Comment of Knowledge Ecology International
In Response to "Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access; Public Meeting; Request for Comments."
Docket ID: FDA-2017-N-3615

Submitted on November 17, 2017

Scott Gottlieb, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Gottlieb,

Knowledge Ecology International (KEI) is a not for profit non-governmental organization. We are concerned about high drugs, and propose several reforms, including several that would lower drug prices, and others that address mechanisms to ensure robust funding of R&D, without high drug prices.

Table of Contents

Transparency

Policies regarding drug pricing greatly benefit from accurate information about the economics of drug development and the markets for drugs. One area where the evidence base is weak or non-transparent concerns the costs associated with the research and development (R&D) of new products. The most economically significant R&D outlays are those for clinical trials. Knowing what was spend on those trials is useful, when considering.

Clinical trial costs

The Food and Drug Administration (FDA) should require disclosures of the costs of each clinical trial used to support the marketing approval of a drug, vaccine or other regulated technology.

The disaggregation of the cost data by year and trial is important. The modeling of the incentives needed to stimulate investment should take into consideration the timing of R&D outlays as well as the risks and subsidies that are relevant.[1]

Just knowing the total spent on the trials is not sufficient, since there is the expectation that one consider adjustments to out-of-pocket-costs for the risks of failures, and in some cases, the costs of capital. Consider the case of a product that took seven years to bring to market, and whose trials had an estimated likelihood of approval (LoA) of 0.12 for Phase 1, 0.2 for Phase 2 and 0.56 for Phase 3,[2] and a cost of capital of 8 percent. The adjustments for risks of failures and capital costs associated with an early Phase 1 trial would be different from a later Phase 3 trial.

Instead of having R&D cost data for specific drugs, policymakers now rely upon averages. Averages for drug development costs can be estimated, and the most widely quoted averages are those presented by Professor Joseph DiMasi and his co-authors, including more recently his 2016 published paper that estimated the cost of developing a new drug to be $2.588 billion, in 2013 dollars.[3] DiMasi and his colleagues frequently consult with PhRMA member companies. The $2.6 billion figure was based upon his claim that on average, companies spent $25.3 million on Phase 1 trials, $58.6 million on Phase 2 trials and $255.4 million on Phase 3 trials, for a total of $339.3 million. Once adjusted for the risk of failures, DiMasi assigned $965 million to trial costs, before the cost of capital, and $1.46 billion inclusive of the costs of capital. Another $1.098 billion was estimated to have been spent on pre-clinical outlays, inclusive of $668 assigned to the cost of capital for the pre-clinical research.

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[1] James Love, “When governments mandate transparency of R&D costs, the details are important,” Medium, March 6, 2016. https://medium.com/@jamie_love/when-governments-mandate-transparency-of-r-d-costs-the-details-are-important-6be001f9e052

[2] The LoA parameters from: DiMasi et. al., *J Health Econ.* 2016 May;47:20-33. doi: 10.1016/j.jhealeco.2016.01.012.

[3] J.A. DiMasi et al., Journal of Health Economics 47 (2016) 20–33.

The DiMasi estimates were based upon a set of projects in a sample that is secret, and for which there are few details known, such as the number of patients enrolled in the trials, and certainly not the name of the drugs.

We know that there are many drugs that have much different costs from DiMasi's average, but also that in general, averages can be misleading. In some years, the FDA will approve new drugs based upon evidence from few than 100 patients in trials, and other drugs with more than 30,000 patients in trials. Drugs for cancer have, on average, roughly 1/3 or 1/4 of the number of patients in trials than non-oncology drugs, and there are large differences in the enrollment for orphan drugs, compared to non-orphan drugs. Also, the likelihood of approvals, are quite different for different diseases and molecule types.[4]

Data from the Orphan Drug program

To illustrate our skepticism of the relevance of the DiMasi average cost figure, consider data from the Orphan Drug Tax Credit (ODTC).

