

FUTURE OF INNOVATION IN MEDICINE: INCENTIVES FOR  
NEW MEDICAL TREATMENTS AND GLOBAL HEALTH

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CITE AS: R JACOB, WASH. J.L. TECH. & ARTS 211 (2017)  
<http://digital.law.washington.edu/dspace-law/handle/1773.1/1735>

ABSTRACT

*The Future of Innovation in Medicine Conference (“Conference”) proceedings contained in this Symposium Issue are about the problem of incentivizing research into new uses for established medicines. Putting the problem into the wider context of financing pharma research generally gives an important perspective.*

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## I. THE PHARMACEUTICAL RESEARCH MODEL

### A. *Who Pays for Pharmaceutical Research Today*

For many years, and still today, the brunt – the heavy lifting – of research and development (“R&D”) of pharmaceuticals has been carried out by the pharmaceutical industry or rather that section of it which consists of very large, research-based companies, often called “big pharma.” My research assistant did a rough and ready internet search on R&D spending in 2014. For the top 30 companies the figure was \$120 billion; for governments and charities (notably the Gates and Wellcome Foundations) the figure is \$30 billion. I am sure more precise figures can be obtained. They do not matter for present purposes. The \$120 billion come from the gross profits that big pharma currently makes. Those profits largely come from medicines which have some form of legal monopoly. – A patent (or something like it such as a supplementary protection certificate, or regulatory exclusivity). This because, as soon as exclusivity is lost, generic competition starts, prices and profits from the medicine concerned fall rapidly. So, it is sales of the medicines which are subject to exclusivity which form the major contributor to the profits from which the \$120 billion comes.

Putting this in homely terms it works out that about 20% of the price in a high price country (the US, most of Europe and similar) of a widely prescribed patented medicine will be spent on R&D.

The take home point is simple: it is the patented medicines of today which pay for the research for the medicines of tomorrow. Governments and charities can and do a lot less by comparison – most particularly they simply do not have the resources for the huge cost of regulatory compliance. Of course, big pharma makes profits – and good ones too if things are going well. But investment in pharma is risk money. For instance, if R&D now and of the next few produces little or nothing, the company will be staring at failure. Indeed, without new products, any research-based pharma company will be reduced to a commodity, generic, company in about 12 years. By then exclusivity in all of a company’s products will be gone.

True, it is that a lot of money is also spent on “promotion.” But most of this is really about educating doctors – and they are no longer getting the great perks of yesteryears. Only in the US is

consumer advertising allowed – an obviously silly practice to an outsider!

### *B. Current Problems*

There are a number of factors which increasingly threaten the current, longstanding, industry model:

First. The discovery of new medicines is becoming rare. Perhaps this is because in the past the industry previously gathered low-hanging fruit which is now exhausted. But now for whatever reason, the stream of new “blockbuster” medicines coming on the market, if not running dry, is flowing less abundantly.

Second. The period of practical (i.e. from first marketing to expiry of patent plus Supplementary Protection Certificate or “SCP”) new drug exclusivity is falling. A piece of research which will be published shortly by Tony Rollins shows that the time taken for regulatory approval has grown so much that the combined period of effective exclusivity provided by a drug patent and a follow up Supplementary Protection Certificate is now about the same as the period of effective exclusivity before the SPC system came into operation in Europe. That period was thought to be too short (hence the SPC system). It very probably is too short again, yet it is very doubtful that the legislators anywhere will provide a longer period of exclusivity. Whether the increased time for regulatory approval can be brought down I do not know – it certainly needs looking at. Perhaps in some cases regulation is over-precautionary.

Third. The pricing of medicines which actually cure is becoming increasingly problematic. Many of the “blockbusters” of the past, e.g. the statins, require daily doses for life. The price of an individual dose, albeit quite a bit greater than manufacturing cost, does not sound too high. But if a medicine cures – perhaps with only a few doses - the size of the market is much smaller. Yet the cost of ongoing research and regulatory compliance remains the same. So how much for a pill or injection that cures a serious disease? There was huge row with politicians crying “the sick cannot afford this” about Gilead’s price of nearly \$100,000 for sovaldi. It is used for a 12-week treatment period which cures (not alleviates) the most common form of hepatitis C. In the broader context, such a cost is actually cheap compared with the alternative – years of various

treatments and patients who, because of their illness, are drains on both society and their families. Some of the new immunotherapy cancer treatments will fall into the same box. No matter that a few injections may make expensive surgery, radiotherapy and chemotherapy unnecessary, there will be loud voices complaining about prices and the wicked drug companies. We are in a strange world where the better and quicker a medicine cures, the more people complain about its price.

