

Annex

The following is a draft working document that will eventually be part of a study for WIPO on alternatives to the patent system. It is attached to the KEI WHO proposal for an Antibiotics Innovation Funding Mechanism, in order to provide some comparisons and contrasts with other proposed mechanisms.

Approaches to simulating innovation for the development of new antibiotic drugs

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Introduction

"What makes antibiotics unusual is that their very use undermines their future usefulness, as bacteria evolve resistance."¹

There are large challenges associated with the development of new antibiotic drugs and diagnostic

¹ Eric Kades, Eric, "Preserving a Precious Resource: Rationalizing the Use of Antibiotics," (2005) 99 Northwestern University Law Review, . 615 2004-2005. Page 626. Available at Faculty Publications. Paper 52. <http://scholarship.law.wm.edu/facpubs/52>. Citing the earlier works by Clem Tisdell, Exploitation of Techniques That Decline in Effectiveness With Use, 37 Public Finance /Finances Publique 428 (1982), and Gardner Brown and David Layton, Resistance Economics: Social Cost and the Evolution of Anti-biotic Resistance, *Environment and Development Economics*. 349, 354 (1996).

tests that will reduce their misuse, and in recent years there have been a number of proposals to stimulate innovation for new antibiotic drugs. These can be divided into proposals to (1) increase public sector funding, tax credits and other subsidies of R&D (2) reduce regulatory costs and barriers for registering products (3) extending terms for patents and other intellectual property rights, (4) using innovation inducement prize type incentives to reward innovation, and (5) other.

(1) R&D Subsidies.

Recommendations to stimulate the production of new drugs typically include proposals to expand government funding of R&D, as well as the provision of other subsidies, such as special tax deductions or credits, or concessionary financing.

Government funding of research and development of new antibiotic drugs and relevant diagnostics, while falling short of what many health experts feel is needed, is important. The US NIH/NIAID has a number of initiatives underway that they describe as "Combating Drug Resistance With Basic Research," which are designed to:

- Develop new insights into the mechanisms of resistance,
- Develop new insights into how pathogens cause disease,
- investigate the role of host factors,
- deciphering microbial genomes,
- develop next generation sequencing technologies, and
- develop new computer-assisted modeling efforts.

NIH/NIAID funding supplements funding by other U.S. government agencies², the European Union,³ and other governments.

In some cases, the public sector funding in the area of antibiotic drugs has a component that is partly designed to enhance the capacity and competitiveness of domestic industries. Examples of this would include the the U.S. Biomedical Advanced Research and Development Authority (BARDA)⁴ and the European Union Innovative Medicines Initiative (IMI).

Despite the obvious cross-border importance of the development of new antibiotics and relevant diagnostics, the public sector funding of R&D is not currently part of global trade negotiations, other than the restrictions on public sector R&D funding found in the WTO Subsidies and Countervailing

² Including specialized programs relating to public health emergencies and bio-warfare, and the Orphan Drug Tax Credit.

³ Including, for example, the action plan against the rising threats from antimicrobial resistance adopted by the European Commission in answer to the Council Conclusions and European Parliament resolution to "establish an EU-wide plan to combat AMR, the New Drugs for Bad Bugs program."

⁴ See, the BARDA Strategic Plan 2011-2016. "Where vaccine and biological therapeutics manufacturing capacity is concerned, BARDA will continue to enter into public-private partnerships with manufacturers to build and/or retrofit medical countermeasure production facilities within the U.S., increasing domestic access to medical countermeasures."

Measures (SCM) agreement.⁵

(2) Policies regarding regulatory barriers for registering products.

In recent years, the U.S. Congress and the U.S. FDA have taken steps to lower the costs of registering new antibiotic drugs. Title VIII of Food and Drug Administration Safety and Innovation Act (FDASIA), entitled Generating Antibiotic Incentives Now (GAIN), provides that an antibiotic drug may be designated as a qualified infectious disease product (QIDP), and is eligible for fast track designation and priority review, measures which effectively lower the costs of R&D.

While beneficial in terms of lowering R&D costs for the QIDP, fast track and priority review status involve a lowering of the standards for establishing the safety and efficacy of new products, increasing the risk of adverse events associated with the use of the drug, and also are associated with a slower approval for the non-antibiotic drugs that do not qualify for fast track or priority review.

