# 1AC - Evergreening

## The Advantage is Evergreening

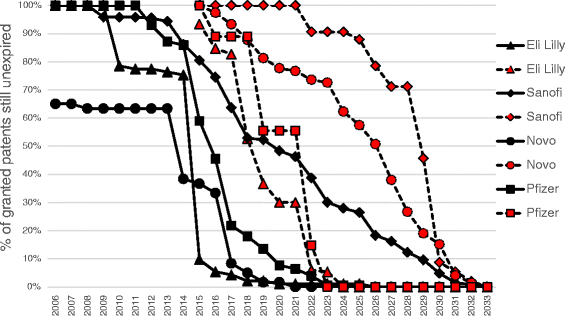
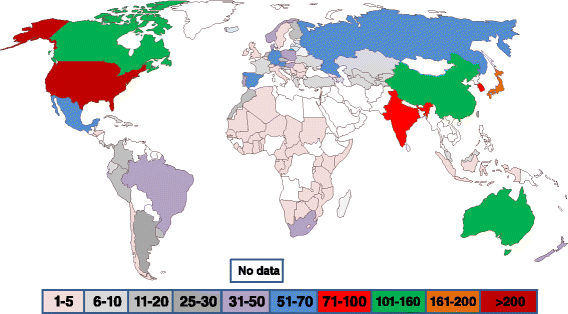
#### Patent evergreening is a crucial factor in the Opioid epidemic, AIDS epidemic, and cost of even basic allergy drugs – the fix is easy and improves market innovation

**AV 20** (“‘Evergreening’ Stunts Competition, Costs Consumers and Taxpayers.” Arnold Ventures, Arnold Foundation, 24 Sept. 2020, [www.arnoldventures.org/stories/evergreening-stunts-competition-costs-consumers-and-taxpayers/.)//LK](http://www.arnoldventures.org/stories/evergreening-stunts-competition-costs-consumers-and-taxpayers/.)//LK) [Accessed 8/23/2021]

In 2011, Elsa Dixler was diagnosed with multiple myeloma. That August, she was prescribed Revlimid, a drug that had come on the market six years earlier. By January 2012, she went into full remission, where she has remained since. So long as Revlimid retains its effectiveness, she will take it for the rest of her life. “I was able to go back to work, see my daughter receive her Ph.D, and have a pretty normal life,” said Dixler, a Brooklyn resident who is now 74. “So, on the one hand, I feel enormously grateful.” But Dixler’s normal life has come at a steep financial cost to her family and to taxpayers. Revlimid typically costs nearly $800 per capsule, and Dixler takes one capsule per day for 21 days, then seven days off, and then resumes her daily dose, requiring 273 capsules a year. Since retiring from The New York Times at the end of 2017, she has been on Medicare. Dixler entered the Part D coverage gap (known as the donut hole) “within minutes,” she said. She estimates that adding her deductible, her copayment of $12,000, and what her Part D insurance provider pays totals approximately $197,500 a year. Revlimid should have been subject to competition from generic drug makers starting in 2009, bringing down its cost by many orders of magnitude. But by obtaining 27 additional patents, eight orphan drug exclusivities and 91 total additional protections from the U.S. Food and Drug Administration (FDA) since Revlimid’s introduction in 2005, its manufacturer, Celgene, has extended the drug’s monopoly period by 18 years — through March 8, 2028. “I cannot fathom the immorality of a business that relies on squeezing people with cancer,” Dixler said, noting her astonishment that Revlimid has obtained orphan drug protections when it treats a disease that is not rare and does not serve a very limited population. She also observed that Revlimid’s underlying drug is thalidomide, which has been around for decades. “They didn’t invent a new drug, rather, they found a new use for it,” she said. “The cost of Revlimid has imposed constraints on our retirement,” Dixler said, “but when I hear other people’s stories, I feel very lucky. A lot of people have been devastated financially.” Revlimid is a case study in a process known as “evergreening” — artificially sustaining a monopoly for years and even decades by manipulating intellectual property laws and regulations. Evergreening is most commonly used with blockbuster drugs generating the highest prices and profits. Of the roughly 100 best-selling drugs, more than 70 percent have extended their protection from competition at least once. More than half have extended the protection cliff multiple times. The true scope and cost of evergreening has been brought into sharper focus by a groundbreaking, publicly available, comprehensive database released Thursday by the Center for Innovation at the University of California Hastings College of Law and supported by Arnold Ventures. The Evergreen Drug Patent Search is the first database to exhaustively track the patent protections filed by pharmaceutical companies. Using data from 2005 to 2018 on brand-name drugs listed in the FDA’s Orange Book — a listing of relevant patents for brand name, small molecule drugs — it demonstrates the full extent of how evergreening has been used by Big Pharma to prolong patents and delay the entry of generic, lower-cost competition. “Competition is the backbone of the U.S. economy,” said Professor Robin Feldman, Director of the UC Hastings Center for Innovation, who spearheaded the database’s creation. “But it’s not what we’re seeing in the drug industry. “With evergreening, pharmaceutical companies repeatedly make slight, often trivial, modifications to drugs, dosage levels, delivery systems or other aspects to obtain new protections,” she said. “They pile these protections on over and over again — so often that 78 percent of the drugs associated with new patents were not new drugs coming on the market, but existing drugs.” In recent decades, evergreening has systematically undermined the Drug Price Competition and Patent Term Restoration Act of 1984, which created the generic drug industry. Commonly known as the Hatch-Waxman Act, it established a new patent and market exclusivity regime in which new drugs are protected from competition for a specified period of time sufficient to allow manufacturers to recoup their investments and earn a reasonable profit. When that protection expires, generic drug makers are incentivized to enter the market through a streamlined regulatory and judicial process. Drug prices typically drop by as much as 20 percent when the first generic enters the market, and with more than one generic manufacturer, prices can plummet by 80 to 85 percent. “Hatch-Waxman created an innovation/reward/competition cycle, but it’s been distorted into an innovation/reward/more reward cycle,” Feldman said. “To paraphrase something a former FDA commissioner once said, the greatest creativity in Big Pharma should come from the research and development departments, not from the legal and marketing departments.” Feldman led the development of the Evergreen Drug Patent Search in response to repeated requests from Congressional committees, members of Congress, state regulators and journalists for information about specific drugs and companies. “We want to make it so anyone can have the question about drug protections at their fingertips whenever they want,” Feldman said. “It’s designed to be easy and user-friendly, and to enhance public understanding about how competition may be limited rather than enhanced through the drug patent system.” The database was created through a painstaking process of combing through 160,000 data points to examine every instance where a pharmaceutical company added a new drug patent or exclusivity. “Most of it was done by hand,” Feldman said, “with multiple people reviewing it at every stage. And along the way we repeatedly made conservative choices. We erred on the side of underrepresenting the evergreen gain to be sure we were as fair and reasonable as possible.” Among the 2,065 drugs covered in Evergreen Drug Patent Search, there are many examples of the evergreening strategy used by pharma to delay the entry of competition, especially generics, often for widely prescribed drugs, including those used to treat heartburn, chronic pain, and opioid addiction. Nexium Before Nexium, there was Prilosec, a popular drug to treat gastroesophageal reflux disease (GERD). But its patent exclusivity was due to expire in April 2001. In the late 1990s, with a precipitous drop in revenue looming, Prilosec’s manufacturer, AstraZeneca, decided to develop a replacement drug. Using “one-half of the Prilosec molecule — an isomer of it,” the result was Nexium, which received approval in February 2001. Essentially an evergreened version of Prilosec, Nexium’s exclusivity was then extended by more than 15 years, as AstraZeneca received 97 protections stemming from 16 patents. These included revised dosages, compounds, and formulations. Feldman said that tinkering changes such as Nexium’s do not involve the substantial research and development required for a new drug, nor do they constitute true innovations, yet for a decade and a half, patients and taxpayers were forced to pay far more than was warranted for GERD relief. In fact, in 2016 — one year after patent exclusivity expired — Nexium still topped all drugs in Medicare Part D spending, totaling $1.06 billion. Suboxone Use of this combination of buprenorphine and naloxone for treating opioid addiction has exploded in the wake of the opioid epidemic. Since its approval, Suboxone’s manufacturer, Reckitt Benckiser (now operating as Indivior), extended its protection cliff eight times, gaining nearly two extra decades of exclusivity through early 2030. The drug maker gained six patents for creating a film version of the drug — notably around the time protection was expiring for its tablet version. (The therapeutic benefits of the film and tablet are identical.) An earlier version of Suboxone also obtained an orphan drug designation, despite an opioid epidemic that has expanded Suboxone’s customer base to millions of potential customers. Suboxone generates more than $1 billion in annual revenue and ranks among the 40 top-selling drugs in the U.S. Truvada When Truvada, commonly referred to as PrEP, was approved in 2004, this HIV-prevention drug was a breakthrough. But 16 years later — and 14 years after its original exclusivity was to expire — it retains its monopoly status. Truvada’s manufacturer, Gilead, has received 15 patents and 120 protections since it came on the market, extending its exclusivity for more than 17 years, until July 3, 2024. In countries where generic Truvada is available, PrEP costs $100 or less per month, compared to $1,600 to $2,000 in the U.S. As a result, Truvada is unaffordable to many people who need protection from HIV. Barred from access, they are left vulnerable to infection. “We’re establishing a precedent that a pharmaceutical company can charge whatever it wants even as it allows an epidemic to continue, and the government refuses to intervene,” said James Krellenstein, co-founder of the group PrEP4All. “That should scare every American. If it’s HIV today, it will be another disease tomorrow.” EpiPen First approved in 1987, the EpiPen has saved the lives of countless numbers of people with deadly allergies. But it is protected from competition until 2025 — 38 years after its introduction — because its owner, Mylan, has filed five patents, four since 2010, all involving tweaks to the automatic injector. The actual medication used, epinephrine, has existed for more than a century — the innovation here is in the delivery device. Because these small changes to the injector have maintained its monopoly for so long, the cost of an EpiPen package (containing two injectors) has risen from $94 when Mylan purchased the device to between $650 and $700 today. For many people, especially parents of children with severe reactions to common allergens like peanuts, EpiPen’s increasing price tag imposes an onerous financial burden. 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."

