Synthetic biology: ensuring the greatest global value

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Abstract Synthetic biology (SynBio) has tremendous, transformative potential. Like other technologies, it can be used for good or ill. Currently, the structure of the allocation of potential benefits and risks is biased in favor of richer countries. The underlying problem is simple: most risks from SynBio are universal and affect both the rich and the poor with equal force; but benefits from SynBio can be expected to accrue chiefly to the rich. The risk/benefit balance is therefore skewed in a way that may lead to inefficient and unfair decisions. One potential solution is presented in this paper, using the principles that underlie the Health Impact Fund (HIF). The HIF is designed to reward companies based on assessed health impact, no matter where it occurs in the world, so that extending the life of a poor person is as profitable as extending the life of a rich person. This paper considers both the potential benefits and costs of SynBio; examines how the current global pharmaceutical industry is structured; introduces the HIF proposal; and finally explores how the principles underlying the HIF could be used productively with SynBio for global health.

Keywords SynBio · Health Impact Fund · Incentives

Introduction

Synthetic biology (SynBio) has tremendous, transformative potential. Like other technologies, it can be used for good or ill. Currently, the structure of the allocation of potential

benefits and risks is biased in favor of richer countries. The underlying problem is simple: most risks from SynBio are universal and affect both the rich and the poor with equal force; but benefits from SynBio can be expected to accrue chiefly to the rich. The risk/benefit balance is therefore skewed in a way that may lead to inefficient and unfair decisions. One potential solution is presented in this paper, using the principles that underlie the Health Impact Fund (HIF). The HIF is designed to reward companies based on assessed health impact, no matter where it occurs in the world, so that extending the life of a poor person is as profitable as extending the life of a rich person. This paper considers both the potential benefits and costs of SynBio; examines how the current global pharmaceutical industry is structured; introduces the HIF proposal; and finally explores how the principles underlying the HIF would interact productively with SynBio.

Benefits and costs of SynBio

SynBio offers enormous potential for important medical improvements. The types of improvements could arise in various ways. First, reduced costs of production can arise in some cases through replacement of some natural biological process. For example, synthetic artemisinin is produced at lower cost and with greater consistency. Second, SynBio may enable the production of new drugs and vaccines that effectively address health needs. For example, SynBio might enable viruses that are programmed to deliver chemical agents to malignant cancer cells. Both types of SynBio innovation offer the potential for significant gains in health globally.

In principle, SynBio's potential benefits extend to all of humanity. However, if a particular use of SynBio is

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expensive to develop, it is most likely that, like other technologies, SynBio will be employed chiefly where there is a large commercial market to be exploited. This means, in turn, that SynBio will be used chiefly to provide products for wealthy people.¹ Poor people typically do not provide a large commercial market for new goods, simply because their incomes are too small. We can therefore anticipate that the benefits from the use of new SynBio health technologies will chiefly be initially captured chiefly by wealthy people.

There are also likely to be benefits for sellers of SynBio-related products. Since SynBio is a complex technology, it is typically capital intensive. Investors and workers in developed countries will therefore capture a large share of the benefits to sellers.

Trying to predict the benefits of an inherently unpredictable technology is of course difficult. The use of mobile phones is an interesting example of how of a technology can have especially large benefits for poor people. Older hardwired technology was too costly for use in many parts of the world, and cell phones have enabled a much more extensive adoption of a communications technology that was otherwise likely to remain inaccessible.

In medicine, many technologies have been developed principally for use by people in rich countries, or for rich people in poor countries. For example, statins, which have well-known benefits for people with cardiovascular disease, are very little used in most developing countries (Ong 2006). At the same time, of course, many medicines developed for commercial markets in rich countries have seen their use expanded into developing countries. Anti-retroviral medicines for people with HIV/AIDS are widely used in developing countries. Nevertheless, it seems extremely likely that rich people will capture more benefits (on a *per capita* basis) from the use of SynBio products, simply because rich people are able to pay for the products. This would be broadly consistent with the use and benefits of other pharmaceuticals, which are much more heavily used in rich countries. IMS Health reports that in 2010, Asia (excluding Japan), Africa and Australia collectively constituted under 15 % of the global market for pharmaceuticals.²