(3) Extending terms for patents and other intellectual property rights

There are a number of proposals to extend the duration of exclusive rights in patents, test data, and other types of regulatory or intellectual property rights associated with antibiotic drugs. In 2012, the U.S. Congress enacted “Generating Antibiotic Incentives Now (GAIN)” amendments to the U.S. Food and Drug Administration laws that expanded certain regulatory market monopolies for certain antibiotic drugs.⁶

Some would go further. For example, in his 2005 paper,⁷ “Preserving a Precious Resource: Rationalizing the Use of Antibiotics,” Eric Kades makes a case for “infinite-term patents on antibiotics.” Kades was not only interested in increasing incentives to develop new drugs, he saw the high monopoly price as a useful in order to “prolong the useful life of the drug, and create incentives for drug makers to hold some antibiotics in reserve to meet the extraordinary demand that will arise if and when there is a bacterial plague.”

Taken by themselves, the proposals to extend the commercial monopoly for the antibiotic drugs undoubtedly increase investor returns, but not without costs to users, and increases perverse incentives as regards the promotion of use of antibiotic drugs.⁸ In a number of realistic scenarios, an

⁵ And similar restrictions within Europe, under Article 107 of the Treaty on the Functioning of the European Union.

⁶ For example, in the US, July 9, 2012. P.L. 112-144, Title VIII—Generating Antibiotic Incentives Now, Sec. 801. Extension Of Exclusivity Period For Drugs.

⁷ Eric Kades, Eric, "Preserving a Precious Resource: Rationalizing the Use of Antibiotics," (2005) 99 Northwestern University Law Review, . 615 2004-2005. Page 626. Available at Faculty Publications. Paper 52. <http://scholarship.law.wm.edu/facpubs/52>. An earlier version of the paper is available as Eric A. Kades, Plagues, Policy, & Patents: Addressing Overuse of Antibiotics, William & Mary Law School Working Paper No. 2003-Kades-1, March 11, 2003.

⁸ Kevin Outterson, Balch Samora and Keller-Cuda, "Will Longer Antimicrobial Patents Improve Global Public

expanded term of the monopoly will extend the period when the drug developer has an economic incentive to promote high utilization of the antibiotic drugs, undermining the longer term value of the resource.

Long product monopolies create incentives to take into consideration the longer-run life cycle value of the antibiotic resource. But offsetting these potentially positive conservation effects are the high private rate of discount used to evaluate future sales, as well as the firm's interest in exploiting the resource before it is removed from the market for safety reasons, or replaced by a better drug.

(4) Innovation inducement prize type incentives to reward innovation and/or conservation

A variety of proposals have been made to use innovation inducement prizes to stimulate innovation for new antibiotic drugs. Innovation inducement prizes can be implemented in different ways, and this is reflected in the diversity of proposals for such prizes. The most interesting proposals are those that completely de-link the returns to investors from the prices of products, and which effectively eliminate the current incentives to unhelpfully promote the low value uses of the drugs undermining conservation goals.

Innovation Inducement Prizes

Among those endorsing a radical delinkage of R&D incentives from product prices is Richard Bergström, currently the Director General of the European Federation of Pharmaceutical Industries and Associations (EFPIA).⁹

“Incentives that separate the financial return from the use of a product are the only way to change this behaviour,” said Bergström at a conference held at Uppsala University in September 2010. “Intelligent pull incentives, such as advance commitments and prizes, provide financial rewards to the developer that are not based on the volume of use of the novel antibiotic. With the right set-up, pharma companies will have no incentive to drive use. Maybe they will not do any promotion at all. Use would be agreed with public policy-makers, purchasers and national health systems.”

The use of prizes to reward antibiotic drug development has been proposed by a number of authors.¹⁰

Health? 7 *Lancet Infectious Diseases* 559-66 (2007),, and Kevin Outterson, "All Pain, No GAIN: Need for Prudent Antimicrobial Use Provisions to Complement the GAIN Act," 30 APUA Clinical Newsletter 13 (2012). Robert Weissman and Anthony So, "Generating Antibiotic Incentives Now: GAIN -- Or Just Greed," *the Huffington Post*, June 6, 2012. Glyn Moody, How Extending Patent Protection For Antibiotics Creates Perverse Incentives To Render Them Useless. from the monopolizing-ourselves-to-death dept. TechDirt. June 29, 2012.

⁹ Quoted in "Race against time to develop new antibiotics," Bulletin of the World Health Organization 2011;89:88–89. doi:10.2471/BLT.11.030211/

¹⁰ James Love and Tim Hubbard. "The Big Idea: Prizes to Stimulate R&D for New Medicines," *Chicago-Kent Law Review*, Volume 82, Number 3 (2007); James Love. "Prizes, not prices, to stimulate antibiotic R&D.," *SciDev.net*. March 26, 2008; Tyler Cowen, To Fight Pandemics, Reward Research, New York Times, May 4, 2013; Editorial. Drugs win prizes; New incentives are needed in search for antibiotics. *Financial Times*. June 4, 2012; Anthony D