#### A – patent evergreening guts access to insulin

**Kaplan 17** (Kaplan, W.A., Beall, R.F. The global intellectual property ecosystem for insulin and its public health implications: an observational study. J of Pharm Policy and Pract 10, 3 (2017). [https://doi.org/10.1186/s40545-016-0072-8 [Affiliations. Warren A. Kaplan: Department of Global Health, Boston University School of Public Health; Reed F. Beall: Population Health Program, Faculties of Medicine and of Law, University of Ottawa])//LK](https://doi.org/10.1186/s40545-016-0072-8%20%5bAffiliations.%20%20Warren%20A.%20Kaplan:%20Department%20of%20Global%20Health,%20Boston%20University%20School%20of%20Public%20Health;%20Reed%20F.%20Beall:%20Population%20Health%20Program,%20Faculties%20of%20Medicine%20and%20of%20Law,%20University%20of%20Ottawa%5d)//LK) [Accessed 8/22/21]

Background Lack of access to insulin and poor health outcomes are issues for both low and high income countries. This has been accompanied by a shift from relatively inexpensive human insulin to its more expensive analogs, marketed by three to four main global players. Nonetheless, patent-based market exclusivities are beginning to expire there for the first generation insulin analogs. This paper adds a global dimension to information on the U.S. patent landscape for insulin by reviewing the patent status of insulins with emphasis on the situation outside the US and Europe. Methods Using the term “insulin”, we searched for patents listed on the United States Food and Drug Administration’s (USFDA) Orange Book and the Canadian Online Drug Product Database Online Query and its Patent Register. With this information, we expanded the search globally using the World Intellectual Property Organization (WIPO) PatentScope database, the European Patent Office’s INPADOC database and various country-specific Patent Offices. Results Patent protected insulins marketed in the U.S. and other countries are facing an imminent patent-expiration “cliff’ yet the three companies that dominate the global insulin market are continuing to file for patents in and outside the U.S, but very rarely in Africa. Only a few local producers in the so-called "pharmerging" markets (e.g., Brazil, India, China) are filing for global patent protection on their own insulins. There is moderate, but statistically significant association between patent filings and diabetes disease burden. Conclusions The global market dominance by a few companies of analog over human insulin will likely continue even though patents on the current portfolio of insulin analogs will expire very soon. Multinationals are continuing to file for more insulin patents in the bigger markets with large disease burdens and a rapidly emerging middle class. Off-patent human insulins can effectively manage diabetes. A practical way forward would be find (potential) generic manufacturers globally and nudge them towards opportunities to diversify their national insulin markets with acceptable off-patent products for export. Background The disease burden of diabetes has been steadily rising and improving access to insulin, long considered an "essential medicine" by many countries as well as the World Health Organization (WHO) [1], has taken on increasing importance [2]. Essential medicines satisfy the priority health care needs of societies and are considered as a basis for public procurement or reimbursement decisions, yet fully one third of the world’s population currently has no guaranteed access to essential medicines [3]. More than 2 billion people in low and middle income (LMIC) countries face significant barriers in accessing basic health services. Nevertheless, the challenge of access to essential medicines is not limited to low and middle income countries [4]. A recent situational review of global insulin access [5] notes that although insulin was discovered in 1921, the drug is unattainable to many globally. There is a wide range and complexity of factors that contribute to this unattainability. This review noted that “… little has been done globally to address the issue of access, despite the UN’s political commitment to address non-communicable diseases and ensure universal access to drugs for these disorders.” Lack of access to insulin is a common issue in the United States [6] and Europe [7]. Insulin sales in the USA for 2011 totalled US$8.3 billion, a 14.9 % increase compared with 2010 and U.S. government reimbursement costs for insulin have been steadily rising as well, complicating access to this vital therapeutic to un- and under-insured populations [8]. Between 1991 and 2014, there was a near-exponential upward trend in Medicaid payments on a per-unit basis for a wide variety of insulin products regardless of formulation, duration of action, and whether the product was patented [8]. It has been almost a century since the first patient was treated with insulin and recombinant human insulin has been off-patent around the world for a decade and a half [9, 10]. Yet reimbursements for newer, patent-protected insulin analogs increased at a faster rate than reimbursements for older insulins [8], and older porcine- and bovine insulin products are no longer available on the American market. We note that manufacturing of beef insulin for human use in the U.S. was discontinued in 1998 as was the manufacturing of pork insulin (Iletin II) for human use in 2006. According to the U.S. Food and Drug Admininstration (FDA) discontinuation of animal-sourced insulins was a voluntary withdrawal of these products made by the manufacturers and not based on any FDA regulatory action [11]. All this has been accompanied by a shift from human insulin to its analogs, marketed by three or four main global players [12]. In 2000, 86.3 % of insulin used in the UK was human and 10.7 % analog insulins. By 2008, however, the use of human insulin had fallen to 23.2 %, with analogs representing 76.1 % of the total [5]. This trend toward increasing use of insulin analogues is occurring despite a 2011 World Health Organization (WHO) report which asserted while many comparative clinical trials “… find a statistically significant difference between analogue insulins and standard recombinant human insulin for some blood glucose measurements, there is no evidence of a clinically significant difference in most outcomes” [5]. We will not speculate as to whether this move towards analogue insulin was motivated by better clinical outcomes or by commercial and marketing interests [13]. This paper adds a global dimension to the previous information on the U.S. patent ‘landscape’ for insulin [9]. We review the patent status of insulin from a public health lens with emphasis on the situation outside the US and Europe. In a recent study of national Essential Medicines Lists [1], six of 32 countries (19 %) had selected insulin analogs as essential medicines, all of which were amongst the upper middle income countries and predominantly from the region of the Americas (4 out of 6 countries). We show that while the present suite of marketed insulins has already expired- or will soon expire- globally (the so-called insulin patent-expiration “cliff’) the companies that dominate the global market are continuing to file for insulin patents in and outside the U.S, albeit rarely in Africa. We further show that only a few manufacturers in the "pharmerging" markets (e.g., Brazil, India, China) are filing for global patent protection on their own insulins. We then discuss the possible implications of this intellectual property (IP) global ecosystem for access to insulin. Methods Patents Using the term “insulin”, we searched the United States Food and Drug Administration’s (USFDA) Orange Book [14] (OB). Companies with marketed products in the US are required by law to list each of their patents protecting “… the drug or a method of using the drug… with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product” [15]. Companies with medicines on the Canadian market are similarly required to list patents associated with their marketed products with Health Canada (HC) [16–18]. As others have focused on the insulin landscape in the United States [9], we also collected data in Canada to further diversify our product and patent datasets. We relied on the Orange Book [14] and Canada’s Drug Product Database Online Query [16] for our list of marketed insulin products, regardless of patent status. Luo and Kesselheim [9] consulted the U.S. Patent Office database to locate other US products that may have not been included in the Orange Book. Their product list was the same as ours and our respective Orange Book patent lists were identical. See Additional file 1 for the list of products (INN and proprietary name) included for the present analysis. We also checked the DrugBank website [19] which contains a historical log of patents that have been previously disclosed in the US or Canada in order to capture important additional patents that may have expired in the United States, but might not have expired elsewhere. We then sorted these data by the supplier company (e.g., Sanofi, Novo Nordisk, Eli Lilly, Pfizer) and then by the type of insulin (i.e., human or analog). The term “insulin” provided a better retrieval of relevant patents than “analog” or any combination of these two terms (see Additional file 2). Since the Orange Book and Health Canada databases do not contain, for example, process patents or patents for insulins that are not approved for marketing (i.e., under development), we undertook a supplemental search using several free, public patent databases. We briefly note that the European Patent Office (EPO) and World Intellectual Property Organization (WIPO) facilitate patent procedures and communications on a global or regional level. These organizations have the most official and complete information on applications as well as adjunct information. There are well over 100 countries with a patent office [20] who will have their own website with patent information but not all have the ability to search for patents online. There are many commercial and other third party patent databases, not used in this study, except as otherwise noted. Our first patent search used the WIPO PatentScope database [21]. Although there are no globally-applicable patents, WIPO keeps record of the nearly global patent application system. We searched WIPO PatentScope for patent publications containing the word “insulin” on the cover page, with a filing date more recent than 1 January 1994, and that were submitted by the four insulin suppliers identified during the previous phase of the project, namely, Eli Lilly, Pfizer, Novo Nordisk, and Sanofi Aventis. We documented all results found in WIPO PatentScope in the same fashion as for the OB and HC. Further, we consulted the EPO's International Patent Documentation (INPADOC) database. INPADOC is publicly available, has bibliographic information from over 95 countries and provides information about patent families, i.e. corresponding patent applications, i.e., patent applications in different countries which claim the same first filing date and which normally disclose the same invention. It also provides information concerning the legal status of patent applications and patents in those countries which report status changes [22]. We input all of our starting OB/HC and WIPO publication numbers and retrieved a list of related patent publications from around the world by pulling the entire INPADOC extended patent families (a group of related patents internationally) that were connected to our starting patent