In 2013, the last year for which we have actual rather than projected data on the credit (from the IRS Statistics of Income), the total amount of the credit from all 132 corporate tax returns that claimed the credit was just over $1 billion, nearly the same amount as the DiMasi estimate of $965 million in outlays for a single drug. The ODTC represents 50 percent of the pre-credit outlays on qualifying clinical trials. In 2013, the FDA granted 265 orphan designations and approved 33 orphan indications, including 8 novel products which were approved for an orphan drug lead indication.

We have examined several years of data from the FDA and the IRS on Orphan Drug designations and approvals and the credit reported to or projected by the IRS, and estimated the average amount of money spent on the qualifying trials for orphan products, including the costs of failures, to be $86 to $102 million, per FDA approved indication.[5]

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[4] James Love, Orphan Drugs Designations and Approvals have Something to Say about Risks, September 25, 2017. Bill of Health. http://blogs.harvard.edu/billofhealth/2017/09/25/orphan-drugs-designations-and-approvals-have-something-to-say-about-risks/

[5] James Love, What does the Orphan Drug Tax Credit tell us about the Costs of Clinical Trials? Bill of Health, November 15, 2017. http://blogs.harvard.edu/billofhealth/2017/11/15/what-does-the-orphan-drug-tax-credit-tell-us-about-drug-development-costs/

DiMasi's $965 million average is for the risk adjusted cost of Phase 1-3 trials is not realistic for most cancer drugs and orphan products in general. These are many of the drugs with the most shocking prices.

Unfortunately, the amount of the ODTC claimed for specific drugs and for specific trials is not public.

Recommendation: The ODTC is a public investment in specific trials, including often for drugs that are very expensive. If the ODTC survives, the amount of the qualifying expenditures should be public, for the specific trials the credit is claimed.

Costs of trials for government funded research

It is difficult to get data on the costs of specific trials from companies, and even from the NIH, BARDA and other federal agencies.

The NIH itself used to publish annual data on the costs of trials, but has not done so in recent years.

Below is a table from the NCI DCP Cooperative Group trials and funding, taken from a 2003 report on excessive pricing prepared for the South African Competition Commision. The table reported the NIH's own reporting of its cost per patients in NIH funded oncology trials from fy 1993 to fy 1999.

Table RND 2.8-1: NIH DCP Cooperative Group Treatment Trials and Funding, 1993 to 1999

FISCAL YEAR	Number of trials	Number of of Accruals	Cost of Trials	Cost per patient	Cost per trial
FY93	478	21018	$ 81,159,000	$ 3,861	$ 169,789
FY94	477	18788	$ 82,362,000	$ 4,384	$ 172,667
FY95	445	17548	$ 82,327,000	$ 4,692	$ 185,004
FY96	428	18305	$ 96,969,000	$ 5,297	$ 226,563
FY97	451	19891	$ 97,846,089	$ 4,919	$ 216,954
FY98	446	20662	$ 102,547,000	$ 4,963	$ 229,926
FY99	415	20780	$ 128,883,848	$ 6,202	$ 310,563

Source: National Cancer Institute

These are three things federal agencies could easily do to provide useful information on drug development costs, without the need for new legislation.

Recommendation: The NIH, BARDA, the CDC, the VA, the Army and other government agencies should collect and report data on the costs of each clinical trial they fund.

Recommendation: Government agencies should require that licenses to federally owned or funded inventions require reports from license holders on the costs of each clinical trial undertaken on the licensed products.

Recommendation: The FDA should require each company that receives an extension of its patent or other exclusive rights for pediatric testing to disclose the amount of money spent on the trial used to obtain the extension of the monopoly.

Asset acquisition costs.