In 2012, in a bill regarding the reauthorization of certain FDA programs, the U.S. Senate voted to ask the National Academies to undertake a study of the feasibility, costs and benefits of using innovation inducement prizes to reward the development of new drugs.¹¹ The Infectious Disease Society of America endorsed this study:¹²

“IDSA also is pleased to support Sec. 906 of the legislation, which calls the National Academies of Science to evaluate the feasibility and possible consequences of the use of innovation inducement prizes to reward successful medical innovations in targeted areas, including antibiotics. IDSA has long held that according to economic modeling a combination of incentives are necessary to spur new antibiotic R&D. Prizes are one potential incentive that could be a useful component of a larger effort to drive innovation. We also suggest requesting NAS experts to consider and make recommendations about formation of public private partnerships to support antibiotic development.”

The Senate wanted the National Academies to consider the approaches set out in legislation to create the Medical Innovation Prize Fund [S.627, 113th Congress]. The legislation, introduced by Senator Sanders, would create a system of end product, interim and open source dividend prizes¹³ to reward developers of new prescription drugs and vaccines, as a substitute for the grant of a monopoly.

The Sanders legislation was designed to eliminate monopolies on new drugs, and use prizes to induce innovation that was responsive to health needs. Section 9(c) of S.627 sets out the criteria for prize valuation. Two provisions directly and indirectly address the valuation of antibiotic drugs.

(6) In the case of antibiotics or other products for which drug resistance is a significant public health problem, the expected life cycle benefits of the antibiotic or other product, with appropriate adjustments that reward the conservation of the resources, taking into account drug resistance that is related to use of the product.

(7) In the case of products used in stockpiles for potential threats to the public health, the risk adjusted benefits of stockpiling the products.

Some academic observers have proposed prize type mechanisms that are not designed to eliminate drug monopolies, or lower drug prices, including several that propose large cash rewards to induce conservation.

So, Neha Gupta, Otto Cars, Tackling antibiotic resistance. Concerted action is needed to provide new technologies and conserve existing drugs. *BMJ* 2010;340:c2071. doi: 10.1136/bmj.c2071; Time for the EU to lead on innovation: EU policy opportunities in biomedical innovation and the promotion of public knowledge goods. HAI Europe/ TACD Policy Paper, April 2012. Elias Mossialos, Chantal M Morel, Suzanne Edwards, Julia Berenson, Marin Gemmill-Toyama, David Brogan. Policies and incentives for promoting innovation in antibiotic research. World Health Organization 2010, on behalf of the European Observatory on Health Systems and Policies.

¹¹ Kevin Outterson, Antibiotic prize study in PDUFA V reauthorization bill, the *Incidental Economist*, April 24, 2012.

¹² April 24, 2012 letter, Mark A. Leasure, CEO of IDSA to Senators Harkin and Enzi, regarding Prescription Drug User Fee Act (PDUFA) reauthorization legislation..

¹³ James Love and Tim Hubbard, "Prizes for Innovation of New Medicines and Vaccines," *Annals of Health Law*, Vol. 18, No 2, Summer (2009) pages 155-186.

Antibiotic Conservation and Effectiveness (ACE) program

In 2011, Aaron Kesselheim and Kevin Outterson proposed the creation an Antibiotic Conservation and Effectiveness (ACE) program that would create \$10 billion or more annually in incentives to companies, to stimulate R&D and also reduce consumption of antibiotics in order to achieve conservation objectives. This proposal would effectively bribe drug manufacturers to manage antibiotics more efficiently, using massive “enhanced” reimbursements conditioned on meeting conservation targets. Kesselheim and Outterson see the drug manufacturers as politically active and influential actors that currently are undermining conservation goals, and see the new, more expensive reimbursement policies as the price for harnessing their efforts in a socially responsible manner.¹⁴

. . . formulary restrictions and preauthorization requirements can be effective stewardship tools, but pharmaceutical manufacturers generally disfavor such measures since they dampen demand for their products. These managed-care techniques restrict access to their products through tiered formularies or as part of step therapy.¹⁴¹ The industry has fought these restrictions in many ways, including litigation in the highest courts.¹⁴² Since pharmaceutical companies are such powerful institutional actors, any public health program that faces strident drug company opposition will have difficulty succeeding. Our ACE proposals are designed to align private financial incentives with public health goals in a way that makes the drug companies full partners in antibiotic conservation efforts. . . . Make no mistake: we are proposing a very substantial increase in payments for antibiotics, driven by the social value of these important drugs.”

An enhanced reimbursement of \$10 billion annually would indeed be likely to induce socially useful changes in marketing efforts by some companies, in some countries, but it also goes without saying it is both expensive and of limited benefit when and where the products are off patent and use is not controlled by the developer. To appreciate the size of the proposed subsidy, consider some comparisons.