data from the United States and Canada [23]. We chose INPADOC for retrieving our international data because it is a free source, which is important for reproducibility. As mentioned above, “premium” international patent databases such as Derwent exist [24], as well as enhanced premium versions of INPADOC, such as LexisNexis Total Patent, Thomson Innovation, and Delphion [22]). There were no patents from India in our results, and so we undertook a supplementary search with the Indian Patent Office directly for patent applications and issued patents filed by these companies [25]. We were careful to group the output data by the starting patent publication, as this allowed us to clearly trace each patent publication to a marketed product by one of the four suppliers in the North American market or to a publication found in WIPO PatentScope. INPADOC returns patent publication threads. A thread starts from a single patent application filing and may include multiple legal events or publications that eventually culminate in a patent grant. Since multiple legal events are contained in the same file, we report the number of INPADOC threads, not the number of individual publications or issued patents within a given thread, unless otherwise noted. We have taken this approach because not all threads in INPADOC are complete, especially for developing countries, nor do they necessarily end with the granting of a patent. While our data may not provide the most up-to-date information on the legal status of a given filing, our data provide a sound global perspective on where patent rights are being pursued by various insulin manufacturers. We are further able to use this data to distinguish the type of technology described in different patent documents (e.g., insulin itself, method of manufacturing insulin, method of using insulin). Manufacturers A list of putative insulin manufacturers [26] was generated based from two major sources: first, a literature review of global market research using LexisNexis® Academic, ProQuest®, various country market reports (e.g., Frost & Sullivan Market Report Reviews, Business Monitor International Pharmaceutical & Healthcare Industry Reports) [27, 28] and second, a review of the websites of various pharmaceutical companies and Medicine Regulatory Authorities (MRAs). We reviewed this generated list of putative insulin producing companies and searched WIPO PatentScope using the company name and the search term “insulin” found anywhere in either the front page of the WIPO published patent application or in the Abstract of the patent application, with a filing date more recent than 1 January 1994. Data storage and analysis We created a single database for our main analysis, removed duplicates as well as any documents related to applications filed more than 20 years ago. In order to maintain focus upon insulin itself, we also set aside filings describing devices related to insulin administration. The complete dataset is in Additional file 3. Our findings in the area of insulin devices have been published elsewhere [29] and are briefly mentioned in the Discussion. Beginning with patent filings as of 1995, we analyzed what percentage of all patent threads filed in that year remained in force over time. (See Fig. 1). We performed a simple correlation analysis using the non-parametric Spearman’s rank order correlation using Excel®. This statistical test is independent of whether or not the data is normally distributed. We looked at the association between number of patent threads per country and a) the diabetes disease burden of that country and b) the gross national income per capita of that country. See Additional file 4. Estimates of the average number of persons with diabetes (2007 and 2010) were obtained from the International Diabetes Federation Atlas [30]. The average gross national income per capita (current US dollars) was obtained for various countries from the World Bank for the years 1995–2015 [31]. Fig. 1  The percentage of all granted insulin patents remaining in force in a given year for Eli Lilly, Novo Nordisk, Sanofi Aventis and Pfizer Most patents on insulin products in the world have already expired by 2015 yet many markets continue to be dominated by the brand-name versions marketed by original patent-holders. Figure 1 plots the percentage of all OB/HC granted patents on insulin remaining in force in any given year (based on a 20 year-from-filing patent life (black markers), and shows how relatively quickly the Eli Lilly, Novo and Pfizer insulin OB/HC patents are expiring compared to Sanofi. We confirm that after 2016, between about 5–20% of Pfizer, Eli Lilly and Novo Nordisk patents listed in the OB/HC remain un-expired and these percentages rapidly dimish, except for those of Sanofi who appears to have listed OB/HC patents whose expirations would extend well into 2030 and beyond (i.e., derived from a patent application filed in 2010). Figure 1 also shows the percentage of all granted patents remaining in force on insulin in any given year (based on a 20 year-from-filing patent life) for the WIPO PatentScope data (red markers) for products not on OB/HC. Novo Nordisk has filed their non-OB/HC insulin patent appliations in a manner similar to Sanofi, such that Novo’s expirations tend to be spread out over many years, unlike the Lilly or Pfizer portfolios. This insulin patent portfolio of Eli Lilly is likely to expire at least a decade before that of Novo and Sanofi. The presence of Pfizer in the insulin landscape is mainly for the non-injectable powdered human insulin inhalation product Exubera® but it is certainly worth noting that in 2007, after 11 years of development and barely one full year of sales, Pfizer stopped its production [32]. Although Fig. 1 may look similar to a Kaplan-Meier survivorship analysis, it is not. Unlike a real-world survivorship analysis, there is no censoring of the data because all the “subjects” (i.e.,. patent threads) have the same lifespan, as it were. All threads expire at the end of 20 years from filing and all patent expiries are recorded. The step function is due to the fact that large groups of patent filings often come to the end of their patent term at roughly the same time. The map in Fig. 2 shows the total number of patent threads found in the INPADOC database for Lilly, Sanofi, Novo and Pfizer for patent applications filed after 1995. In Africa, there are two regional patent offices, the Organisation Africaine de la Propriété Intellectuelle (OAPI) and the African Regional Intellectual Property Organization (ARIPO). Each is an intergovernmental organization for cooperation among African states in patent and other intellectual property matters. Both have the capacity to grant applications for patents in its member states who are parties to its patent protocol. OAPI and ARIPO refer to patent filings in countries of primarily French- West Africa and English- East Africa, respectively. Footnote 1 There are in total, 37 OAPI/ARIPO African countries but only between 1 and 5 patent thread filings per country were found (Fig. 2). Fig. 2  A map showing the number of insulin patent threads for Eli Lilly, Novo Nordisk, Sanofi Aventis based on patent applications filed after 1995. The different colors represent the number of insulin patent threads There is "no data" for some countries in Africa and many in the Middle East. This reflects either a lack of country data in INPADOC and/or a lack of interest in filing patent applications on the part of Lilly, Novo, Sanofi and/or Pfizer. Significantly, Africa has a low number of patent threads with South Africa having the highest. Indeed, the largest number of INPADOC patent thread filings are in the NAFTA countries (Mexico, U.S., Canada), the European Union countries (although not all), Japan and the BRIC countries (Brazil, Russia, India, China). Considering all the countries with evidence of INPADOC patent filings, the association between number of patent threads per country and the number of persons with diabetes in that country is moderate but significantly different than zero (Spearman rank correlation coefficient rho = 0.52; p < <0.005; df = 65). The association of patent thread per country with wealth per capita in that country was weaker and not significant (rho = 0.19; p = 0.12; df = 65). The major players in the Canadian, US and European markets have, not surprisingly, filed patent applications outside these markets and have received issued patents on technology claimed by their rapidly expiring Orange Book/Health Canada patents. They will expire at about the same time as the corresponding US patent portfolios (Fig. 1, black markers). Where our study detected Orange Book/Health Canada national patent filings, 64.6% were in high income, 27.7% were upper-middle income, and the remaining 7.7% were in lower middle income countries. Most are restricted to North America, Europe, Australia, India and China. Global insulin manufacturers Issued patents in low income settings were rare, even when we included regional patent regimes such as ARIPO or OAPI (Fig. 2). Particularly in Africa (Fig. 2), third parties may be free to exploit the technology claimed by the existing- and rapidly expiring-OB/HC patents as well as that for human insulin. Julphar (Gulf Pharmaceutical Industries, a UAE company), in early 2015 announced that construction of an insulin factory would start in Ethiopia [33]. Of the 40 putative insulin manufacturers identified in low- and middle-income countries, as of this writing we found only four (Biocon, Wockhardt, Tonghua Dongbao, Zhuhai Laboratories) that had any publicly available patent applications related to insulin. These four foreign manufacturers are filing patent applications primarily in Europe, the United States, Japan, China, India, South Korea, Israel, Russian Federation, Mexico, Malaysia, Canada, Australia, Ukraine, New Zealand and Egypt. Discussion It has been suggested [5] that because 53 % of United States patents on insulin were linked to the delivery devices and not the insulin itself [9], intellectual property is not a barrier for earlier versions of insulin entering the market. Patentable innovations in insulin delivery devices are designed to extend the overall patent protection of medicine/device product combinations. Such innovations are incremental but very common [29]. The statement that insulin IP is not a barrier to market entry is accurate only for the presently marketed insulins not linked to devices (Fig. 1: black symbols), and the main insulin producers are continually filing for patents on analog insulins in their R&D pipelines so their market exclusivity (assuming that these patent applications mature into issued patents) are likely to continue for years to come (Fig. 1: red symbols). In short, analysis of publicly-available data on global insulin patents and manufacturers indicates that the vast majority of the world’s insulin markets are dominated by brand-name manufacturers long after the original product and process patents have expired. The North American insulin market is dominated by the small number of companies who are the sole suppliers of one or more of six insulin analogs, which are available exclusively as brand name products. There is no US or Canadian human, non-analog insulin. Although third parties are likely free to exploit technology claimed by expiring OB/HC patents, it is possible that existing (i.e., non-expired) IP portfolios of Lilly, Novo, Sanofi and Pfizer in the U.S. and Canada (Fig. 1: red symbols) would prevent or hinder such exploitation. Given