

# INSTRUMENTAL VARIABLES

## How the UK can become a world leader in medical innovation

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BRIEFING PAPER

### INTRODUCTION

A little under a year ago, the New York Times reported on do-it-yourself insulin pumps. Tech savvy people, mostly parents to diabetics, were pairing glucose sensors with insulin pumps.<sup>1</sup> These would allow caregivers to constantly monitor glucose levels. Some even made what are, in effect, artificial pancreas, with the glucose sensor triggering the insulin pump, automating insulin delivery.

In September, the FDA approved MiniMed 670G, a mostly automated insulin pump, for sale to the general public.<sup>2</sup> The device was made available spring 2017. The device is only available in the US, and Medtronic, the device manufacturer, has stated there is no timeline to bring it to other markets—diabetics can only access the years old previous version.

Automated insulin pumps illustrate two important aspects of drug and medical device regulation. First, existing regulatory systems have been slow to adapt to changes in the development of new medical devices, and medical innovation more broadly. Second, safe and effective medical devices are often unavailable in the UK, while British newspapers abound with stories of life-saving drugs unavailable in Britain.

Brexit gives the UK the opportunity to tackle both challenges and to become a leader in medical innovation. The European Medicines Agency (EMA), as well as the Medicines & Healthcare products Regulatory Agency (MHRA), the UK's own regulatory body, were both designed for a different era. They were created for big medicine, when large, multi-national corporations were the primary drivers of innovation. The world is in the early stages of changes in the nature of medical innovation. The era of big medicine will soon be behind us. To take full advantage of the coming changes in the structure of innovation, regulatory policy must adapt.

The UK has two advantages which could allow it to lead the charge in medical innovation. First, the UK has a well-educated population, even relative to other developed countries, scoring near the top of the pack in maths and science, according to the multi-national TIMSS exams. It also has disproportionately strong higher education, with more universities in the world top 10, top 50, and top 500 than any

<sup>1</sup> [https://nces.ed.gov/pubs2017/2017002\\_timss\\_2015\\_results.pdf](https://nces.ed.gov/pubs2017/2017002_timss_2015_results.pdf)

<sup>2</sup> see e.g. <http://www.shanghairanking.com/ARWU2016.html>

country except for the US, according to most rankings. It has the human capital necessary to be at the cutting edge of innovation.

Second, Brexit caused a large regulatory shock. Most regulatory changes take substantial time because of slow moving bureaucracies. Because of Brexit, the UK must make rapid changes. The question is, what type of changes should they make?

## MEDICAL INNOVATION

Medical innovation is evolving. No longer is it driven by multi-billion dollar companies; instead, startups are changing the landscape. Even tinkerers—small-scale home innovators like the amateurs and semi-professionals who powered the Industrial Revolution—are creating their own solutions when regulation precludes commercial scale innovation.<sup>3</sup> These trends are likely to continue and accelerate, giving the UK has the opportunity to create an environment where such innovations can flourish.

The MHRA regulates based on old assumptions and categories that have not grown to encompass a new wave of high-tech inventions. Their regulation of apps is a useful illustration of the arbitrariness of their approach.<sup>4</sup>

Apps which magnify texts for people with visual impairment are regulated as medical devices, while apps which magnify texts, but make no mention of visual impairment are not regulated. It is difficult to imagine what harms MHRA believes will occur by making apps designed to magnify text for the visually impaired.

Similarly, apps which estimate the amount of insulin diabetics need based on their diet are counted as medical devices.<sup>5</sup> Apps which measure sensors and alert the user if critical thresholds are reached are counted as medical devices. Apps and software that are intended to make recommendations to seek further advice based on user entered data are counted as medical devices. All of these are therefore subject to close oversight. Such overly onerous regulations slow down innovation. By requiring approval for apps that have extremely low risk of harm, MHRA deprives patients of tools which would be able to simplify, or even save, their lives.