In contrast to the distribution of benefits skewed towards the rich, it seems likely that the costs of SynBio may be skewed towards the poor. The most serious risks are likely “adverse effects of intentional or inadvertent release of the organisms engineered using synthetic biology” especially

if those organisms proliferate without adequate means to limit reproduction (Presidential Commission 2010, p. 67). This would indeed be a calamitous outcome, and it could have global implications. It is quite likely that protective efforts, if feasible, would be most effectively and rapidly deployed in wealthy settings. While it seems likely that SynBio will be used chiefly for good, one should not entirely discount the possibility of significant negative outcomes resulting from the development of exotic materials and species.

Imbalance in the potential benefits and costs

In considering the benefits and harms of further exploitation of SynBio, it seems likely that SynBio is likely to have net benefits. Nevertheless, if the benefits accrue chiefly to one group of countries, and the costs are evenly distributed, there is the risk of a distortion in decision-making. In particular, it appears that the benefits will largely be captured by people in wealthy countries, who also are in the position of making decisions about investment in SynBio. In the language of economics, there is a “negative externality” imposed on people in poor countries, who do not have the opportunity to decide on investment or rules for the safe and effective exploitation of SynBio.³

What is needed, of course, is a mechanism to ensure a more even balance in the distribution of the benefits of SynBio, to reflect the balance in the distribution of the potential harms. This is consistent with Recommendation 18 of the US 2010 Presidential Commission report.

Problems (and solutions) in global pharmaceutical markets

Fundamentally, any problems that arise in the distribution of benefits of SynBio-related pharmaceuticals are likely to be similar to the problems in the distribution of “traditional” pharmaceuticals. It is therefore important to understand reasons for the poor allocation of pharmaceutical benefits globally.

First, firms have little commercial incentive to develop drugs that will principally benefit poor people, since the users do not constitute an attractive market (WHO 2006). For example, tropical diseases have tended to be neglected. There are many causes for this: first, people in poor countries tend not to have insurance for drugs. Second, in developing countries, drug insurance programs (where they

¹ Despite these observations, it is wonderful that one of the first commercial applications of SynBio in medicine is for an antimalarial drug.

² See http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-line%20Market%20Data/2010%20Top-line%20Market%20Data/Total_Regional_Market_Size.pdf.

³ In a way, this resembles the problem of global warming, in which CO₂ producing technologies were first exploited on a large scale in developed countries, while creating potentially negative effects on a global scale.

exist) typically cover only certain generic drugs from which the innovator cannot profit. Third, poor people—and particularly poor sick people—are unable to pay for expensive drugs out of pocket. Fourth, accurate diagnosis is often unavailable, limiting the benefits from the use of new drugs. Fifth, distribution systems are often incomplete in very poor settings, allowing existing distributors to exercise market power through high mark-ups. Finally, counterfeit medicines commonly displace sales of legitimate medicines (The Lancet 2012).

Even for drugs that are already approved for another purpose, it has been commercially unattractive to run clinical trials to establish the usefulness of the drug for new uses when the target population is relatively poor. For example, Bayer's antibiotic, moxifloxacin has been used as a treatment for tuberculosis for some years, but it required support from the TB Alliance for clinical trials to proceed. "Product-Development Partnerships" such as the TB Alliance have made some significant progress in developing treatments for so-called "neglected" diseases (Moran et al. 2010), but this investment is to a very large extent funded by the Gates Foundation.

Even when drugs are developed and tested for uses in developing countries, a relatively poor market may inhibit distributional efforts. For example, many drugs are never submitted for approval in smaller developing countries, since the costs of applying for marketing approval exceed the expected revenues. Drug regulation is, as Hill and Johnson (2004) show, a complex process that varies immensely across countries. While some countries simply rely on approval in other jurisdictions (Cohen-Kohler et al. 2007), the costs of applying for marketing approval may still be enough to deter some companies from small markets (van Weely and Leufkens 2004). The problem for SynBio drugs may be particularly severe, if there is less confidence in these more complex products and a more comprehensive assessment process is demanded by the regulator.