that the IP for recombinant human insulin, including DNA sequences and vectors is long off-patent, the existing insulin portfolios are unlikely to be sufficient to block production of human, recombinant insulin. Patent barriers are not the main reason for a lack of a generic version of recombinant human insulin in the U.S. marketplace or indeed, anywhere else in the world. Moreover, insulin markets have evolved towards containing the newest, most expensive analog products not only in the US and Europe but in every measured insulin market in the world. These shifts greatly complicate access to medicines for the 2.8 billion people living on less than $2 a day, and for many living on higher incomes as well. Stimulating markets for acceptable, yet older products is critical for changing insulin market dynamics; otherwise, brand name companies will continue to introduce upgraded and patented products, deeming their older offerings as obsolete and pulling them from the market. We do not know what fraction of the domestic production of insulin in areas outside the US and Canada is based on producing insulin under license for Novo Nordisk, Lilly, Sanofi and possibly for Pfizer. The positive relationship between INPADOC patent threads for these four large multinational companies and diabetes prevalence (Additional file 3) we infer as manifestation of the scaling effect of market size. We observed that only 10 % of the 40 putative insulin manufacturers identified in low- and middle-income countries were filing patent applications related to insulin. From this, we infer that they have intentions to market their own insulin in these countries and/or are already marketing their own insulin. For example, there are many companies making insulins for the Indian market and these products include, among others, purified bovine insulin (Bovine Longact® from USV), recombinant human insulin (Wosulin®: rDNA human monocomponent isophane Insulin from Wockhardt; Insugen®, human insulin from Biocon) and various insulin analogs (Lantus®- insulin glargine from Sanofi Aventis; Novomix-30®, Soluble insulin aspart 30 %, insulin aspart protamine 70 % from Novo Nordisk; Glaritus®, Insulin glargine from Wockhardt; Basalog®, insulin glargine from Biocon;) and combinations (e.g., Mixulin®, Porcine Insulin 30 %, Isophane Insulin 70 % from Cadila) [34–36]. Consider the following thought experiment: Assume Company X is producing both human analog insulin and human non-analog insulin in Ethiopia and wants to export both (i.e., respectively, a Lantus® and Humulin® equivalent) into the United States, Europe and a low income country (LIC). At the outset, we reiterate that within a few years patents in all these destinations (U.S., Europe and the LIC), if they exist at all, are unlikely to be a barrier to commercialization of the analog and there are no IP barriers to production of recombinant human insulin. What regulatory options exist to stimulate more competitive insulin markets? First, if imported into the US or made in the US under contract with Company X, both insulins will be regulated as a “drug” not as a biologic [37] and the regulatory dossier would be under the ANDA (“Abbreviated New Drug Application” pathway of US FDA Section 505(b)2. Indeed, this pathway was already used in 2006 for approval of a generic recombinant growth hormone product, Omnitrope® by Sandoz relying in-part on the FDA’s prior approval of Pfizer’s pioneer rhGH product, Genotropin® [38]. In August 2014, the US FDA granted tentative approval for Eli Lilly’s Basaglar®, a recombinantly produced insulin glargine analog for treating diabetes. As a 505(b)(2) product, approval relied in part on clinical studies carried out for the originator, Sanofi's Lantus® (insulin glargine). Basaglar® does not have final approval due to patent litigation involving Sanofi's patents. Time to tentative approval was rapid, however. It was exactly ten months [39]. The same product was approved as a “biosimilar” in 2014 in Europe. In the US and Europe, a recombinant version of non-analog human insulin would follow the same respective pathways [40]. Analog insulin glargine has recently been approved in Mexico [41] according to the biocomparable approvals pathway defined in 2012 (i.e., Galactus®, under license to PiSA Pharmaceuticals). A key issue, at least for the United States FDA, is whether a biosimilar insulin can be freely substituted at the pharmacy level [42]. The interchangeability of different small-molecule generics leads to substantially reduced drug pricing. When there is no interchangeability, it is not clear whether or not price competition will have an impact unless there is coherence with other policy interventions [43]. It is an open question as to whether or not the LICs could rely on the regulatory authorities in the US, India or Mexico and allow marketing of a version of glargine or human insulin. Notwithstanding the relative ease of US and European approval of Basaglar®, different manufacturing processes may result in subtly different insulin products. Such differences between versions of all insulins and their respective reference products could be expected [43]. Regulatory solutions can only partly address the structural problems contributing to uncompetitive off-patent insulin markets, if they do not address the broader problems of physician and patient preference. One of the biggest barriers to widespread access is the fact that doctors may be influenced by claims that insulin analogs are superior to human insulin when the evidence is equivocal. According to the WHO, no clear advantage (with lack of clinically important benefits) of analog insulin over recombinant human insulin has been established [44]. To be sure, if there are clinical complications associated with human insulin use, patients may indeed not want to switch from analog products to a human generic. In markets dominated by analogs, when a patient gets diagnosed (and needs insulin), he/she will likely be given the (multinational) analog insulin. If the patient feels better, they would want to continue with the same (analog) insulin and not switch to other (human) products/brands. Switching to another insulin would mean that a patient will have to regularly visit the doctor for tests/readings, and the patient would likely prefer to remain stable with one insulin. Simply put, the multinational companies have a wide physician network which reinforces their brand perceptions. In low- and middle-income countries where human insulin is still the predominant market share [45] this behavioral situation may well be less onerous yet, irrespective of insulin type, we suspect physician acceptance is a critical access barrier to overcome. Finally, once approved for market, the buyers of, as well as the payers for, these generic human insulins will need to negotiate for price, although in the US this opportunity is limited [46]. At present, the major sellers of insulin are well organized and their buyers are not. As pointed out recently [5], by contrast with antiretrovirals, which were paid for by donors such as the Global Fund, insulin is not purchased by donors, but rather directly from country budgets. In situations where pooled procurement of essential medicines is ongoing [47, 48] or proposed [49], its implementation may have a great influence on procurement prices for insulins of all types. Pooled procurement, in principle, avoids the costs of sustaining local production facilities that may not be viable in any case. However, it is difficult to investigate the extent to which such pooled procurement is effective in significantly increasing medicine penetration at the national level. But if the end result is that lower prices are being offered and more patients have access to medicines, the health system still benefits. One lesson from the ARV situation is that a possible barrier to pooled procurement is a lack of regulatory and procurement capacity at the country level [50]. Another option that has been used is a restricted tender system (in contrast to open tenders) for purchasing from well-known pre-qualified suppliers whose products have been previously authorised and with whom the procurement authority has had satisfactory results. However, a potential concern is that restricted tendering rounds may increase the likelihood of market concentration if the same suppliers win contracts, so that competitors let their product market authorisations expire. This is challenge for buyers to be mindful of. Some level of competition is naturally critical for tendering to work effectively, bearing in mind that quality and the continuity of supply are also important considerations [51]. Some arrangements allowing for tenders might be set up in a way that several manufacturers are selected for supplying the medicine at the same price. If this can be done so that competition is still suppressing prices, this might, in principle, prevent excessive concentration and its negative effects on future prices [52]. Further, the time period for which tenders are awarded could be limited to encourage more diversity in the market. Other criteria besides price can be included in a request for tender, such as quality of the product, quality of the delivery system (e.g., insulin vials versus insulin pens) and security of supply. The tendering system could be structured to ensure patients and their doctors retain adequate choice of subsidised treatments. A limitation of our method is that, in order for our study to be feasible and replicable, we confined our international patent search to the only international patent databases freely available (i.e., the EPO’s INPADOC via Espacenet, WIPO PatentScope) and India’s national patent database where many major generic pharmaceutical companies are based. However, there are other premium international patent databases (e.g., Derwent) and all other national patent databases [20, 53] which may yield additional records. Nonetheless, the EPO and the WIPO facilitate procedures and communications on a global or regional level. These organizations have the most official and complete information on global applications as well as adjunct information. They should always be used for any serious research that has legal and financial ramifications and for verifying information found in other sources. Conclusions This global analysis of patents and producers of global insulin documents that for most of the world there is little to no alternatives to brand-named analog insulins and non-analog human alternatives in low- and middle-income countries. The market dominance of analog over human insulin is not a function of intellectual property exclusivity as patents on human insulin have expired long ago. Although patents on the current portfolio of analogs will expire very soon, there are many patent filings and granted patents on insulins that are not marketed in the United States so a very few companies are enjoying complete monopolies in these markets for a surprisingly long time. The moderate, but statistically significant association between patent filings and diabetes disease burden suggests these multinationals are filing for more patents in the bigger markets with large numbers of persons with diabetes and an rapidly emerging middle class, although these bigger markets (Brazil, India, China) are not the wealthiest per capita. This should not be a surprise to anyone. Mapping the patent estates on insulins is a first step in encouraging manufactures globally to consider this opportunity to enter other, far smaller markets.