In a recent testimony on a proposal in Maryland to require transparency of R&D costs, KEI provided notes on the types of disclosures drug companies make on R&D costs in their current SEC filings to shareholders.[6] In 2015, BMS claimed $1.7 in "license and asset acquisition charges" as an R&D expense. Pfizer's 2016 10-K report claimed $1.2 billion for the fair market value of a deal giving Merck KGaA certain co-promotion rights for Xalkori, as an R&D cost, These type of transactions may represent the costs to BMS and Pfizer of developing a specific product, because they have to obtain the intellectual property rights to make and sell a compound, but it is confusing to policy makers when these expenses are used to describe R&D spending, that policymakers think is spent on experiments and science.

Recommendation: The SEC should require all drug companies, including those reporting under SIC 2834 for pharmaceutical preparations, to provide different line items for (1) asset acquisitions related to drug development, and (2) R&D expenses, exclusive of such asset acquisition costs. This can also eliminate some of the double counting that occurs in looking at aggregate data on R&D costs.

Licensing

The NIH and other federal agencies undertake research and fund others to undertake research. The federal government needs to have policies to promote the transparency of the terms of the

[6] KEI Note Pharmaceutical Company R&D Cost Disclosures in SEC Filings
James Love, March 16, 2017,
https://www.keionline.org/wp-content/uploads/SECFilings-16March2017.pdf

licensing of (at least) federally funded and subsidized inventions. Note that companies do make the licenses public when the license and the terms are considered material to shareholder interests. And, the Medicines Patent Pool is able to publish the full terms, un-redacted to all of its licenses on drugs for HIV and HCV. We would like the licensing terms be made public because they are material to the interests of the public as patients and taxpayers.

Recommendation: All HHS and other federal agency licenses agreements involving to drug patents should be fully transparent, and this obligation should also be extended to any patent license that involves Bayh-Dole rights in the patent, such as the University of California licenses to the patents for Xtandi, or the Cold Spring Harbor license to the patents on Spinraza.

Access to Knowhow, data and materials

We grant temporary monopolies for drugs and vaccines, and this is a privilege. There needs to be broader obligations to disclose knowhow, data and materials, in order to ensure that the public has access to safe and affordable generic and biosimilar versions, once the legal monopolies expire.

Recommendation: In order to obtain a license to a government funded patented invention or a federal CRADA, or to register a drug or vaccine with the FDA, the company must agree to the following conditions:

1) [The party] agrees to make available the following to any generic drug manufacturer seeking marketing approval for any small molecule and biologic product in any OECD country or for WHO prequalification for any biologic drug or vaccine:

- a) Materials:,
  - i) Cellular clones and hybridoma stocks
  - ii) Plasmids, plasmid maps, and sequences of antibody complementarity determining regions (CDR)
  - iii) Physicochemical/ biophysical characterization
- b) Methods:
  - i) Growth conditions and protocols
  - ii) Attenuation or inactivation protocols
  - iii) Extraction and purification protocols
  - iv) Synthetic work-up and schemes
- c) sufficient quantities of the approved medication for a generic developer's testing; and to
- d) allow the developer to join, a single, shared system of elements to assure safe use (ETASU) of the medication.

Non-Voluntary use/Compulsory licenses/Exceptions to Rights and Remedies

Drug prices are high because governments create legal monopolies and then rely upon high prices and profits from the temporary monopoly to create an incentive to invest in R&D.

Predictably, there are abuses of the legal monopoly, including excessive prices. In such cases many patients forgo access, and insurance/reimbursement entities withhold or restrict reimbursements or impose high copayments or products. All of these actions harm patients.

If the United States negotiates prices in the Medicare program, the primary leverage exercised by the government will be to restrict reimbursements, and as noted, that harms patients.

For any excessive pricing case, the federal government needs to have options that do not harm patients. In particular, the government needs the legal mechanism, available in most countries, to authorize third parties to make, use and sell products and services protected by patents or other regulatory exclusivities, such as the Orphan Drug or biologics test data exclusivities.