Similarly, under the normal price system, innovator firms have little or no interest in how their products are used. Regardless of the use to which a given medicine is put, the reward for the innovator is the same. The firm is paid the same price whether the product is well or poorly used. Thus, there is no reason for firms not to encourage physicians to prescribe the product even in circumstances where the likely benefit is small or zero. Of course, there are regulations in many countries against promoting a drug for off-label uses; but there are no regulations against promoting the drug for use by patients who would see little benefit.

Consider, for example, the hypothetical case of a drug which could be prescribed in two different situations: (A) for a common condition, in which the benefit to the

patient is small and alternative drugs would lead to an equally good outcome; (B) for a rare condition with no good alternative therapies, with a large benefit to the patient. If the drug is priced the same for these two uses, the company may find it most profitable to try to increase sales by primarily promoting the first use. In effect, the company is motivated to increase revenues rather than to increase health. In most cases, there will be a positive correlation between revenues and health benefits; but this is clearly not universal and it depends on good, effective regulation of corporate marketing behavior.

A particularly severe problem in pharmaceutical markets is that prices tend to be too high for newer drugs to be effectively available to billions of people. Moon et al. (2011) show that many of the prices charged by originator companies are far above the ability of individual patients to pay, or even for their cash-strapped governments to consider. As Flynn et al. (2009) show, the problem is likely to be particularly severe in countries with high income inequality, since in those countries rich people present an attractive commercial target which can only be exploited if the company sets prices high. In wealthy countries, drug prices have been increasing rapidly, with many new drugs priced at over \$50,000 per course of therapy. Evidently, prices can't be set so high that no one buys; however, a profit-maximizing pricing policy dictates that prices will not be set so low that everyone can afford the product.

These problems are complex and multifaceted: so there won't be a single solution, and indeed there are many different proposals and approaches to addressing the urgent needs to develop and supply medicines to poor people in need. A key solution to increase access is differential pricing, so that prices are low in low-income countries. Some companies, such as GSK, have implemented differential pricing on a wide scale. However, prices will very often be so high as to exclude many potential consumers. Another approach to attaining lower price is for the government to use compulsory licensing to enable generic competition. India has recently taken a leading role in this, following a grant of a compulsory license for the anti-cancer agent Nexavar (Economist 2012). Of course, merely reducing the price, while it may increase access, will also reduce the profits of the pharmaceutical company, and in turn lead to weaker incentives for innovation. One could argue that since the companies are going to make very small profits in the poorest countries in any case, the reduction in incentives for innovation are minimal. This argument seems particularly pointed for drugs that have global markets; however, for diseases principally endemic in developing countries, low prices may erase all incentives to develop drugs.

Another important set of solutions is mechanisms that pay for drugs. The Advanced Market Commitment for a pneumococcal vaccine has enhanced not only access but also

increased incentives to invest in the necessary manufacturing capacity to supply this product. It has been reasonably effective in meeting its goals (Cernuschi et al. 2011), though it has also attracted some criticism as being a relatively expensive way to achieve its goals (e.g., Light 2009).

The leading approach to enhancing innovation is product development partnerships (PDPs). These organizations are typically disease-focused research coordination hubs that bring together financial support from diverse sources with technical skills and compound libraries from drug companies to explore the most interesting therapies. While PDPs have had some important success, there are questions regarding sustainability of this approach. An important consideration is that PDPs do not effectively harness the profit motive and so can expect to face continuous challenges of raising new funding. Currently about half of all PDP funding comes from one source: the Bill and Melinda Gates Foundation (Moran et al. 2010). A change in focus at the Gates Foundation would seriously challenge the PDP model.

There are useful discussions of these different approaches in four successive WHO reports (2006, 2008, 2010, 2012). The thousands of pages of documents and submission summarized in these four reports is a testament to great interest in reforming systems of innovation in a way that will increase innovation and access in developing countries. The last of these reports recommends a binding global treaty in which countries would allocate a share of national income (0.01 %) to investment in research into neglected diseases. Since currently net aid averages around 0.45 % of GDP in rich countries, the recommendation is to direct approximately 2 % of all net aid towards research into neglected diseases. Presumably the Consultative Expert Working Group that wrote the 2012 report expected that any contributions towards research into the health needs of developing countries would be additional to existing aid budgets. They do not, however, indicate why this should be true, if indeed they considered the problem of competition between different funding needs.