CNN reports that Stanford researchers developed a computer program that could identify melanoma with the same level of accuracy as a dermatologist.<sup>6</sup> Once developed into an app, such a computer program would offer very low cost methods of early cancer detection, likely saving many lives. Requiring such an app to go

<sup>3</sup> P.A. Smith, "A Do-It-Yourself Revolution in Diabetes Care", The New York Times (Feb 22, 2016)

<sup>4</sup> MHRA, "Guidance: Medical device stand-alone software including apps" [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/564745/Software\\_flow\\_chart\\_Ed\\_1-02.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/564745/Software_flow_chart_Ed_1-02.pdf)

<sup>5</sup> J. Whalen and K Limbaugh, "FDA Approves Medtronic's New Automated Insulin Pump", The Wall Street Journal (Sept 28, 2016) <http://www.wsj.com/articles/fda-approves-medtronics-new-automated-insulin-pump-1475093556>

<sup>6</sup> S. Scutti, "'Automated dermatologist' detects skin cancer with expert accuracy", CNN (Jan 26, 2017) <http://www.cnn.com/2017/01/26/health/ai-system-detects-skin-cancer-study/>

through a costly approval process inevitably means delaying the diagnosis for some individuals with melanoma.

MHRA's response to apps typifies the changing ecosystem of medical innovation. Apps are low cost to develop, and can have rapid and repeated improvements. In short, apps are the domain of tinkerers, not grand designs. As such, MHRA has been unable to keep up. They have claimed regulatory powers over a broad swathe of apps which pose no conceivable harm to users. The result is that useful apps will be delayed or - more likely - remain undeveloped, depriving customers of their benefits.

MHRA's overly cautious approach to apps is illustrative of their tendency to over-regulate more widely. Such unnecessary caution lowers the amount of investment in medical innovation. Sergei Brin, the co-founder of Google, has stated that "generally, health is just so heavily regulated. It's just a painful business to be in."<sup>7</sup> It is important to note that Brin was referring to the American regulatory system. His statement, however, illustrates the opportunity the UK has to create a regulatory system that can attract the most innovative companies.

The time for regulatory reform is now. There are a number of coming innovations which require an improved regulatory system. Broadly speaking, these innovations fall into four categories: personalized medicine, 3D printed organs, gene therapy, and improved sensors.

Currently drugs are made to be safe and effective for anyone. However, as the cost of gene sequencing falls, and our knowledge grows, it will be possible to produce drugs for genetically similar members of a population. Pharmacogenomics is the practice which identifies how genes affect drug responses in individual patients. Mancinelli et al. identify pharmacogenomics as "therapy with the right drug at the right dose in the right patient."<sup>8</sup>

One example of an application of this technology is matching cancerous tumors to a drug. The Wall Street Journal reports that "some cancers can appear as at least a dozen different genetic diseases, some of which have been shown to respond uniquely to a specific drug." By testing a tumor sample for genetic mutations, doctors can prescribe drugs which target the tumor specifically based on the information of what caused it (or words to that effect).<sup>9</sup>

3D printing appears primed to change the organ market. Anthony Atala, Director of the Wake Forest Institute for Regenerative Medicine is leading the charge.<sup>10</sup>

<sup>7</sup> D. Shaywitz, "Google Co-Founders To Healthcare: We're Just Not That Into You", Forbes (July 4, 2014) <http://www.forbes.com/sites/davidshaywitz/2014/07/04/google-co-founders-to-healthcare-were-just-not-that-into-you/#4c78eb5f3f7b>

<sup>8</sup> L. Mancinelli, M. Cronin, W. Sadee, "Pharmacogenomics: The promise of personalized medicine", *Pharmsci* (March 7, 2000) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2750999/>

<sup>9</sup> R. Winslow, "The Future of Medicine Is Now" *The Wall Street Journal* (Dec 31, 2012) <http://www.wsj.com/articles/SB10001424127887323530404578205692226506324>

<sup>10</sup> M. Shaer, "Need a New Organ? Surgeon Anthony Atala Sees a Future Where You Can Simply Print It Out" *Smithsonian Magazine* (December 2016) <http://www.smithsonianmag.com/innovation/miracle->

The idea is to use a patient's own cells to grow the organ, then when the organ is mature to implant the organ in them. Because the organ is grown from their cells, there is no risk of rejection. He has already implanted cartilage, bone, and muscle tissue in animals successfully and is awaiting FDA approval to begin human trials.