- The fiscal year 2013 budget for the entire U.S. FDA was \$4.031 billion.
- The total cumulative value of the U.S. Orphan Drug Tax Credit subsidy was \$3.03 billion, over its first 25 years.¹⁵

The annual cost is greater than:

- the U.S. PEPFAR program budget, or
- the combined federal outlays on the National Institutes of Cancer and the National Institute of Allergy and Infectious Diseases (NIAID).

Strategic Antibiotic Reserve (SAR)

In the same 2011 paper, Kesselheim and Outterson also proposed a separate initiative, a Strategic

¹⁴ Aaron S. Kesselheim and Kevin Outterson, *Improving Antibiotic Markets For Long Term Sustainability* , 11 *Yale Journal of Health Policy, Law & Ethics* (Winter 2011)

¹⁵ The total is from 1983 to 2010, and includes the most recent data available from the IRS. The credit was not in effect in 1995-1997.

Antibiotic Reserve (SAR). Comparing it to programs that pay farmers to not grow crops, Kesselheim and Outterson propose that “companies . . . be rewarded today for not selling the antibiotic, preserving a precious resource for dire future needs.” Funded through “supplemental cash prizes for placing important new antibiotics in the Strategic Antibiotic Reserve,” the authors say “These amounts must be quite substantial in order to properly align incentives, ranging towards a billion dollars per year for an important drug class.” Like ACE program, Kesselheim and Outterson would make “the financial arrangement with the company . . . entirely voluntary, based on a contract with the government.” They add, “If a company tried to hold out with a critically important antibiotic . . . the government would retain the ability to use a compulsory license, with payment of just compensation for the taking.”

Unclear is for how long such a large subsidy would be paid, given the objective of holding the products off the market for some unforeseen future need, or how the subsidy would work in places and times when patents and other intellectual property rights did not exist.

Pricing of antibiotics

In discussing both proposals, Kesselheim and Outterson dismiss concerns over the pricing and affordability of drugs:

“Generic access to cheap antibiotics is not entirely positive for public health, even on a merely static basis. Cheap (or free) antibiotics drive resistance and reinforce the overall low reimbursement levels in this drug class.¹⁶”

While Kesselheim and Outterson belittle concerns over the affordability of drugs, citing a study of Wal-Mart’s low cost pricing of generic antibiotics, their proposal for the SAR gives as an example the patented antibiotic daptomycin, which is hardly cheap. In 2009, the Canadian Expert Drug Advisory Committee (CEDAC) recommended that daptomycin (Cubicin) not be listed as reimbursable for the treatment of complicated skin and skin structure infections and *Staphylococcus aureus* bloodstream infections, citing, among other things, its high cost.¹⁷

¹⁶ The article includes a footnote, which refers to the text quoted here:

“Recently, antibiotics have been featured prominently in low-cost generic drug dispensation programs by many national retail pharmacies. For example, Wal-Mart’s low-cost program allows patients to buy 12 different varieties of the antibiotic amoxicillin for \$4 per month. See Wal-Mart \$4 Medication List, <http://www.usatoday.com/money/industries/health/drugs/walmart-druglist.pdf> (last visited September 2, 2009). While such generic drug programs have been rightly extolled for helping promote access and adherence to essential medicines, low-cost antibiotic access has been linked to overuse of these drug, particularly in lower-income settings. Beatriz Espinosa Franco et al., *The Determinants of the Antibiotic Resistance Process*, 2 *INFECT. DRUG RESIST.* 1 (2009). See also Karen Caffarini, *Antibiotic Giveaways Stoke Fear of Patient Pressure*, *AM. MED. NEWS*, Jan. 29, 2009, <http://www.ama-assn.org/amednews/2009/01/26/bisc0128.htm>. For a recent empirical analysis finding increased antibiotic consumption with free programs, see Shanjun Li & Ramanan Laxminarayan, *Are Physicians’ Prescribing Decisions Sensitive to Drug Prices? Evidence from a Free-Antibiotics Program* (2010) www.ssrn.com/abstract=1598804.