One proposal that integrates the need for low prices and the need for investment into innovation is the HIF. I next summarize this proposal and how it responds to the needs in the global pharmaceutical market and how it differs from other solutions. While the HIF obviously cannot be a panacea, the principles underlying it may provide a useful framework for thinking about how to ensure that the benefits of SynBio are spread appropriately on a global basis.

Patents and SynBio

An important problem in the system of incentives currently in place is that much research that is essential to the

development of new drugs takes place far in advance of commercialization (Roin 2009; Syed 2009). Commercialization is typically delayed substantially by clinical testing, which is followed by regulatory approval. Thus, many of the inventions that are relevant to the development of a specific drug may occur many years in advance of the product actually being approved and sold. This represents an important commercial problem: if an invention is patented 15 years before the drug arrives on the market, the 20-year patent offers only 5 years of protection from imitation by generic competitors.⁴ There are other forms of protection, including data exclusivity, but there are also significant holes in protection in many countries. This means that the patent system may fail to provide adequate protection. Protection from imitation through supplementary measures, such as data exclusivity and patent term extensions, is weak, or completely absent, in most developing countries. The effect is that the expected returns from developing drugs that primarily address the needs of people in developing countries is further weakened, since protection from generic competition is short-lived.⁵

It seems likely that the SynBio-related drugs would likely face some problems with reduced effective exclusivity periods relating to the long period from initial inventions to market approval. The reason is that, at least in the near future, SynBio drugs may face additional scrutiny from regulators, as well as facing further obstacles in the production-development process. It is also possible that the technical challenges of developing and testing SynBio products may extend the time from patent application to market entry. The United States effectively recognized this problem in its decision to extend data exclusivity for biologic products to 12 years, while other pharmaceuticals obtain data exclusivity of only 5 years.⁶

For products that chiefly address developing country needs, it would be helpful to have a mechanism in which the rewards are not based on the patent status of the product, so that the incentives for new drug development in this area would not be impaired.

⁴ Many developed countries have provisions for “patent term restoration” of up to five additional years to account for the time the patent is unavailable for exploitation due to regulatory review of the product.

⁵ It is worth noting that there are good reasons for developing countries to avoid imposing so-called “TRIPS plus” intellectual property protections. In particular, extended exclusivity periods may result in higher prices and hence reduced access to new drugs for many people. Thus, it is not my intention to argue that countries should offer extended exclusivity, but simply to observe that shorter exclusivity periods may limit the commercial attractiveness of developing country markets and hence reduce investment into drugs chiefly intended for those markets.

⁶ Data exclusivity for biologic products was extended to 12 years in the Biologics Price Competition and Innovation Act of 2009.

The Health Impact Fund proposal

The purpose of the HIF proposal is to create incentives for companies to develop new medicines of great therapeutic value for markets that would otherwise lack commercial viability, and to ensure widespread access to those medicines for individuals in need. Details of the proposal are available in Hollis and Pogge (2008) and at www.healthimpactfund.org. The proposal entails the following key points. The HIF would be established to pay rewards for new, registered drugs. Registration would require the company that owned the rights to the drug would have to commit to supply the drug wholesale at a price that would cover only the costs of manufacturing and distribution.⁷ In exchange, the company would be paid rewards by the HIF, based on the assessed health impact of the drug. Rewards would be paid annually for 10 years following approval of the product by the competent regulatory authority for each country, following which the company would have to offer zero-royalty licenses to enable generic production of the drug. Notably, the duration of rewards would be fixed and independent of the remaining patent life of the product. Funding for the HIF would come from participating governments, which would, however, save substantially on the cost of new medicines, since registered drugs would be priced much lower than in the absence of the HIF.