Gene therapy offers the potential to cure debilitating genetic illnesses by replacing defective genes with normal functioning ones. CRISPR, , and the simple targeted gene-editing tool CRISPR-Cas9, has revolutionized the potential for gene therapy to treat a wide range of ailments, including cancer, hepatitis B, and heart disease. The first of such to be approved by Western regulators was Glybera in 2012, a treatment for the ultra-rare disease lipoprotein lipase deficiency. However, the process to achieve approval was poorly designed. For example, regulators expected a clinical trial of 342 people despite the fact that only 250 Europeans had the disease.<sup>11</sup> And editing many types of gene is simply illegal in the UK and elsewhere.

Lastly, cheaper sensors can democratize access to health information. Imagine a Fitbit that can tell whether the wearer is suffering a heart attack and call an ambulance, or the aforementioned apps that can identify melanoma.

Each of these technologies is in its early stages of development. Each technology is also new, and substantially different from prior technologies. An overly cautious regulator could kill the potential of each technology, while an enlightened, permissive MHRA could adapt and become a beacon for medical innovation.

## REGULATORY PRINCIPLES TO SPUR INNOVATION

There are two strategies the MHRA could take when adapting to the new era of medical innovation. The first is accepting the world standard, the second lowering the cost of innovation. The first principle is easy to translate into policies. The second principle less so.

Accepting the world standard means adopting the best drug and medical device regulatory practices from around the world. One example is reciprocity, which is where countries allow the use of drugs and medical devices that have been approved by the regulatory agencies of other developed countries.<sup>12</sup> For the UK this includes the EMA, the Food and Drug Administration (FDA) of the USA, Health Canada, and Japan's Pharmaceutical and Medical Devices Agency.

The UK, which will be regulated by the EMA up until Brexit, should continue to allow drugs and medical devices approved by the body in order to retain access to them - and they do not even need to join the European Economic Area to do so.

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maker-anthony-atala-winner-smithsonian-ingenuity-awards-2016-life-sciences-180961121/

<sup>11</sup> A. Regalado, "The World's Most Expensive Medicine Is a Bust" MIT Technology Review (May 4, 2016) <https://www.technologyreview.com/s/601165/the-worlds-most-expensive-medicine-is-a-bust/>

<sup>12</sup> Though many commentators, as well as the senate bill, call these arrangements "reciprocity", the agreements are not always reciprocal—some, such as ours, are just as desirable from the UK's perspective if they are unilateral. Mirroring, or unilateral mirroring, would be a more appropriate term.

By widening the extent of its reciprocity beyond the EU, the UK could gain further access to safe and effective drugs, while at the same time cutting costs.

Drug reciprocity is a well-known idea. Economists Alex Tabarrok and Daniel Klein have been championing it for years. In 2015, a bill for the United States to adopt drug and medical device reciprocity was floated by Senators Ted Cruz and Mike Lee.<sup>13</sup> In fact, the EMA, by offering a centralised authorization procedure<sup>14</sup> for drug approval, provides what is in effect reciprocity for the European market.

A second aspect of choosing the world standard approach is adopting regulatory best practices. Japan, for instance, has Free to Choose Medicine (FTCM), which allows the sale of not yet approved drugs after early stage safety and efficacy trials.<sup>15</sup> Of course, proper safeguards would need to be put in place to ensure fully informed consent of the individuals who choose to receive those drugs. Bartley Madden and Nobel Laureate Vernon Smith have elaborated on how it could be applied to the United States.<sup>16</sup>

A similar process could be followed in the UK where doctors could recommend drugs which had only passed early stage safety and efficacy trials to particularly needy patients. Unfortunately, the failure of the Medical Innovation Bill which would have permitted this, informally known as the Saatchi Bill, shows reluctance to embrace innovation.