#### Lack of generics impacts millions – evergreening specifically is key

**Dewar et al 15** (Dewar, Heather, et al. “Why People with Diabetes Can't Buy Generic Insulin.” Johns Hopkins Medicine, 18 Mar. 2015, www.hopkinsmedicine.org/news/media/releases/why\_people\_with\_diabetes\_cant\_buy\_generic\_insulin. )//LK [Accessed 8/22/21]

Fast Facts: Drug companies have made incremental improvements that kept insulin under patent for more than 90 years. Insulin can cost $120 to $400 per month for patients with no prescription drug coverage. Many patients with diabetes have lapses in medication that can lead to serious complications requiring hospitalization. A generic version of insulin, the lifesaving diabetes drug used by 6 million people in the United States, has never been available in this country because drug companies have made incremental improvements that kept insulin under patent from 1923 to 2014. As a result, say two Johns Hopkins internist-researchers, many who need insulin to control diabetes can’t afford it, and some end up hospitalized with life-threatening complications, such as kidney failure and diabetic coma. In a study published March 19, 2015, in the New England Journal of Medicine, authors Jeremy Greene, M.D., Ph.D., and Kevin Riggs, M.D., M.P.H., describe the history of insulin as an example of “evergreening,” in which pharmaceutical companies make a series of improvements to important medications that extend their patents for many decades. This keeps older versions off the generic market, the authors say, because generic manufacturers have less incentive to make a version of insulin that doctors perceived as obsolete. Newer versions are somewhat better for patients who can afford them, say the authors, but those who can’t suffer painful, costly complications. “We see generic drugs as a rare success story, providing better quality at a cheaper price,” says Greene, an associate professor of the history of medicine at the Johns Hopkins University School of Medicine and a practicing internist. “And we see the progression from patented drug to generic drug as almost automatic. But the history of insulin highlights the limits of generic competition as a framework for protecting the public health.” More than 20 million Americans have diabetes, in which the body fails to properly use sugar from food due to insufficient insulin, a hormone produced in the pancreas. Diabetes can often be managed without drugs or with oral medications, but some patients need daily insulin injections. The drug can often cost from $120 to $400 per month without prescription drug insurance. “Insulin is an inconvenient medicine even for people who can afford it,” says Riggs, a research fellow in general internal medicine and the Berman Institute of Bioethics at Johns Hopkins. “When people can’t afford it, they often stop taking it altogether.” Patients with diabetes who are not taking prescribed insulin come to Riggs’ and Greene’s Baltimore-area clinics complaining of blurred vision, weight loss and intolerable thirst — symptoms of uncontrolled diabetes, which can lead to blindness, kidney failure, gangrene and loss of limbs. The two doctors decided to find out why no one makes generic insulin. A University of Toronto medical team discovered insulin in 1921, and in 1923, the university, which held the first patent, gave drug companies the right to manufacture it and patent any improvements. In the 1930s and 1940s, pharmaceutical companies developed long-acting forms that allowed most patients to take a single daily injection. In the 1970s and 1980s, manufacturers improved the purity of cow- and pig-extracted insulin. Since then, several companies have developed synthetic analogs. Biotech insulin is now the standard in the U.S., the authors say. Patents on the first synthetic insulin expired in 2014, but these newer forms are harder to copy, so the unpatented versions will go through a lengthy Food and Drug Administration approval process and cost more to make. When these insulins come on the market, they may cost just 20 to 40 percent less than the patented versions, Riggs and Greene write.

#### B – Patent evergreening causes AIDS backsliding – kills almost a million people EACH YEAR

**Frontline AIDS** (“How Patents Affect Access to Hiv Treatment.” Frontline AIDS, 2 October 2019, frontlineaids.org/how-patents-affect-access-to-hiv-treatment/)//LK [Accessed 8/25/2021] \*pppy = per person per year

Since the world acknowledged the global AIDS epidemic in the 1980s much has changed. With better treatment and prevention options, AIDS is no longer seen as a death sentence. Better treatment for co-infections, particularly multi-drug resistant tuberculosis (MDR-TB) and for viral hepatitis have also emerged in the past decade. However, despite the huge progress made, 1.7 million people acquired HIV last year and 770,000 died of AIDS-related illness. For those people – the parents, children, siblings, and friends who unnecessarily lost their lives – the declarations of success are hollow. UNAIDS, which NGOs have been criticising for years for its unduly optimistic reporting, has now acknowledged in its 2019 Epidemic Update that “the annual number of HIV infections has increased in three regions: Eastern Europe and Central Asia (29% increase), Middle East and North Africa (10% increase) and Latin America (7% increase)”. HIV advances that had been made, are now reversing. The over-positive reporting resulted in a serious side-effect. Donors, with competing priorities, bought into the success narrative, and overall global funding for AIDS was reduced. Investment in the HIV responses of low- and middle-income countries decreased by $900 million in just one year. We must act now to ensure the response is fully funded and barriers to accessing medicines, including to second and third line HIV treatment and co-infection treatments, are effectively tackled. Frontline AIDS and the International Treatment Preparedness Coalition (ITPC) have released a joint report looking at one of these crucial barriers – the problem with patents in middle-income countries (MICS). In 2019, people aren’t dying because the drugs for treating HIV, MDR-TB, hepatitis C and many other diseases don’t exist. People are dying because they can’t access them. With an increasing focus on voluntary mechanisms to provide access to medicines, the problem with patents in MICs is being seriously over-looked; as are the legitimate tools that governments can use to increase access and availability and decrease prices. The use of legal mechanisms like TRIPS flexibilities by governments has proven highly effective; in the use of these legal tools, governments, global health agencies and civil society all have an essential role to play. It will not be possible to achieve a sustainable response to HIV without tackling intellectual property (IP) barriers, particularly in MICs. The problem with patents One of the most critical barriers that has existed since treatment for HIV was first approved relates to patents. Patenting of medicines has increased considerably since 2005. More worrying is the trend of ‘evergreening’ patents. Evergreening is a tactic used by pharmaceutical companies to extend their exclusivity over a medicine by applying for, and usually getting, multiple, overlapping patents on a single medicine. Most medicines are covered by several patents, known as patent ‘thickets’ and are used to delay or complicate generic production. Over-pricing as a result of unmerited and extended monopolies puts a huge strain on health budgets. While in theory a government may commit to universal access, in reality the budget may not stretch. Prices for HIV treatment can vary from under $100 to tens of thousands of dollars per person per year (pppy) – for the same drug. Take dolutegravir (DTG) for example. In July 2019, the World Health Organization (WHO) recommended all countries immediately adopt DTG-based regimens as the preferred first-line treatment for HIV. Prices pppy range from $75 for countries that are in a ‘voluntary license’, up to $9656 for those that are not. Middle-income, high burden Typically, MICs are worst affected by the patent problem. Nearly 38 million people live with HIV and a majority of them live in MICs. The countries’ income classification means they are frequently left out of pricing deals or voluntary agreements and have funding reduced by health and development agencies, and so face the dual burden of high prevalence and high costs. Evergreening is just one of the tactics employed by pharmaceutical companies to maintain monopolies and pave the way for this arbitrary pricing. Our report details other tactics as well as how they can be legitimately challenged. Within the Sustainable Development Goals themselves our recommendations are backed. SDG3b reaffirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) regarding flexibilities to protect public health, and, in particular, provide access to medicines for all. Unless TRIPS flexibilities are more routinely put into practice we risk undermining the commitments made to the HIV response.