¹⁷ *Recommendations and Reasons: Daptomycin*, Committee to Evaluate Drugs (CED), Ministry of Health and Long-Term Care, November 2009

“The drug cost for daptomycin (Cubicin) is \$165 per day. This is more expensive than other alternative treatments such as vancomycin (\$92.54), cloxacillin (\$0.70-\$14.40) and linezolid (\$141.28). . . . The Canadian Expert Drug Advisory Committee (CEDAC) recommended that daptomycin (Cubicin) not be listed. . . . Executive Officer Decision: Based on the CED’s recommendation, the Executive Office decided not to fund daptomycin (Cubicin). Status: Funding not available through the Ontario Public Drug Programs”

Antibiotics Health Impact Fund (aHIF)

In a similar vein, Outterson, Pogge and Hollis have also separately proposed a specialized antibiotics health impact fund that would offer a “completely voluntary . . . alternative revenue stream of up to several billion dollars per drug over the ten-year registration period.”¹⁸ The ability of the aHIF to regulate use is stronger when products are patented and use can arguably be controlled by the developer, but patent coverage is normally limited by place and time. Outterson, Pogge and Hollis propose that the control over the drug be enhanced through “an international agreement not to permit other firms to sell aHIF-rewarded antibiotics, regardless of the patent status,” effectively turning the proposal into a permanent global monopoly with regulated prices and large annual subsidies.

In both the ACE and aHIF proposals, Kesselheim, Outterson, Pogge and Hollis recommend antitrust waivers, to permit some level of collaboration among firms in order to achieve conservation objectives.

Collectively the ACE, SAR and aHIF proposals provide little support for and indeed, create new barriers to efforts by developing countries to maintain the capacity to manufacture affordable and accessible antibiotics.

Antibiotics Innovation Funding Mechanism (AIFM).

In the context of a WHO call from proposals to demonstration new models for R&D that featured open innovation, delinkage of R&D costs from product prices, and innovative and sustainable financing mechanisms, KEI has proposed the creation of the Antibiotics Innovation Funding Mechanism (AIFM). The AIFM is a proposal to impose taxes or user fees on the use of antibiotic drugs, including human and agricultural uses, and use the revenue from the taxes or user fees to finance a system of grants and innovation inducement prizes. Like the current Sanders prize fund legislation, the innovation inducement prizes would include prizes for end products, interim results and an open source dividend.

The KEI WHO proposal would use innovation inducement prizes to reward innovation for new antibiotics, but would rely upon regulatory measures to control utilization. These regulatory measures could include regulatory quotas, by geographic area of field of use, decentralized mechanisms to manage quotas, and possible monetization and trading of quota amounts, subject to limits on the transfer of a quota amount from a low income country to a high income country.

The various Outterson et al. proposals would use prize type rewards to both stimulate innovation and regulate use, focusing on the role of the drug developer as the global regulator, ultimately with enhanced powers to enter into collusive contracts and extend market exclusivity beyond the scope of

¹⁸ Kevin Outterson, Thomas Pogge, and Aidan Hollis, "Combating Antibiotic Resistance Through The Health Impact Fund," chapter in *The Globalization of Health Care*, Oxford University Press (2012).

current patent law.

In the KEI proposed system, the regulatory regime would reinforce the policy of a switch to a delinkage regime, where rewards for innovation are not tied to product prices and sales.

Regulatory limits on use would make it less expensive to induce participation in voluntary prize fund schemes (particularly important in cross border implementation of regimes) or patent buyouts or takings.

In the Outterson proposals, the prize system would compete with the option of promoting and selling antibiotics, with fewer regulatory restrictions. The various measures to strengthen monopolies would be consistent with higher prices for products outside of the subsidy regimes. And, the amount of the subsidy to induce socially appropriate restrictions on use would grow with escalations of the threats of inappropriate utilization.

Both KEI and the Outterson proposals endorse or provide for greater public investment in R&D for new antibiotics.

KEI, Outterson and Kesselheim have endorsed¹⁹ the use of compulsory licenses or other measures to limit the exercise of patent rights. Pogge has opposed the use of compulsory licensing of patents.²⁰ Hollis has both proposed²¹ and opposed²² the use of compulsory licensing of patents, in various articles.

(5) Other

Pigouvian Taxes

One obvious and often proposed intervention to discourage low value uses of antibiotic drugs is to impose taxes on their use. In theory, a tax could be designed to correct market prices so the private costs match the social costs of the consumption. This approach is sometimes referred to a Pigouvian tax, after the economist, Arthur C. Pigou, who proposed using taxes (or subsidies) to discourage (or encourage) actions which caused negative (or positive) externalities.

¹⁹ Aaron S. Kesselheim and Kevin Outterson, Improving Antibiotic Markets For Long Term Sustainability , 11 *Yale Journal of Health Policy, Law & Ethics* (Winter 2011).

²⁰ Aidan Hollis and Thomas Pogge, The Health Impact Fund, Making New Medicines Accessible for All, A Report of Incentives for Global Health, 2008, Page 53-54. "It may seem as though compulsory licenses — as envisioned in the TRIPS Agreement and reaffirmed in the 2001 Doha Declaration — are a practical solution to this dilemma. By issuing a compulsory license, a government can force down the price of a patented invention by compelling the patent holder to license it to other producers for a set percentage (typically below 10 percent) of the latter's sales revenues. Yet, compulsory licenses cannot fully solve the dilemma because, insofar as governments actually use them to improve access by the poor to patented medicines, compulsory licenses weaken the innovation incentives that were supposed to result from the extension of strong intellectual property rights into the less developed countries. See also: Excerpts from HIF: compulsory licensing.