Rather than permissiveness, the MHRA currently follows the precautionary principle. Under the precautionary principle the burden of proof falls upon innovators, who must prove that their new drug, treatment or medical device is safe and effective to a high degree of certainty. The treatment of text magnification apps as a medical device is an example of the precautionary principle at its worst.

The MHRA should instead lean toward permissionless innovation.<sup>17</sup> Permissionless innovation is the idea that innovation by trial and error should be allowed without prior restraint. Rather than thinking of all the possibilities which could go wrong, the emphasis should be placed on ensuring informed consent, balancing potential benefits against potential costs, rather than requiring all treatments prove they have no risks.

Adopting permissionless innovation literally is perhaps a step too far for the MHRA. Nevertheless, it can adopt the spirit of permissionless innovation. Its focus should

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<sup>13</sup> C. Friedersdorf, "Ted Cruz's Best Idea for Overhauling the FDA" *The Atlantic* (Dec 18, 2015) <https://www.theatlantic.com/politics/archive/2015/12/ted-cruzs-best-idea-for-overhauling-the-fda/421158/>

<sup>14</sup> European Medicines Agency "Authorisation of Medicines" [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000109.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp)

<sup>15</sup> B. Madden and V. Smith, "Give The FDA Some Competition With Free To Choose Medicine" *Forbes* (Dec 1, 2015) <http://www.forbes.com/sites/realspin/2015/12/01/give-the-fda-some-competition-with-free-to-choose-medicine/#1410d37142a4>

<sup>16</sup> *Ibid.*

<sup>17</sup> T. Adam, "Permissionless Innovation: The Continuing Case for Comprehensive Technological Freedom" *Mercatus Center*. (March 10, 2014)

be on accelerating innovation, not attempting to prevent every last bad scenario, no matter the probability. The default of regulators should be to say “go ahead.”

Of course, accelerating medical innovation does carry risks. New treatments could be ineffective, or even unsafe. Thalidomide, the poster child for delaying drug approval, caused two thousand infant deaths and an additional two thousand stillborn infants.<sup>18</sup> This was a tragedy.

But no less tragic are the lives lost that could have been saved by better medical technology, or technology approved more quickly. Delaying lifesaving technology costs lives. Take, for example, 3D printed organs. Every year 600 British people die waiting for organ transplants.<sup>19</sup> Accelerating the introduction of 3D printed organs by one year would save 600 lives in the UK alone, not to mention alleviating the suffering of those reliant on dialysis.

## CONCLUSION

The MHRA has become too risk averse, creating an environment inhospitable to medical innovation. Rapid technological change means regulators should be adaptive, and as the pace of medical innovation continues to accelerate, the MHRA should not bind itself to past models. Personalized drugs require a different regulatory apparatus than gene therapy, which requires a different regulatory apparatus than blockbuster drugs.

The world of medical innovation is rapidly changing and Brexit has given the UK the opportunity to become a leader in it. However, doing so requires rethinking the role of the regulator. The MHRA should become a partner to innovation, not a hindrance.

New medical technologies such as gene therapy, 3D printed organs, diagnostic apps, and personalized medicine are on the horizon. Whether UK citizens are able to benefit from these new technologies depends on the regulatory inclinations of the MHRA.

Brexit has given the MHRA the opportunity to rethink their regulatory approach. With sovereignty returned to the UK, it can adopt regulations which encourage innovation and are reflective of the changing new entrepreneurial medical environment.

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<sup>18</sup> J. Mickle, “Thalidomide ‘caused up to 10,000 miscarriages and infant deaths in UK’” The Guardian (Mar 6, 2016) <https://www.theguardian.com/society/2016/mar/06/thalidomide-caused-up-to-10000-miscarriages-infant-deaths-uk>

<sup>19</sup> NHS Organ Donation (Nov 20, 2015) <https://www.organdonation.nhs.uk/news-and-campaigns/news/nhs-blood-and-transplant-reveals-nearly-49-000-people-in-the-uk-have-had-to-wait-for-a-transplant-in-the-last-decade/>