

## **A conversation with Dr. Aaron Kesselheim, January 21, 2016**

### **Participants**

- Dr. Aaron Kesselheim – Associate Professor of Medicine, Harvard Medical School/Brigham and Women’s Hospital
- Dr. Nick Beckstead – Program Officer, Scientific Research, Open Philanthropy Project

**Note:** These notes were compiled by the Open Philanthropy Project and give an overview of the major points made by Dr. Kesselheim.

### **Summary**

The Open Philanthropy Project spoke with Dr. Kesselheim of Harvard Medical School as part of its investigation into research and strategy on improving pharmaceutical research and development (R&D) policy. Conversation topics included the role of the Food and Drug Administration (FDA) in pharmaceutical innovation, factors inhibiting pharmaceutical innovation, potential interventions, and other individuals and organizations working in this area.

### **Role of the FDA in pharmaceutical innovation**

Dr. Kesselheim believes that contrary to widely held belief, the FDA is not a significant impediment to the release of important new drugs onto the market. Before the FDA held its current mandate, the market was flooded with unsafe or ineffective prescription drugs, and the lack of standards actually inhibited important innovation by making it difficult for consumers to distinguish between good and bad products. Because of the FDA, drugmakers must study the products they hope to sell, which enforces a minimum standard of quality and provides information to guide these drugs’ use in patient care. This gives consumers access to innovative products that work rather than products that are new but not necessarily effective. Without such requirements, drugmakers would generally not subject their products to rigorous study; as an example of this, see the present-day market for nutritional supplements.

Additionally, the FDA already takes steps to facilitate the entrance of new drugs on the market. It currently approves over 50% of all new drugs on the basis of surrogate endpoints, which measure the effects of a treatment using biomarkers or other proxies for real clinical outcomes. The FDA also approves two-thirds of new drugs based on studies that last six months or less. It approves drugs based on studies that average a few hundred patients in size, and approximately one-third of new drugs are approved on the basis of a single pivotal study that is supposed to be adequate and well-controlled.

### **Use of surrogate endpoints**

Surrogate endpoints must be validated before they can be used. Many surrogate endpoints have been suggested for use in approving drugs, only to later be found to

correlate poorly with the clinical endpoints the drugs were meant to achieve. In those cases, prescribing drugs based only on data from surrogate endpoints has led to worse outcomes for patients.

## **Challenges of pharmaceutical innovation and access**

Under the current system of pharmaceutical development, several factors may affect how rapidly important new drugs reach patients who need them:

- The extent of physicians' knowledge of FDA-approved new drugs and how to prescribe them, and patients' ability to adhere to their treatment regimens
- The cost of drugs
- The current pharmaceutical intellectual property (IP) environment, which equally rewards incremental improvements or changes in existing treatments rather than revolutionary new developments

## **Incremental versus revolutionary innovation**

Pharmaceutical IP law as currently written and interpreted makes it easy to secure new patents on minor changes to drugs that do not significantly impact their efficacy. The FDA also does not require that investigational drugs be tested against treatments already on the market in order to be approved. Reviews of recently-approved drugs indicate that 50% of new drugs are tested against placebos. This can be less useful than comparing them to other available treatments for a given condition, which is much less commonly done. As a result, there can be numerous drugs approved that all do the same thing without any knowledge about which variations are better for which patients.

## **Lack of independent guidance on drug value**

The United States government currently has no organization that exists to help healthcare payors judge the value of various drugs or gather evidence on drug quality and examine it from a neutral perspective. The vast majority of government support of science is directed at basic and translational science. As a result, most drug clinical trials and post-approval observational analyses are conducted by groups sponsored by the pharmaceutical companies themselves. The Agency for Healthcare Research and Quality (AHRQ) has funded such work in the past, but its budget is limited and in the past few years Republicans in Congress have targeted this institution for elimination. There is an opportunity for more research in this area to explore comparative drug analysis and help identify low-value from high-value therapeutics.

## **Potential interventions**

Refocusing the pharmaceutical industry away from low-value drug development may require removing some of the incentives for incremental development and increasing the incentives for revolutionary ideas.

## **Providing better information to guide payors on drug quality**

A US version of the UK's National Institute for Health and Care Excellence (NICE), which would guide payors on drug value, may help reduce some of the incentive to focus on incremental innovation. Having this guidance available would mean that even after a pharmaceutical company secures FDA approval of a new drug, it might have difficulty finding payors for it if it does not add substantial value. NICE's work is specific to the UK, so its recommendations are not commonly translated to the US market, where products and cost of care may differ. More rigorous studies of drugs' value could also better inform policymakers and provide incentives to encourage higher-value innovation.