<http://keionline.org/blogs/2008/11/18/excerpts-from-hif-compulsory-licensing>.

²¹ Aidan Hollis, The link between publicly funded health care and compulsory licensing, *Canadian Medical Association Journal*, 2002 October 1; 167(7): 765–766. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC126509/>.

²² Hollis and Poge, 2008.

Antibiotic Innovation and Conservation (AIC) fee

In a 2011 policy paper, the Infectious Disease Society of America (IDSA) proposed an Antibiotic Innovation and Conservation (AIC) fee.²³ 75 percent of the AIC fee be used to fund R&D for new antibiotic drugs, and 25 percent be used to fund “antimicrobial stewardship.”

Transferable Patent Extensions

There have been a number of proposals to create transferable patent extensions, sometimes referred to as “wild card” patent extensions, as a reward for developing new antibiotic drugs.²⁴ The mechanism is the grant of a legal right to extend the life of a patent, on a non-antibiotic drug. If the patent extension is fully transferable, it can be used for any product, including a highly profitable drug sold by a different firm, including products with monthly sales exceeding hundreds of millions of dollars. The value of the transferable patent extension depends upon the term of the patent extension.

The transferable patent extension works like a prize, the value of which is expected profit from the extension of the monopoly of the non-antibiotic drug. Under most proposals, the transferable patent extension would be an uncertain and non-transparent economic benefit to the developer of the antibiotic drug²⁵, and would impose large costs on society.

For several reasons, the transferable patent extension is expected to impose larger costs on society than the benefit to the developer of the antibiotic drug. Consider the following.

²³ IDSA Policy Paper, CID 2011:52 (Supl 5). From page S407 of the report: “With respect to public monies, IDSA proposes creation of an Antimicrobial Innovation and Conservation (AIC) Fee. The AIC Fee would be a flat fee (e.g., \$3 per daily dose, inflated by the consumer price index annually) charged against the wholesale purchase of every daily dose unit of antibiotics (both branded and generic) in the US, including for human, animal and plant agriculture, and aquaculture use. The fee would be paid by the dispensing entity (e.g., pharmacy, animal feed mill, aquaculture company, etc.) at the time of wholesale purchase from the supplier. The rationale for such a fee is that effective antibiotics represent a “shared societal benefit,” and every antibiotic manufacturer, prescriber, and user must share the responsibility to maintain this benefit. Antibiotic resistance resulting from antibiotic use (both appropriate and inappropriate) is an example of the “tragedy of the commons”. A prescription may help the individual patient, plant, or animal, but such use also causes collective erosion of the benefit (effectiveness of antibiotics) for society as a whole. Analogously, use of highways by a vehicle has a cost to all users. Tolls (and differential rates) are means to have users pay their fair share of societal costs for establishing and maintaining a shared benefit. Because of the emergence of resistance, use of antibiotics differs from use of all other drugs that affect only the individual patients taking them. Hence, an AIC Fee would be charged to maintain the “shared societal benefit” of effective antibiotic therapy. Obviously, safeguards need to be incorporated into the AIC Fee structure to ensure that any costs passed on to consumers will not negatively impact vulnerable populations’ access to these important drugs.”

²⁴ Crossing The Valley Of Death: Bringing Promising Medical. Countermeasures To Bioshield. *Hearing Before The Subcommittee On Bioterrorism And Public Health Preparedness of The Committee On Health, Education, Labor, And Pensions United States Senate*. 109th Congress. June 9, 2005. S. Hrg. 109-148; Walter E. Stamm, Letter to Senator Richard Burr, regarding wild-card patent extension. June 24, 2005; Li-Hsien Rin-Laures and Kevin M. Flowers, Using Wild-Card Patent Extensions to Bolster Drug Research, *The National Law Journal*. September 8, 2005; Spellberg B, Miller LG, Kuo MN, Bradley J, Scheld WM, Edwards JE. Societal Costs Versus Savings from Wild-Card Patent Extension Legislation to Spur Critically Needed Antibiotic Development. *Infection*, June 2007, Volume 35, Issue 3, pp 167-174; J. Sonderholm, “Wild-Card Patent Extensions as a Means to Incentivize Research and Development of Antibiotics,” *Journal of Law, Medicine & Ethics* 37, no. 2 (2009): 240-245.