#### C – Evergreen patents increase costs and stifle drug innovation – almost 80% of new patents were not for new drugs

**Robin 18** (Robin Feldman, May your drug price be evergreen, Journal of Law and the Biosciences, Volume 5, Issue 3, December 2018, Pages 590–647, [https://doi.org/10.1093/jlb/lsy022 [Robin Feldman, Hastings College of the Law, University of California])//LK](https://doi.org/10.1093/jlb/lsy022%20%5bRobin%20Feldman,%20Hastings%20College%20of%20the%20Law,%20University%20of%20California%5d)//LK) [Accessed 8/23/21]

IV.A. Overview The study results demonstrate definitively that the pharmaceutical industry has strayed far from the patent system's intended design. The patent system is not functioning as a time-limited opportunity to garner a return, followed by open competition. Rather, companies throughout the industry seek and obtain repeated extensions of their competition-free zones. Moreover, the incidence of such behavior has steadily increased between 2005 and 2015, especially on the patent front and for certain highly valuable exclusivities. Most troubling, the data suggest that the current state of affairs is harming innovation in tangible ways. Rather than creating new medicines—sallying forth into new frontiers for the benefit of society—drug companies are focusing their time and effort extending the patent life of old products. This, of course, is not the innovation one would hope for. The greatest creativity at pharmaceutical companies should be in the lab, not in the legal department.[115](about:blank) The following sections describe the results obtained through our analysis in detail, but below are the key takeaways from the study: Rather than creating new medicines, pharmaceutical companies are recycling and repurposing old ones. In fact, 78% of the drugs associated with new patents in the FDA’s records were not new drugs coming on the market, but existing drugs. In some years, the percentage reached as high as 80%. Adding new patents and exclusivities to extend the protection cliff is particularly pronounced among blockbuster drugs. Of the roughly 100 best-selling drugs, more than 70% extended their protection at least once, with more than 50% extending the protection cliff more than once. Looking at the full group, almost 40% of all drugs available on the market created additional market barriers by having patents or exclusivities added to them. Many of the drugs adding to the Orange Book are ‘serial offenders’—returning to the well repeatedly for new patents and exclusivities. Of the drugs that had an addition to the Orange Book, 80% of those had an addition to the Orange Book on more than one occasion, and almost half of these drugs had additions to the Orange Book on four or more occasions. The number of drugs with a high quantity of added patents in a single year has substantially increased. For example, the number of drugs with three or more patents added to them in one year has doubled. Similarly, the number of drugs with five or more added patents has also doubled. Overall, the quantity of patents added to the Orange Book has more than doubled, increasing from 349 patents added in the year 2005 to 723 in 2015. The number of drugs that had a patent added to them in the Orange Book almost doubled. There were striking increases in certain exclusivities, such as orphan drug exclusivity, new patient population exclusivity, and new product exclusivity. In particular, the number of drugs with an added orphan drug exclusivity tripled. In addition, the number of times a use code was added to a patent more than tripled, suggesting that this has become a new favored game. To provide a broad sense of the types of metrics we are using, some could be characterized as ‘intensity’ measures, which capture the breadth and depth of patent and exclusivity activity in the industry. Another set of our metrics can be characterized as ‘temporal’ measures, which evaluate whether there are any trends in the behavior under examination across time during our 11-year timeframe from 2005 to 2015. IV.B. Number of drugs that had patents and/or exclusivities added to them in the Orange Book, compared to the total number of drugs available As an initial inquiry, we wanted to determine the extent to which companies are adding patents and exclusivities to drugs. Is this a limited activity, confined to well-worn anecdotes that everyone repeats, or does it occur throughout the industry? Our results demonstrate that adding patents and exclusivities is a common behavior, endemic to pharmaceuticals. In fact, between 2005 and 2015, almost 40% of all drugs available on the market had patents, exclusivities, or other changes added to them. Table [1](about:blank) shows the total number of FDA-approved drugs available on the market in each year of our study. Table [2](about:blank) shows the number of drugs that had a patent or exclusivity added to them as a percentage of the total number of drugs. The figure is broken down in terms of the number of drugs with an added patent, the number of drugs with an added exclusivity, and the number of drugs that had any relevant change made to it (which includes not only adding a patent and/or exclusivity, but also other significant changes such as adding a use code.)

#### Innovation solves disease, bioterror, antimicrobial resistance, and a host of existential threats. The response to COVID is the exception, not the rule, and more needs to be done to incentivize innovation even when high risk impacts aren’t viewed as such by the general public

**Marjanovic and Feijao 20** (Marjanovic, Sonja and Carolina Feijao, Pharmaceutical Innovation for Infectious Disease Management: From Troubleshooting to Sustainable Models of Engagement. Santa Monica, CA: RAND Corporation, 2020. <https://www.rand.org/pubs/perspectives/PEA407-1.html)//LK> [Accessed 8/30/31]

We need to ensure scalable and sustainable approaches for pharmaceutical innovation in response to infectious disease threats to public health As key actors in the healthcare innovation landscape, pharmaceutical and life sci-ences companies have been called on to develop medicines, vaccines and diagnostics for pressing public health challenges. The COVID-19 crisis is one such challenge, but there are many others. For example, MERS, SARS, Ebola, Zika and avian and swine flu are also infectious diseases that represent public health threats. Infectious agents such as anthrax, smallpox and tularemia could present threats in a bioterrorism con-text.1 The general threat to public health that is posed by antimicrobial resistance is also well-recognised as an area in need of pharmaceutical innovation. Innovating in response to these challenges does not always align well with pharmaceutical industry commercial models, shareholder expectations and compe-tition within the industry. However, the expertise, networks and infrastructure that industry has within its reach, as well as public expectations and the moral imperative, make pharmaceutical companies and the wider life sciences sector an indispensable partner in the search for solutions that save lives. This perspective argues for the need to establish more sustainable and scalable ways of incentivising pharmaceu-tical innovation in response to infectious disease threats to public health. It considers both past and current examples of efforts to mobilise pharmaceutical innovation in high commercial risk areas, including in the context of current efforts to respond to the COVID-19 pandemic. In global pandemic crises like COVID-19, the urgency and scale of the crisis – as well as the spotlight placed on pharmaceutical companies – mean that contributing to the search for effective medicines, vaccines or diagnostics is essential for socially responsible companies in the sec-tor.2 It is therefore unsurprising that we are seeing indus-try-wide efforts unfold at unprecedented scale and pace. Whereas there is always scope for more activity, industry is currently contributing in a variety of ways. Examples include pharmaceutical companies donating existing com-pounds to assess their utility in the fight against COVID-19; screening existing compound libraries in-house or with partners to see if they can be repurposed; accelerating tri-als for potentially effective medicine or vaccine candidates; and in some cases rapidly accelerating in-house research and development to discover new treatments or vaccine agents and develop diagnostics tests.3,4 Pharmaceutical companies are collaborating with each other in some of these efforts and participating in global R&D partnerships (such as the Innovative Medicines Initiative effort to accel-erate the development of potential therapies for COVID-19) and supporting national efforts to expand diagnosis and testing capacity and ensure affordable and ready access to potential solutions.3,5,6 The primary purpose of such innovation is to benefit patients and wider population health. Although there are also reputational benefits from involvement that can be realised across the industry, there are likely to be rela-tively few companies that are ‘commercial’ winners. Those who might gain substantial revenues will be under pres-sure not to be seen as profiting from the pandemic. In the United Kingdom for example, GSK has stated that it does not expect to profit from its COVID-19 related activities and that any gains will be invested in supporting research and long-term pandemic preparedness, as well as in developing products that would be affordable in the world’s poorest countries.7 Similarly, in the United States AbbVie has waived intellectual property rights for an existing com-bination product that is being tested for therapeutic poten-tial against COVID-19, which would support affordability and allow for a supply of generics.8,9 Johnson & Johnson has stated that its potential vaccine – which is expected to begin trials – will be available on a not-for-profit basis during the pandemic.10 Pharma is mobilising substantial efforts to rise to the COVID-19 challenge at hand. However, we need to consider how pharmaceutical innovation for responding to emerging infectious diseases can best be enabled beyond the current crisis. Many public health threats (including those associated with other infectious diseases, bioterror-ism agents and antimicrobial resistance) are urgently in need of pharmaceutical innovation, even if their impacts are not as visible to society as COVID-19 is in the imme-diate term. The pharmaceutical industry has responded to previous public health emergencies associated with infec-tious disease in recent times – for example those associated with Ebola and Zika outbreaks.11 However, it has done so to a lesser scale than for COVID-19 and with contribu-tions from fewer companies. Similarly, levels of activity in response to the threat of antimicrobial resistance are still low.12 There are important policy questions as to whether – and how – industry could engage with such public health threats to an even greater extent under improved innova-tion conditions. The COVID-19 pandemic is a game-changer among global public health threats. The risk to human life (both in terms of morbidity and quality of life), the economic risks, the epidemiology of the disease and speed of escalation have led to a crisis-response by many governments around the world. This has in turn influenced the immediate indus-try efforts. Many other infectious disease threats may not manifest as crises in the short term and in the same way as COVID-19, but they could nevertheless escalate. They are not considered to be crises from a short term perspective because they are contained to specific regions and affect fewer people at present – or are re-emerging (e.g. Ebola) – or their impacts have not yet materialised at a scale that would qualify as an immediate crisis (e.g. growing risks of antimi-crobial resistance to some infectious pathogens). However, such diseases and issues are recognised as global threats that could become crises in the future.13 The emerging threats raise important policy questions about how government and the pharmaceutical industry can work together to ensure that pharmaceutical industry innovation is incentivised sustainably and at scale. This is important to help mitigate against current and emerging threats becoming crises further down the line. At present, there are no clear and specific criteria to determine when a disease can trigger the types of healthcare-innovation-re-lated policy actions that have been deployed in response to the COVID-19 crisis. For example, this applies to criteria for securing financial resources for innovation-related activities, reforming regulation to accelerate trials and regulatory approval processes, and securing reimburse-ment mechanisms that help enable industry engagement and the search for rapid solutions. The WHO guidance on what constitutes a pandemic phase does provide guidance on national policy response options, but not specifically as they relate to healthcare innovation activity.14 There are also questions as to whether such policy initiatives and incentives should only be applied in crisis situations, or also as part of proactive government and industry efforts to innovate in the areas of public health threats in order to prevent future global calamities. A crisis and ‘emergency mode’ response may be inevitable for some diseases, but more can be done to mitigate against the need for such a response – especially in cases where emerging threats and their consequences can be foreseen and are known to be a risk. We need to anticipate and act now in terms of how we plan and incentivise better for the future, and how we distinguish between different types of infectious disease threats and phases in framing incentives and regulation.