### **Removing legal impediments to coverage restrictions by government payors**

Medicare and Medicaid are subject to various laws limiting their ability to negotiate prices with pharmaceutical manufacturers, including restrictions on their ability to exclude low-value FDA-approved drugs from coverage. This means that if a US equivalent to NICE produced a report that discouraged buying a particular drug, Medicare and Medicaid may not be able to refuse to cover it.

By contrast, the Department of Veterans Affairs (VA) has more control over which drugs it covers and so often gets much better prices than other government payors. The VA drug formulary is well-regarded for this reason. So far, there have been no concerted efforts to convert Medicare and Medicaid to a similar system. In the last few months, some policymakers have suggested that Medicare should be allowed to negotiate drug prices, but this discussion has not progressed very far.

### **Subsidies, prizes, and public-private partnerships**

Researchers who have had revolutionary ideas often report getting little attention or funding until they were able to prove that their concepts worked. Government or philanthropic funding could help sustain researchers as they develop important new treatments. This could be done through direct funding, prizes, or public-private partnerships.

### **Taxes or mandatory reinvestment for pharmaceutical companies**

One possible negative effect of fueling innovation through public funding is that the drug company responsible for final stages of development gets the credit for the product, and usually is the sole owner of the product patent, which provides it with most of the revenue from sales. The drugmaker does not have to credit or reinvest in the public source that helped fund the earlier, riskier stages of the drug's development. Currently, large pharmaceutical companies spend about 15–20% of their revenues on R&D, and by one estimate 70–80% of that amount is spent on incremental innovation. Possible solutions that could be investigated include requiring drug companies that bring forward a drug derived from public investment to invest a certain percentage of their revenues in R&D. A system that more equitably rewards all key contributors to a drug's invention, rather than only the company that takes the final step, could also help to better align incentives and reduce inefficiencies.

## Gaps in the treatment landscape

Dr. Kesselheim believes it is rare for a revolutionary product to be developed but remain unfunded due to the misaligned incentives of the current system. Drugs that are proven effective and fill an unmet need will generally find funders and manufacturers. However, anecdotes from medical history show that some ideas for important innovations, such as the coronary artery stent, were repeatedly rejected before finally being developed. In the current environment, drugs that lack patent protection are at increased risk for such outcomes, though it may be possible to secure intellectual property protections on older drugs (as the current manufacturer of thalidomide did after the drug, which famously contributed to a major public health crisis in the 1960s when sold an anti-nausea medication, was later found to be effective in treating a certain rare type of cancer). One researcher, Vikas Sukhatme at Beth Israel Deaconess Medical Center, has founded a nonprofit organization, GlobalCures, which promotes investment in testing unpatented pharmaceutical products.

## Others working on improving pharmaceutical R&D policy

Other key researchers in this field include:

- **Bhaven N. Sampat** – associate professor in the Department of Health Policy and Management at Columbia University who has worked on IP issues related to drug development.
- **Amy Kapczynski** – professor of law at Yale Law School and faculty director of Yale’s Global Health Justice Partnership.
- **Joseph Ross** – associate professor of medicine and public health at Yale School of Medicine
- **Steven D. Pearson** – founder and president of the Institute for Clinical and Economic Review (ICER). Dr. Pearson works primarily on evaluating the evidence for already-approved medical treatments.

## Status of policy advocacy work

There is evidence of broader recognition that the current pharmaceutical innovation system makes it too easy to secure patents and to get poor quality patents approved. Some recent Supreme Court decisions have made steps in the right direction by raising the bar for what might earn a patent in the context of gene sequences, diagnostic tests, and business methods. By contrast, recent policy proposals in Congress have been less useful. For example, in the last year, the most significant policy development related to transformative drug innovation was the 21<sup>st</sup> Century Cures Act (which passed the House in 2015 but has been formally introduced in the Senate as of March 2016). All of the policies in the act related to lowering FDA standards in order to further facilitate the approval of new drugs or devices. At meetings of the National Academy of Medicine, proposals for how to incentivize innovation in a particular medical arena frequently involve changing FDA standards or making the exclusivity period for new drugs longer.

### **Groups working on policy advocacy**

According to Dr. Kesselheim, organizations that are advocating for helpful policy changes in this area, though he does not necessarily always agree with their positions, include:

- Public Citizen
- The National Center for Health Research
- Knowledge Ecology International

*All Open Philanthropy Project conversations are available at <http://www.openphilanthropy.org/research/conversations>*