Fourth. Individualized treatment – personal medicine – is becoming increasingly important. Diagnosis is becoming more and more patient specific, and doctors are more and more becoming able to predict whether a particular drug will work for a particular patient. Blanket, scattergun, mass prescribing is going to fall. Medically, that is most welcome – no-one wants to give or take a medicine which does not in fact help the specific patient. But a fall in mass prescriptions also means less sales, – again reducing pharma’s income unless prices are put up correspondingly.

The upshot is that there are real risks to the current commercial incentives to do R&D.

### *C. The Practical Effect of Exclusivity for Research*

The hard commercial truth is simple – it is legal exclusivity which allows the makers to charge a high price. It is high prices which pay for ongoing R&D. It is the prospect of those high prices which is the key driver for the spending of that \$120 billion on new medicine R&D. Without that prospect, how could the CEOs of pharmaceutical research-based companies justify their expenditures?

### *D. What Happens if Exclusivity for a Possible Research Candidate is Not Possible, or Would be Weak or Too Short?*

The answer is both obvious and inevitable. Commercial investment in R&D for these candidates is, at best, unlikely. But more likely will not happen. We see the effects of this now. Thus, there is the much reduced level of big pharma research for new antibiotics. Antibiotics are cures or largely so. Also, widespread sales of antibiotics are not as likely as they were in the past because,

rightly, of the concern that bacteria will develop resistance. Government leaders wring their hands – but do not promise an extended period of exclusivity.

## II. NEW USES FOR ESTABLISHED MEDICINES

Medical history is littered with examples of new uses for known drugs providing substantial advances in the treatment of patients. For example, rapamycin was first used as an anti-fungal agent but was subsequently discovered to be a powerful immunosuppressant; allopurinol was first used in the treatment of gout but was subsequently found to be effective as an anti-neoplastic agent; zoledronic acid was first used in the treatment of tumour-induced hypercalcemia and later found to be effective against osteoporosis; and finasteride was first used in the treatment of prostate disorders but was subsequently discovered to be effective in the treatment of alopecia. Furthermore, if you think about it, it does not seem probable that the first medical use of a new substance will be its only medical use. We even see frequent reports in the ordinary press of possible beneficial side effects of established medicines. Often they sound very hopeful – a recent one was a possibility that a drug for a type of leukemia may even reverse Parkinson's. Few of these possibilities are followed up.

The cost of developing a new indication for a known drug is substantial, although not generally as high as the cost of developing a new drug. In particular, the drug having been developed for the earlier indication there is no or much less need to investigate safety. But there is a need for expensive clinical trials in large groups of patients (Phase III trials) to be carried out before marketing approval can be obtained for the new indication. Such trials are very expensive. Maybe the costs of development of an established medicine are one third to a half of the cost of development of a totally new medicine. Again, precise numbers do not matter

So, what are the current incentives for this type of research? In many cases the answer is none or little. Speakers at the Conference examined: 1) patent protection and 2) regulatory exclusivity.

### *A. Patent Protection*

That which is old or obvious cannot be patentable. Often the first disclosure of a possible valuable further use is before any possible patent application can be filed. For instance, a treating team of doctors talking about the possible new use at a medical conference or in a short letter to the *Lancet* or the like. There are also risks associated with prior disclosure during the course of a clinical evaluation of a possible new use, yet such trials may be necessary to justify a patent. If any of these prior disclosures occur, the patent route is foreclosed.

### *B. Regulatory Exclusivity*

(a) Patent protection? That which is old or obvious cannot be patentable. Very often the first disclosure of a possible valuable further use is before any possible patent, for instance by, a treating team of doctors talking about the possible new use at a medical conference or in a short letter to the *Lancet* or the like. And there are of course risks of prior disclosure during the course of a clinical evaluation of a possible new use. Yet such trials may be necessary to justify a patent.<sup>1</sup> If any of these prior disclosures happen the patent route is foreclosed.

Even if patent protection is available it is necessarily limited in effectiveness as discussed in detail at the conference.

(b) Regulatory exclusivity? This may arise because some important jurisdictions do not allow a generic company to sell a product for product for a particular use without providing data to support that use. And for a period of time the generic company is not permitted to rely on the data of the originator. During that time, since it will not have data of its own, it cannot sell with an indication of the new use. But it can sell with the data for the old use.

The Conference examines in detail the controversial and complicated way in which both patent and regulatory protection for new uses of established medicines work in practice. Particularly, it examines the “skinny label” problem, where a generic company sells an established medicine only with the information about the established use but doctors prescribe, or pharmacists supply, the

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medicine for the new use. If there is patent or regulatory protection, is anyone liable? Should or could the payers (the NHS in the UK, insurance companies in most countries) be made to pay a premium for the actual new use to which the product is put? And how prevalent, effective, or safe is “off-label” prescribing anyway?

At its end, the Conference considers what, if anything, can be done to provide an adequate incentive for research into new uses for established medicines, and what can be done to facilitate such research. Can or should prescriptions include the intended use. Would that not only encourage such research but facilitate it from the data which would be generated?