The reward mechanism is a key component of the HIF proposal. As structured, participating countries would contribute a fixed amount of money annually to the HIF. Registered products would create an entitlement to a share of rewards proportional to the assessed health impact of the product. Health impact would be assessed compared to a baseline expected outcome, so only the incremental improvement would create eligibility for rewards. The baseline would be the expected outcome given expected actual treatment, not just the gold standard alternative. (Even if a drug were therapeutically very similar to others in the class, it could be eligible for rewards if it increased treatment rates.) Firms would compete for the available rewards by achieving health impact, measured in terms of quality-adjusted life-years (QALYs), or a similar metric. Assessment of health impact would be performed by the HIF, using data it collected or commissioned, data from the firms, and data from governments.

A key component of the HIF proposal is that *all human lives would be valued equally when determining the rewards*, in contrast to the current situation in which ability to pay is a key determinant of the attractiveness of a

pharmaceutical market. This would have several important effects. First, the HIF would make it commercially attractive to develop new medicines that chiefly affect poor people, wherever they are. This wouldn't require companies to make such investment on the basis of corporate social responsibility: instead, they would be making investments to maximize the returns they can pay to shareholders. Second, firms would have incentives to ensure that their products actually reached poor as well as rich people. Third, firms would have incentives to focus promotional efforts on those patients who would benefit the most from use of the drug, and a positive incentive to avoid sales of their product to patients would be harmed by consuming it.

Thus, incentives under the HIF would differ substantially from those under the ordinary price system; at the same time, products that were registered with the HIF would be available at much lower prices globally than otherwise, increasing access especially for people in developing countries. While the benefits of the HIF would be global, it is especially the poor who would reap the largest benefits, not only through development of new medicines to treat diseases chiefly prevalent among poor people, but also through access to those medicines at low prices. To the extent that SynBio is important in the arsenal of new medicines in the years ahead, the HIF would enable it to be used more effectively in addressing the important health needs of poor people.

The HIF would have other attractive characteristics. First, products would compete across therapeutic classes for the same pool of money. This would create an automatic mechanism directing investment into the most productive innovations, since companies could be expected to be responsive to financial opportunities. Second, the HIF would automatically regulate rewards, since a high rate of reward per unit of health impact would encourage more products to be registered; if the rate fell too low, fewer products would be registered, or products might be withdrawn. Third, by construction, governments would pay less per QALY for all products in the HIF than for products outside it, since if a firm could get more for a product outside the HIF, it would not register it in the HIF.

Generally, the core component of the HIF reward is that it is a competitive pay-for-performance scheme. The HIF administrators would not need information on the costs of drug development or other unknowable data, and would instead only reward results. This creates efficient incentives for innovation, since firms would want to invest in the projects with the highest expected therapeutic benefit/cost ratios.

One important feature of the HIF is that it requires ongoing monitoring of the health impact of the drugs being rewarded. This ongoing effort is necessary to deter firms from trying to obtain rewards through fraudulent (non-

⁷ This could be achieved through an administered price; through tendering production to competitive manufacturers; or by zero-royalty licensing to enable generic competition. See Hollis (2009) for a discussion of these possibilities.

existent) sales. Such an effort, however, has the merit of allowing collection of data about the characteristics of patients, which would enable the HIF to adjust payments based in part on evidence about the effectiveness of the drug in practice. This, in turn, would create attractive incentives for companies to try to increase sales only for patient who would actually benefit.

One way of seeing the HIF is that it resembles an insurance program. The financing for the HIF is therefore not as daunting as one might imagine. There would be savings to participating governments from reduced prices of HIF-registered drugs that would (at least partly) compensate for the cost of financing the rewards. At present, most of the spending that supports the development of innovative drugs takes place in rich countries and with the HIF, most funding for innovation would still come from wealthier countries. However, the direction of innovation would be re-oriented slightly, to encourage investment into areas with the largest potential therapeutic benefits.

The cost of these attractive properties of the HIF is that it would be necessary to invest heavily in collecting information about health outcomes for registered products. The alternative, of course, is paying for drugs without knowing how effective they are in practice. As it happens, there is considerable value in practice from knowing what drugs are working best and for which sorts of patients, information that is too rarely collected at present.

