of erythromycin. Despite the obvious price advantage to the patients, we find this trend troubling. **Lower prices** often **lead to wider prescription of a given drug**, especially in resource-limited settings. **If** second-line **antibiotics**—such as levofloxacin and azithromycin—**are made available at lower prices** than first-line antibiotics, **there is a high probability of their overuse and subsequent development of resistance**. In the face of **very low costs of medication**, patients are unlikely to complain of escalating medical expenses. The issue assumes more gravity when one considers the fact that levofloxacin is an important second-line drug for the treatment of tuberculosis [2]. Its widespread use in the community **is likely to lead to emergence of resistance** **among** **mycobacteria** **and** delayed diagnosis of **tuberculosis** [3]—an occurrence that India, with its large population of tuberculosis-affected patients, cannot afford. We believe we have encountered a situation where **low prices of antibiotics are likely to cause more harm than good**. In the post World Trade Organization treaty scenario, governments in resource-limited countries should use their privileges of essential drug control to ensure that the costs of first-line antibiotics remain lower than those of second-line drugs. Such a government-instituted ladder in antibiotic pricing is essential to prevent the misuse of antibiotics in the community and to ensure that antibiotic resistance is kept at low levels.

#### 2] Alt causes outweigh innovation – antibiotics just aren’t profitable.

**Paton and Kresge 20** [James Paton and Naomi Kresge, James is a reporter at Bloomberg Business covering health, pharma, and Covid-19. Naomi is a reporter for Bloomberg Business covering pharmaceuticals. 8-8-2020, accessed on 8-28-2021, archive.is, "Superbugs Win Another Round as Big Pharma Leaves Antibiotics " <https://www.bloomberg.com/news/articles/2018-07-13/superbugs-win-another-round-as-big-pharma-leaves-antibiotics>] Adam

The fight against life-threatening infections suffered another blow when one of the world’s biggest drugmakers waved the white flag. [Novartis AG](https://archive.is/o/hm5Rm/https:/www.bloomberg.com/quote/NOVN:SW) is the latest drug giant to end antibacterial and antiviral research, joining the likes of [AstraZeneca Plc](https://archive.is/o/hm5Rm/https:/www.bloomberg.com/quote/AZLN:LN), [Sanofi](https://archive.is/o/hm5Rm/https:/www.bloomberg.com/quote/SAN:FP), [Allergan Plc](https://archive.is/o/hm5Rm/https:/www.bloomberg.com/quote/AGN:US) and [Medicines Co.](https://archive.is/o/hm5Rm/https:/www.bloomberg.com/quote/MDCO:US) [GlaxoSmithKline Plc](https://archive.is/o/hm5Rm/https:/www.bloomberg.com/quote/GSK:LN) has put some antibiotics assets under review. The pullback revives concern about a world in which routine infections again become lethal as bugs develop resistance to existing drugs. Sales of new antibiotics are too low for big pharma to recoup its investments, and public measures to encourage more activity aren’t moving the needle. “The market is broken,” said David Shlaes, a former pharmaceutical executive and consultant. “We’re at a point now where resistance is moving a lot faster than our ability to provide new antibiotics. This is just another in a long string of really bad news.” The latest retreat comes after a brief period when industry leaders appeared willing to take a [risk](https://archive.is/o/hm5Rm/https:/www.bloomberg.com/news/articles/2016-06-30/superbugs-and-subsidies-draw-big-pharma-back-to-antibiotics) on the field. [Merck & Co.](https://archive.is/o/hm5Rm/https:/www.bloomberg.com/quote/MRK:US) spent $8.4 billion on antibiotics leader [Cubist](https://archive.is/o/hm5Rm/https:/www.bloomberg.com/news/articles/2014-12-10/cubist-deal-a-rare-bright-spot-in-dismal-field-of-antibiotics) in 2014. Novartis, Glaxo and other companies pledged at the World Economic Forum in 2016 to fight the threat of drug-resistant bacteria. The U.S. government offered longer patent protection and subsidies, potentially worth hundreds of millions of dollars, to companies willing to invest. Not Selling But the new antibiotics just haven’t sold. Only five of the 16 brand-name antimicrobials approved from 2000 through last year were able to generate sales of more than $100 million annually, according to a study from Duke University’s Margolis Center for Health Policy. That’s a pittance compared with the billions of dollars for new cancer treatments. The problem for drugmakers is that new antibiotics are usually held in reserve and are not used unless they’re needed because patients develop resistance to an older medicine. Even the most expensive antibiotics, at around $1,000 a day, are cheap compared with a cancer medicine that will be given for months instead of a few days or weeks. Meanwhile, developing new antibiotics is becoming more expensive, said Gabrielle Breugelmans, director of research for the Access to Medicine Foundation. The roughly 275 research projects going on around the world might yield two or three medicines, she said.