One general authority for compulsory licensing of patents in the United States is 28 U.S.C. § 1498(a). This authority requires the patent holder be paid "reasonable and entire compensation for such use and manufacture." This compensation standard has been a hindrance to using 1498 to issue a compulsory license for a medicine when discussed in the past, both when it was proposed to increase availability of Cipro in 2001, and when the Department of Veteran's Affairs proposed it to address the high price of sofosbuvir in 2015.

The UACT proposal

The Union for Affordable Cancer Treatment (UACT) recently submitted a letter to members of Congress regarding proposed legislation which would authorize Medicare to negotiate the price of prescription drugs. UACT's proposal, which KEI supports, would provide a new authority for HHS to limit the remedies for infringement of patent to remedy an excessive price, and also to create exceptions to any other regulatory exclusivity, "*when such action is necessary in order to enable the competitive supply of any drug, vaccine, medical procedure or diagnostic test that is not available at a reasonable price."* The proposed standard for compensation was "payment of a reasonable royalty" under rules and procedures the Secretary would adopt.

Recommendation: Create new authority to limit remedies for infringement to deal with excessive pricing cases.

Remedy for excessive prices
The Secretary of the Department of Health and Human Services or a designee authorized by the Secretary may limit the remedies for infringement of any patent to payment of a reasonable royalty, and create an exception for any regulatory exclusivity, when such action is necessary in order to enable the competitive supply of any drug, vaccine, medical procedure or diagnostic test that is not available at a reasonable price. The Secretary shall adopt the appropriate rules and procedures to carry out this section.

Extending March-in Rights

Another approach would be to extend the federal march-in right procedures, to any medical technolgy regulated by the FDA.

Under the Bayh-Dole rights, the federal government has three different policy tools at its disposal to increase competition in markets of medical inventions.[7] One of the three concerns the "march-in" rights, under 35 U.S.C. § 203, a mechanism where the government can force the rights holder of a federally-funded invention "to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances," or, if the rights holder refuses, the government may itself grant the license.

Utilizing these march-in rights requires a determination that at least one of four conditions (section 203(a)(1-4)) are met, but most relevant to the amendment is the requirement for "practical application" of the invention, which is defined in 35 U.S.C. § 201(f) as making the benefits of the invention "available to the public on reasonable terms."

At present, a handful of important medical technologies can be regulated as to access and pricing via the Bayh-Dole rights in the patents, but most products are not subject to Bayh-Dole rights.

KEI has recommended expanding the march-in authority so that it would apply to any drug, vaccine, or medical technology regulated by the FDA. By adding the language proposed below to 35 U.S.C. § 203, the government's ability to authorize third parties to use patents would have

[7] In addition to the march-in rights, for any invention which was made in part or whole with government funding, according to 35 U.S.C. § 209(d)(1), the federal government shall retain "a nonexclusive, nontransferrable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world." And, for inventions which are owned by the federal government and licensed to another party, the federal agency which owns the invention also has the right to terminate the license under 35 U.S.C. § 209(d)(3).

a more appropriate and useful legal framework than 28 USC 1498(a), which was not intended to address drug pricing concerns.

Recommendation. Add the following new section (c) to 35 USC 203.[8]

> *(c) The Department of Health and Human Services may also authorize a non-voluntary use of a patent on the same procedures and grounds set out in (a), for any patented invention in the field of use for any FDA regulated medical invention, including but not limited to drugs, vaccines, medical devices and diagnostic tests.*

Such a short amendment to 35 U.S.C. § 203 would eliminate the need to use the 28 U.S.C. § 1498(a) compensation standards, which are problematic, and eliminate concern that the use of the march-in rights would uniquely be a burden for a drug manufacturer that licensed a federally funded invention.