²⁵ Amy Kapczynski, Commentary: innovation policy for a new era., *J Law Med Ethics*. 2009 Summer;37(2):264-8. doi: 10.1111/j.1748-720X.2009.00

First, among blockbuster products, there is typically a significant difference in the value of the monopoly. The company that stands to benefit the most from the monopoly normally would need to pay no more for the patent extension than the value of the extension to a company that would benefit less. Thus, there is likely to be a systematic undervaluing of the patent extension, in an auction of the extension. For example, based upon 2012 sales, the three top grossing drugs facing patent expiration in 2013 were:

Drug	Date of patent expiration	2012 Sales
Cymbalta	December 11, 2013	\$4.9 billion
Avonex	December 31, 2013	\$2.9 billion
Humalog	May 7, 2013	\$2.52 billion

A patent extension used for Cymbalta would likely be sold at no more than the value of the extension for the drug Avonex, a drug with sales 40 percent less than the Cymbalta.

Second, the profit margin is less than 100 percent of sales, due in part to the costs of promoting and marketing the product. This may be particularly true for mature blockbuster drugs facing competition within a therapeutic class. For this reason, only a fraction of the higher cost of the consumers will be available as a benefit to the developer of the antibiotic drug.

In light of the above, suppose, for example, that owners of the blockbuster drugs anticipated that a one year extension of the monopoly protects 80 percent of their revenues (at the expense of consumers), and that half of that would be realized as profits. The following highly simplified calculations illustrates inefficiency of the transferable patent extension as a funding mechanism.

<i>Drug</i>	<i>Expected sales, with monopoly (billions)</i>	<i>Cost of patent extension to consumers (billions)</i>	<i>Value of patent extension to firm (billions)</i>	<i>Maximum bid for patent extension, assuming only one extension available. (billions)</i>	<i>Minimum net loss [cost to consumers - maximum bid] (billions)</i>
Cymbalta	\$4.9	\$3.92	\$1.96	\$ 1.16	\$ 2.76
Avonex	\$2.9	2.32	\$1.16	\$.928	\$ 1.392

Humalog	\$2.52	\$1.856	\$.928		
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In this simple example, consumers pay \$3.92 billion in higher prices for Cymbalta to obtain *at best* \$1.16 billion as a reward for development of new antibiotic drugs.

Transferable Priority Review Vouchers

Some have proposed the U.S. priority review voucher program²⁶ be extended to antibiotic drugs. The priority review voucher program creates a transferable right to have the US FDA evaluate the approval of a new drug as if it was a priority medicine.

The priority review voucher was originally created to stimulate investment in the development of drugs for neglected diseases, and it has been controversial.²⁷ Since the voucher is only valuable when used for non-priority medicines, it has the predictable effect of diluting the benefits of priority approval for actual priority medicines, and creating a risky rush to judgement on a drug that has few medical benefits, if any, associated with its approval.²⁸ Since its creation in 2007, the voucher program has been extended to include “rare pediatric diseases.”²⁹ Obviously there are limits to how many drugs can be considered as eligible for “priority” review at the FDA.

The primary advantage and appeal of the transferable patent extensions and the transferable priority review voucher for the Congress is that they are largely off-budget subsidies, and the non-transparency of the costs of the mechanisms are seen as a benefit by their proponents.

Advanced Marketing Commitment (AMC), and Advanced Purchase Commitment (APC)

An advanced marketing commitment is a commitment to provide subsidies for the purchases of drugs. The subsidy is designed to expand the market, in order to induce investments in R&D.³⁰ An advanced

²⁶ David Ridley, Henry Grabowski, J. Moe, Developing drugs for developing countries. *Health Affairs* 25 (2) 313–324. (2006) doi: 10.1377/hlthaff.25.2.313.; David B Ridley, Alfonso Calles Sánchez, Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases, *The Lancet*, Volume 376, Issue 9744, 11–17 September 2010, Pages 922–927; Andrew S. Robertson, Rianna Stefanakis, Don Joseph, Melinda Moree, The Impact of the US Priority Review Voucher on Private-Sector Investment in Global Health Research and Development, *Plos Neglected Tropical Diseases*. Aug 28, 2012. DOI: 10.1371/journal.pntd.0001750.

²⁷ Anderson T Novartis under fire for accepting new reward for old drug. *Lancet* 373 (9673) 1414. (2009) doi: 10.1016/S0140-6736(09)60804-7.

²⁸ Aaron Kesselheim, Drug development for neglected diseases—the trouble with FDA review vouchers. *New England Journal of Medicine* (NEJM) 359: 1981–1983. (2008) doi: 10.1056/NEJMp0806684; Aaron S Kesselheim, Priority Review Vouchers: An Inefficient and Dangerous Way to Promote Neglected-Disease Drug Development. *Clinical Pharmacology & Therapeutics* 85, 573-575 (June 2009). doi:10.1038/clpt.2009.50.