Finally, it is worth commenting that the HIF is yet to be tested in practice, and that there are many obstacles to the implementation of this proposal. Most importantly, getting agreement for government funding will certainly be an important challenge. However, it is useful to see the HIF as a kind of insurance mechanism, which could be substantially financed through reductions in the prices of registered medicines. That is, the HIF is not intended to be a large new multinational funding commitment, so much as a new cooperative rearrangement of existing spending on drugs to achieve more efficient, equitable outcomes.

Conclusions: ensuring the greatest value

Ultimately, SynBio offers tremendous value as a pathway to enable development of useful new pharmaceutical therapies. However, to ensure that investment in SynBio generates the most value for the world, it is important that the investment decisions be directed towards the development of products that are therapeutically valuable *and* available to the widest number of people. At the same time, it is also ethically sound and economically efficient that the benefits of SynBio are spread in a way that matches the potential harms. The HIF proposal embodies the principles that (a) incentives for new investment in pharmaceuticals

should be allocated on the basis of global benefits without giving preference to people with higher income; and (b) that access should not be denied on the basis of income. To the extent that these principles can be applied for investments in SynBio-related pharmaceuticals, the potential value of SynBio can be more effectively achieved.

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References

- Cernuschi T, Furrer E, Schwalbe N, Jones A, Berndt E, McAdams S (2011) Advance market commitment for pneumococcal vaccines: putting theory into practice. *Bull World Health Organ* 89:913–918
- Cohen-Kohler JC, Mrazek M, Hawkins L (2007) Corruption and pharmaceuticals: strengthening good governance to improve access. In Campos E, Pradhan S (eds) *The many faces of corruption: tracking vulnerabilities at the sector level*. Poverty Reduction and Economic Management, World Bank
- Economist (2012) “Tripped up”
- Flynn S, Hollis A, Palmedo M (2009) An economic analysis of compulsory licensing for needed medicines. *J Law Med Ethics* 37(2):184–208
- Hill S, Johnson K (2004) Emerging challenges and opportunities in drug registration and regulation in developing countries. DFID Health Systems Resource Centre
- Hollis A (2009) The Health Impact Fund and price determination, incentives for global health discussion paper no. 1
- Hollis A, Pogge T (2008) The Health Impact Fund: making medicines accessible for all. *Incentives for global health*
- Light D (2009) Advanced market commitments: current realities and alternate approaches. HAI Europe/Medico International, Amsterdam
- Moon S, Jambert E, Childs M, von Schoen-Angerer T (2011) A win-win solution? A critical analysis of tiered pricing to improve access to medicines in developing countries. *Glob Health* 7:39
- Moran M, Guzman J, Ropars AL, Illmer A (2010) The role of product development partnerships in research and development for neglected diseases. *Int Health* 2:114–122
- Ong HT (2006) Evidence-based prescribing of statins: a developing world perspective. *PLoS Med* 3(3):e50. doi:10.1371/journal.pmed.0030050
- Presidential Commission for the Study of Bioethical Issues (2010) *NEW DIRECTIONS—ethics of synthetic biology and emerging technologies*
- Roin B (2009) Unpatentable drugs and the standards of patentability. *Tex Law Rev* 87:503–570
- Syed T (2009) Should a prize system for pharmaceuticals require patent protection for eligibility? *Incentives for global health discussion paper no. 2*
- The Lancet (2012) Counterfeit drugs: a growing global threat. *Lancet* 379(9817):685
- van Weely S, Leufkens HGM (2004) Background paper: orphan diseases. In: Kaplan W, Laing R (eds) *Priority medicines for Europe and the world—a public health approach to innovation*. World Health Organisation, Geneva
- World Health Organization (2006) Public health, innovation and intellectual property rights. Report of the Commission on

- Intellectual Property Rights, Innovation and Public Health, Geneva
- World Health Organization (2008) Resolution WHA59.24, public health, innovation, essential health research and intellectual property rights: towards a global strategy and plan of action
- World Health Organization (2010) Research and development: coordination and financing. Report of the World Health Organization Expert Working Group on Research and Development Financing, Geneva
- World Health Organization (2012) Research and development to meet health needs in developing countries: strengthening global financing and coordination. Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, Geneva