Bayh-Dole Rights

The NIH and other federal agencies currently refuse to enforce the obligations in the Bayh-Dole Act to make inventions available to the public on reasonable terms. For extensive documentation of this issue, see:

- https://www.keionline.org/book/government-funded-inventions/
- https://www.keionline.org/book/government-funded-inventions/nihlicensespatentsdataanddcommentsonproposedexclusivelicenses/

Also, please review our pending request regarding the patents on Zinbrya.

https://www.keionline.org/wp-content/uploads/2017/10/KEI-letter-Zinbryta-14Sep2017.pdf

For products covered by insurance, reasonable incentives is a better framework than reasonable pricing alone.

Controversies over drug pricing can be seen as disputes over the value of a treatment, given alternatives, but also about excessive returns earned because of the monopoly.

A key and under-discussed fact is that when drugs have very different patient populations, the relationship between prices and the incentive change.

[8] See: https://www.keionline.org/23189/

We are finishing a policy paper that considers a new approach to drug pricing, that would make the prices and/or the term of the temporary monopoly more closely connected to the global revenues on products.

The basic idea is that when a drug has a large (Sovaldi) or small (Soliris) population, the notion that the price should have anything to do with the value can be hard to justify, because the overall fiscal impact of the product is more important. The manufacturer of Soliris wants to justify high prices not on the basis of the "value" of the drug, but because high prices are assumed to be necessary as an incentive, an assertion that should be challenged since the global revenues already exceed $15 billion.

Pediatric Extension

The FDA needs to stop granting the pediatric testing exception when the costs to the public of the 6 months of exclusivity, including through taxpayer funded programs is far greater than the cost of conducting the trials the FDA requests. Direct funding of the trials is preferred. For many drugs, the cost of the PED extension is more than $1 million per enrolled patient, in terms of higher prices. This is stupid and wasteful.

Delinkage

At some point policy makers need to explore and embrace the long overdue reforms that involve delinking the costs of R&D including the incentive to invest in R&D, from the prices of products.

Delinkage is a cost control strategy that expands both innovation and access.

For more on this see: http://delinkage.org.

Here are the benefits of delinkage:

Low prices and expanded access. For many, the most important benefit will be the elimination of high prices on products. Most drugs can be manufactured and distributed at low prices, as commodities benefiting from competition among suppliers of generic alternatives. The high prices for new drugs are enabled by the creation of legal monopolies as the incentive to invest in R&D. As we create new funding mechanisms for R&D, including new cash incentives to reward successful developers of new products, we can eliminate both the monopolies and the high prices associated with the monopolies.

Elimination of price sensitive formularies and high co-payments. When drugs and other products are priced closer to the marginal costs of production, we can expand access and eliminate price-sensitive formularies and high co-payments for drugs.

More efficient incentives. The current system of rewarding innovation through the grant of monopolies is inefficient, for several reasons. For example, companies are rewarded for matching health care outcomes, even when the new products do not improve health outcomes, leading to costly, excessive, and wasteful investments in the development and marketing of products that are relatively unimportant from a medical standpoint. Companies also have incentives to invest in the marketing and inappropriate promotion of products to patients who do not benefit from the drugs. Companies do not have adequate incentives to invest in research that advances science but does not product a monopoly on a commercial product. Under delinkage models, governments can more effectively target incentives to reward products that improve health outcomes (see discussion of end product prizes), and also design incentives for researchers to advance science, and share and provide for royalty-free and non-discriminatory access to data, inventions, and materials (see discussion of the open source dividend and interim results prizes).

Fairness. Under delinkage, prices can be low everywhere, without adverse impacts on innovation, in order to reduce the gaps between the rich and the poor, and making “access to medicine for all” feasible.

Policy coherence. Delinkage aligns the interests of consumers and drug developers, and eliminates the trade-offs between access and innovation. High prices are the enemy of access, the enemy of fairness, and present a fundamental conflict between access and fairness on the one hand, and innovation on the other. Delinkage fixes this problem, by taking high prices out of the equation for innovation. We pay for innovation, but not through artificially high prices under the grant of monopolies.