#### Disease and bioweapons cause extinction – mathematically outweighs, even if they win mitigation.

**Millett & Snyder-Beattie ‘17**. Millett, Ph.D., Senior Research Fellow, Future of Humanity Institute, University of Oxford; and Snyder-Beattie, M.S., Director of Research, Future of Humanity Institute, University of Oxford. 08-01-2017. “Existential Risk and Cost-Effective Biosecurity,” Health Security, 15(4), PubMed

In the decades to come, advanced bioweapons could **threaten human existence**. Although the **probability** of human extinction from bioweapons **may** be low, the **expected value** of **reducing** the risk could **still** be **large**, since such risks jeopardize the existence of **all future generations**. We provide an overview of biotechnological extinction risk, make some rough initial estimates for how severe the risks might be, and compare the cost-effectiveness of reducing these extinction-level risks with existing biosecurity work. We find that reducing human extinction risk can be more cost-effective than reducing smaller-scale risks, even when using conservative estimates. This suggests that the risks are not low enough to ignore and that more ought to be done to prevent the worst-case scenarios. How worthwhile is it spending resources to study and mitigate the chance of human extinction from biological risks? The risks of such a catastrophe are presumably low, so a skeptic might argue that addressing such risks would be a waste of scarce resources. In this article, we investigate this position using a cost-effectiveness approach and ultimately conclude that the expected value of reducing these risks is large, especially since such risks jeopardize the existence of all future human lives. **Historically, disease events have been responsible for the greatest death tolls** on humanity. The 1918 flu was responsible for more than 50 million deaths,1 while smallpox killed perhaps 10 times that many in the 20th century alone.2 The Black Death was responsible for killing over 25% of the European population,3 while other pandemics, such as the plague of Justinian, are thought to have killed 25 million in the 6th century—constituting over 10% of the world's population at the time.4 It is an open question whether a future pandemic could result in outright human extinction or the irreversible collapse of civilization. A skeptic would have many good reasons to think that existential risk from disease is unlikely. Such a disease would need to spread worldwide to **remote populations**, overcome **rare genetic resistances**, and **evade detection**, cures, and **countermeasures**. Even evolution itself may work in humanity's favor: **Virulence and transmission is often a trade-off**, and so **evolutionary pressures** could push against maximally lethal wild-type pathogens.5,6 While these arguments point to a very small risk of human extinction, they **do not rule** the possibility **out** entirely. Although rare, there are recorded instances of **species going extinct due to disease**—primarily in amphibians, but also in 1 mammalian species of rat on Christmas Island.7,8 There are also **historical examples of large human populations being almost entirely wiped out** by disease, especially when multiple diseases were simultaneously introduced into a population without immunity. The most striking examples of total population collapse include **native American tribes** exposed to European diseases, such as the Massachusett (86% loss of population), Quiripi-Unquachog (95% loss of population), and the Western Abenaki (which suffered a staggering 98% loss of population).9 In the modern context, no single disease currently exists that combines the worst-case levels of transmissibility, lethality, resistance to countermeasures, and global reach. But **many diseases are proof** of principle that **each worst-case attribute can be realized independently**. For example, some diseases exhibit nearly a 100% case fatality ratio in the absence of treatment, such as rabies or septicemic plague. Other diseases have a track record of spreading to virtually every human community worldwide, such as the 1918 flu,10 and seroprevalence studies indicate that other pathogens, such as chickenpox and HSV-1, can successfully reach over 95% of a population.11,12 Under optimal virulence theory, **natural evolution** would be an **unlikely** source for pathogens with the **highest possible levels of transmissibility, virulence, and global reach**. But **advances in biotech**nology might allow the creation of diseases that **combine such traits**. Recent controversy has **already emerged** over a number of **scientific experiments** that resulted in viruses with enhanced **transmissibility**, **lethality**, and/or the ability to overcome **therapeutics**.13-17 Other experiments demonstrated that mousepox could be modified to have a 100% case fatality rate and render a vaccine ineffective.18 In addition to transmissibility and lethality, studies have shown that other disease traits, such as incubation time, environmental survival, and available vectors, could be modified as well.19-21 Although these experiments had scientific merit and were not conducted with malicious intent, their implications are still worrying. This is especially true given that there is also a **long historical track record** of**state-run bioweapon research** applying cutting-edge science and technology to design agents not previously seen in nature. The Soviet bioweapons program developed agents with traits such as enhanced virulence, resistance to therapies, greater environmental resilience, increased difficulty to diagnose or treat, and which caused unexpected disease presentations and outcomes.22 Delivery capabilities have also been subject to the cutting edge of technical development, with Canadian, US, and UK bioweapon efforts playing a critical role in developing the discipline of aerobiology.23,24 While there is no evidence of state-run bioweapons programs directly attempting to develop or deploy bioweapons that would pose an existential risk, the logic of deterrence and **m**utually **a**ssured **d**estruction could create such incentives in more unstable political environments or following a breakdown of the Biological Weapons Convention.25 The **possibility of a war** between great powers could also increase the pressure to use such weapons—during the World Wars, bioweapons were used across multiple continents, with Germany targeting animals in WWI,26 and Japan using plague to cause an epidemic in China during WWII.27 **Non-state actors** may also pose a risk, especially those with **explicitly omnicidal aims**. While rare, there are examples. The Aum Shinrikyo cult in Japan sought biological weapons for the express purpose of causing extinction.28 Environmental groups, such as the Gaia Liberation Front, have argued that “we can ensure Gaia's survival only through the extinction of the Humans as a species … we now have the specific technology for doing the job … several different [genetically engineered] viruses could be released”(quoted in ref. 29). Groups such as R.I.S.E. also sought to protect nature by destroying most of humanity with bioweapons.30 Fortunately, to date, non-state actors have **lacked the capabilities** needed to pose a catastrophic bioweapons threat, but this could change in future decades as **biotech**nology becomes **more accessible** and the **pool of experienced users grows**.31,32 What is the appropriate response to these speculative extinction threats? A balanced biosecurity portfolio might include investments that reduce a mix of proven and speculative risks, but striking this balance is still difficult given the massive uncertainties around the low-probability, high-consequence risks. In this article, we examine the traditional spectrum of biosecurity risks (ie, biocrimes, bioterrorism, and biowarfare) to categorize biothreats by likelihood and impact, expanding the historical analysis to consider even lower-probability, higher-consequence events (catastrophic risks and existential risks). In order to produce reasoned estimates of the likelihood of different categories of biothreats, we bring together relevant data and theory and produce some first-guess estimates of the likelihood of different categories of biothreat, and we use these initial estimates to compare the cost-effectiveness of reducing existential risks with more traditional biosecurity measures. We emphasize that these models are highly uncertain, and their utility lies more in enabling order-of-magnitude comparisons rather than as a precise measure of the true risk. However, **even with the most conservative models**, we find that reduction of **low-probability, high-consequence risk**s can be more cost-effective, as measured by **quality-adjusted life year** per dollar, especially when we account for the lives of future generations. This suggests that **despite** the **low probability** of such events, society **still ought to invest more in preventing the most extreme possible biosecurity catastrophes**.