²⁹ Roxanne Palmer. Congress vouchers for priority review of childhood disease, *Nature Medicine* 18, 181 (2012) doi:10.1038/nm0212-181.

³⁰ Adrian Towse and Hannah Kettler. Advance price or purchase commitments to create markets for treatments for diseases of poverty: lessons from three policies. Bulletin of the World Health Organization, April 2005. Owen Barder, Michael Kremer, Heidi Williams. Advance Market Commitments: A Policy to Stimulate Investment in Vaccines for Neglected Diseases. *Economists' Voice*. February 2006; Rachel Glennerster, Michael R. Kremer, Jean Lee, Ruth Levine, Georg Weizsäcker, Heidi Williams. Advance Market Commitments for Vaccines Against Neglected Diseases: Estimating Costs and Effectiveness, *Health Economics*. 2007 May;16(5):491-511.

purchase commitment is a commitment to buy a quantity of drugs at prices high enough to induce investments in R&D. Both the AMC and the APC are typically presented as voluntary offers by governments or other donors, without an obligation on drug developers to sell at AMC or APC prices. The AMC and APC mechanisms can be described as efforts to set a floor on the market. In cases where the government is the only purchaser, such as for certain biodefense agents³¹, or vaccines for poor populations, the AMC and APC are seen as part of a procurement effort that includes both an R&D and a supply component, and like other financing mechanisms, may be combined with grants and other subsidies.³²

Both the AMC and the APC present challenges regarding the information needed to send end-points and the appropriate valuation of prices or purchasing subsidies.³³ The US government use of APCs in regard to its Bioshield program have been controversial, and suppliers of products have lobbied the US Congress to shift risks of development to the government³⁴, and reduce the discretion of the funding agencies to not purchase when products receive FDA approval, including approval using lower standards based only on animal studies.³⁵

Call options for antibiotics

Elias Mossialos and colleagues have proposed a system of Call Options for Antibiotics (COA)³⁶ based upon a Call Option for Vaccines (COV) proposal by Brogan & Mossialos.³⁷ In this approach, governments offer to buy rights to purchase drugs at fixed affordable prices, during earlier stages of development. The money from the option is used by developers to defray R&D costs.

The COA and COV approaches can first be compared to the Advanced Market Commitment (AMC) or Advanced Purchase Commitment (APC) approaches. Whereas the AMC and APC approaches require governments to commit to buy, the COV and COA approaches require developers to sell.

³¹ Chris Schneidmiller, FDA Offers First License to Drug Produced by Bioshield Program, Global Security Newswire. December 17, 2012.; GlaxoSmithKline (GSK) Inks \$196 Million Biomedical Advanced Research and Development Authority (BARDA) U.S. Anthrax Treatment Deal, BioSpace. September 20, 2013.

³² Bolken TC, Hruby DE. Discovery and development of antiviral drugs for biodefense: experience of a small biotechnology company. *Antiviral Res.* 2008 Jan;77(1):1-5. Epub 2007 Aug 15.

³³ Michael Kremer, Creating Markets for New Vaccines Part II: Design Issues, NBER Working Paper No. 7717. May 2000; Donald W. Light. Advanced Market Commitments: Current Realities and Alternate Approaches. A HAI Europe/Medico International Publication. Paper Series Reference 03-2009/01 2009.

³⁴ John Carroll, Traversing the Landscape Of Project BioShield, *Biotechnology Healthcare.* 2007 October; 4(5): 7–8. PMID: PMC2651710.

³⁵ Steve Usdin, Antibiotics reset. GAIN Act, FDA stance only first steps to refilling antibiotic pipeline in U.S. *BioCentury.* November 19, 2012. Alexander Gaffney, In First for Animal Rule Pathway, FDA Approves GSK's Raxibacumab, *Regulatory Focus,* December 17, 2012.

³⁶ Elias Mossialos, Chantal M. Morel, Suzanne Edwards, Julia Berenson, Marin Gemmill-Toyama and David Brogan, Policies and incentives for promoting innovation in antibiotic research, *European Observatory on Health Systems and Policies.* 2010.

³⁷ David Brogan and Elias Mossialos. Applying the concepts of financial options to stimulate vaccine development. *Nature Reviews Drug Discovery* 5, 641-647 (August 2006) | doi:10.1038/nrd2035.

Whereas the AMC and APC approaches only provide funding to developers when products reach the market and are used, and the COA and COV approaches provide cash funding at earlier stages of development.

The COA and COV approaches can also be compared to interim results innovation inducement prizes, with the call option interpreted as an alternative to a license to use an invention, leaving the monopoly intact, but creating a mechanism to negotiate prices at the time of providing funding.