## Advocacy

#### Thus, the plan: the member nations of the World Trade Organization ought to reduce intellectual property protections for medicines by limiting drug innovators to one market exclusivity of their choice for their drug.

#### Solves better than any counterplan – only the aff tackles incentives

**Feldman 19** (Feldman, Robin. “Drug Patent Protection: It's Time for a 'One-and-Done' Approach.” STAT, 11 Feb. 2019, [www.statnews.com/2019/02/11/drug-patent-protection-one-done/. [Robin Feldman is professor of law and director of the Institute for Innovation Law at UC Hastings College of the Law in San Francisco and author of “Drugs, Money, and Secret Handshakes” (Cambridge University Press, March 2019).])//LK](http://www.statnews.com/2019/02/11/drug-patent-protection-one-done/.%20%5b%5d)//LK) [Accessed 8/25/2021]

In a perfect world, the system for conveying medications from their makers to patients should be designed to deliver the lowest-cost drugs. The system in the U.S. doesn’t even come close. Insurers should provide the lowest-cost and highest-quality drug benefit for each plan, public or private. But they don’t. Pharmacy benefit managers should use their volume buying power to obtain rebates that individuals could never obtain on their own and pass those rebates along to patients. But they don’t. Pharmacists, who know the prices of the drugs in their stock and who see patients’ cost-sharing amounts at the cash register, should be motivated to provide their customers with information on how to find the best deal so they can afford their medicines. But they aren’t. Doctors should make medication decisions that are in the best interests of their patients. But they often don’t. All of this occurs against the backdrop of a national conversation to lower drug costs and a policy to expedite and encourage vigorous competition in the pharmaceutical industry through the rapid entry of generic drugs as soon as patents expire. But even though the vast majority of prescriptions are filled with generic drugs, rising prices on existing brand-name drugs and sky-high prices for new drugs are swamping the savings from generics. Why isn’t the system working as it should? Related: Behind the patent thicket: tactics AbbVie allegedly used to thwart biosimilar versions of Humira Some experts believe the U.S. can rein in drug process with value-based pricing, which aims to tie the prices we pay for drugs to the benefits they provide, either in terms of longer life or better quality of life. Others call for dismantling pharmacy benefit managers. Still others want large groups like Medicare to negotiate with drug companies for better drug prices. While each of these might help, they cannot solve the problem alone. Why? Because they do not reach the heart of the problem. As I explain in my new book, “Drugs, Money, and Secret Handshakes,” the government itself is giving pharmaceutical companies the power they are wielding through overly generous drug patent protection. Effective solutions must address that problem. Drug companies have brought great innovations to market. Society rewards innovation with patents, or with non-patent exclusivities that can be obtained for activities such as testing drugs in children, undertaking new clinical studies, or developing orphan drugs. The rights provided by patents or non-patent exclusivities provide a defined time period of protection so companies can recoup their investments by charging monopoly prices. When patents end, lower-priced competitors should be able to jump into the market and drive down the price. But that’s not happening. Instead, drug companies build massive patent walls around their products, extending the protection over and over again. Some modern drugs have an avalanche of U.S. patents, with expiration dates staggered across time. For example, the rheumatoid arthritis drug Humira is protected by more than 100 patents. Walls like that are insurmountable. Rather than rewarding innovation, our patent system is now largely repurposing drugs. Between 2005 and 2015, more than three-quarters of the drugs associated with new patents were not new ones coming on the market but existing ones. In other words, we are mostly churning and recycling. Particularly troubling, new patents can be obtained on minor tweaks such as adjustments to dosage or delivery systems — a once-a-day pill instead of a twice-a-day one; a capsule rather than a tablet. Tinkering like this may have some value to some patients, but it nowhere near justifies the rewards we lavish on companies for doing it. From society’s standpoint, incentives should drive scientists back to the lab to look for new things, not to recycle existing drugs for minimal benefit. Related: WATCH: What is a biosimilar, exactly? I believe that one period of protection should be enough. We should make the legal changes necessary to prevent companies from building patent walls and piling up mountains of rights. This could be accomplished by a “one-and-done” approach for patent protection. Under it, a drug would receive just one period of exclusivity, and no more. The choice of which “one” could be left entirely in the hands of the pharmaceutical company, with the election made when the FDA approves the drug. Perhaps development of the drug went swiftly and smoothly, so the remaining life of one of the drug’s patents is of greatest value. Perhaps development languished, so designation as an orphan drug or some other benefit would bring greater reward. The choice would be up to the company itself, based on its own calculation of the maximum benefit. The result, however, is that a pharmaceutical company chooses whether its period of exclusivity would be a patent, an orphan drug designation, a period of data exclusivity (in which no generic is allowed to use the original drug’s safety and effectiveness data), or something else — but not all of the above and more. Consider Suboxone, a combination of buprenorphine and naloxone for treating opioid addiction. The drug’s maker has extended its protection cliff eight times, including obtaining an orphan drug designation, which is intended for drugs that serve only a small number of patients. The drug’s first period of exclusivity ended in 2005, but with the additions its protection now lasts until 2024. That makes almost two additional decades in which the public has borne the burden of monopoly pricing, and access to the medicine may have been constrained. Implementing a one-and-done approach in conjunction with FDA approval underscores the fact that these problems and solutions are designed for pharmaceuticals, not for all types of technologies. That way, one-and-done could be implemented through legislative changes to the FDA’s drug approval system, and would apply to patents granted going forward. Related: Extraordinary tactics, perverse incentives: Makers of top-selling drugs hike prices in lockstep, and patients bear the cost One-and-done would apply to both patents and exclusivities. A more limited approach, a baby step if you will, would be to invigorate the existing patent obviousness doctrine as a way to cut back on patent tinkering. Obviousness, one of the five standards for patent eligibility, says that inventions that are obvious to an expert or the general public can’t be patented. Either by congressional clarification or judicial interpretation, many pile-on patents could be eliminated with a ruling that the core concept of the additional patent is nothing more than the original formulation. Anything else is merely an obvious adaptation of the core invention, modified with existing technology. As such, the patent would fail for being perfectly obvious. Even without congressional action, a more vigorous and robust application of the existing obviousness doctrine could significantly improve the problem of piled-up patents and patent walls. Pharmaceutical companies have become adept at maneuvering through the system of patent and non-patent rights to create mountains of rights that can be applied, one after another. This behavior lets drug companies keep competitors out of the market and beat them back when they get there. We shouldn’t be surprised at this. Pharmaceutical companies are profit-making entities, after all, that face pressure from their shareholders to produce ever-better results. If we want to change the system, we must change the incentives driving the system. And right now, the incentives for creating patent walls are just too great.

## Framing --- Util

#### The standard is maximizing expecting well being.

#### 1] Util is a lexical pre-requisite to any other framework: Threats to life preclude the ability for moral actors to effectively utilize and act upon other moral theories since they are in a constant state of crisis – that inhibits the ideal moral conditions which other theories presuppose.

#### 2] Extinction matters under any framework:

#### ---A] It precludes the possibility of any kind of moral value – we can’t confer value onto anything if we’re not alive.

#### ---B] Future generations means infinite magnitude – we have to look towards future lives too

## 1AC---Theory

#### ] 1AR theory –

#### ---A] AFF gets it because otherwise the neg can engage in infinite abuse, making debate impossible. No 2nr theory – kills resolvability because judge has to intervene in weighing interp and 2ar counterinterp.

#### ---B] drop the debater – the short 1AR irreparably skewed from abuse on substance and time investment on theory.

#### ---C] no RVIs – the 6-minute 2nr can collapse to a short shell and get away with infinite 1nc abuse via sheer brute force and time spent on theory.

#### ---D] Use competing interps – 1AR interps aren’t bidirectional and the neg should have to defend their norm since they have more time.

#### ] Yes Aff RVIs

#### ---A] I have a 4 minute 1AR to answer T or Theory which skews my time from other arguments. T bites out of a higher percentage of my rebuttal time.

#### ---B] No risk issue for the negative, you can go for it in the 2nr if I undercover but if I overallocated you can just kick it.

#### ] Fairness is a voter – debate is a competitive activity and needs both debaters to be on an equal playing field.