

The Consequences of 'Brexit' for Drug Discovery and Development, and the Regulatory Implications

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1 Introduction

The startling and unexpected result of the UK referendum held on 23 June 2016, in which a narrow majority of British voters opted to leave the European Union (EU), the so-called 'Brexit', has presented the pharmaceutical industry and their academic collaborators with a major challenge. The issue at stake is the UK's exit from the European Medicines Agency (EMA) and the decision of the European Commission (EC) to move the headquarters of this body from London to Amsterdam by 30 March 2019 [1]. It is neither the remit of this editorial to debate the reasons for the outcome of the referendum, nor to comment on the Remainer versus Leaver combat that has raged ever since. However, rather than succumb to the despair that permeates some of the commentariat, exemplified by the concern that patients may die because of the UK's ejection from the EMA and resulting loss of access to new drugs [2], it is our belief that Britain *with Europe* should seek to turn Brexit to mutual advantage. This will necessarily require skilful negotiation and a determination by all parties to compromise. It is unhelpful at this stage to proffer [3] precise figures for the extra expenditure incurred (i.e. by the UK, EU and pharma) if the UK becomes completely independent of the EMA, when it need not.

2 Evaluating the Efficacy and Safety of New Medicines

Following the discovery and development of a new drug, the need for strict evaluation of therapeutic effectiveness and safety prior to extensive clinical application is axiomatic. Determining efficacy requires nuanced reviews of data from animal experiments and clinical trials. Safety is paramount given past catastrophes, most notoriously, but not limited to, thalidomide (1959). However, establishing complete

safety of every therapeutic agent is illusory because even the finest regulatory system cannot avoid such reverses. The assessment of the balance of risks and benefits of a therapy is multi-factorial and requires expert, sometimes subjective, judgement. The complexities of human metabolic processes can present major challenges in the toxicological evaluation of a new chemical entity. Mechanistic toxicology is still a developing science and some lessons have been learned only after the widespread prescription of a drug, later withdrawn because of an adverse reaction. Reliance on animal models has misled investigators as with the thiazolidinone troglitazone, a treatment for type II diabetes, that was found to cause liver damage in ~2% of patients, resulting in withdrawal of the drug only after up to 2 million patients were exposed in the period 1997-2000 [4]. The evaluation of a drug's safety is never ending – ongoing research on the mechanism of the hepatotoxicity of troglitazone is relevant to thiazolidinones still in clinical use.

3 Drug Regulatory Bodies

The genesis of the modern approach to the evaluation of new medicines is well illustrated for the United States by the origins of the Food & Drug Administration (FDA). Already in the 19th Century, driven by the antics of 'snake oil salesmen', the Chemistry Division of the US Department of Agriculture was testing drugs claimed to be effective human medicines, but with the actual chemical composition and dubious branding being issues of particular concern [5]. The organisation was rebadged as the FDA in 1930, with growing reach and powers that continued apace, and led to the multifaceted body existing now, managing an annual budget of nearly \$5 billion (of which \$1.4 billion was allocated to the *Center for Drug Evaluation and Research*: 2016 data [6])

and with a workforce of ~ 15,000 (~ 3600 assigned to 'drug evaluation research' and 270 to 'toxicological research' [7]). The FDA acted on behalf of a population of 321 million in 2016.

The EMA, the European counterpart of the FDA, was set up in 1995 to coordinate drug regulation across the European Union (population ~ 500 million), the primary focus being safety and efficacy of new medicines [8]. The resources of member states were pooled and channelled through 7 committees, with those concerning 'Medicinal Products for Human Use' and 'Orphan Medicinal Products', the latter focussed on treatments for less common diseases, being of most relevance to this editorial. Each country has its own national body or bodies, which are the Medicines and Healthcare Products Regulatory Agency (MHRA) and the National Institute for Health and Care Excellence (NICE) for the UK. NICE liaises with the EMA and determines the effectiveness versus cost of a new drug, which is especially important for the UK's publicly funded National Health Service (NHS). The EMA's annual budget of €323 million and workforce of 890 (2015 data) appears to be substantially below that of the FDA, despite the EMA's scope embracing approximately one third of the world's new medicines.

Both the EMA and FDA have been subject to several criticisms, with funding from the pharmaceutical industry allegedly compromising their independence [9] and time taken to approve new medicines (see below) being matters of contention. Thus, a surprising high proportion of EMA income (83% compared to 45% for the FDA) derives from the pharmaceutical industry, the products of which it is presumed to regulate. The slower approval of new medicines by the EMA compared to the FDA (478 days on average for the EMA as opposed to 304 days for the FDA [10]) may possibly be explained by the EMA's relatively small workforce. One may question whether EMA

committees need a representative from every EU country, rather than being streamlined with a smaller group of the best expertise available. Unfortunately, pressure from politicians, e.g. questioning the speed and import of evaluations, as well as populist media campaigns, may perturb the decision-making process adversely [11]. The difference between the EMA and FDA approval times is quite small compared to the overall time between the concept for a new medicine and its eventual clinical use. For areas of unmet need, many cancers for example, there are already robust mechanisms for accelerating the approval process [10].

There are other individual countries, both smaller and larger in population than the UK, that have perfectly viable, standalone drug regulatory bodies analogous to the FDA, e.g. Australia (Therapeutic Goods Administration), Japan (Pharmaceuticals and Medical Devices Agency) and Switzerland (Swiss Agency for Therapeutic Products), with the latter's confidentially agreement with the EMA [12] perhaps being a template for future UK-EMA cooperation.

4 Some Challenges of Brexit

There are potential severe consequences of Brexit for the effectiveness of pharmaceutical research in the UK and the rest of Europe. Along with the USA, Europe is at the forefront of medicines research and has contributed hugely to past and current innovations in drug therapy. Although many historical discoveries preceded the formation of the EU [13], pan-European research has been stimulated and facilitated by the EU, via free movement of people, goods and services, and opportunities for funded research (e.g. Horizon 2020), all of which could be compromised by Brexit. It has been highlighted that UK pharmaceutical companies are struggling to recruit

talented researchers from Europe since the referendum [14]. Also worrisome is the planned exit, if not flight, of academics and healthcare professionals since the Brexit vote [15]. This may be partly due to misconceptions about the reasons for the Brexit vote, fostered by questionable academic research [16], as well as anxiety about what the future may harbour. However, UK employment policies have not changed (yet), and it is inconceivable that suitably qualified individuals will be barred from working in the UK post-Brexit – but nevertheless concern is widespread and needs to be allayed.

5 Expert Opinion

So how do we solve the conundrum of Brexit versus the EMA? The Brexit decision has prompted fears that the whole process of drug discovery, development and regulation will be severely compromised in the UK [17], with knock-on effects for the rest of Europe. Whatever the outcome of negotiations, additional expenditure that could have otherwise supported new research is almost inevitable. Changes in regulatory policies post-Brexit could lead to extra expenditure because drug companies will need to prepare additional submissions to the putative new UK regulatory body as well as to the EMA [3]. We believe that while the costs should be minimal, companies need to plan for such an eventuality and greater costs may be incurred if policy makers do not provide clarity and reassurance imminently. The decision to relocate the EMA to Amsterdam seems to have been rather hastily reached, but it is probably the best location, if only considering this city's excellent public transportation with fast connection to Schiphol airport. Fretting, as some commentators have [1], that London has lost 36,000 hotel beds to Amsterdam, is a

side-show in the wider context. Rather, the move to Amsterdam should inspire the EMA to improve its market approval process [18].

The future relationship between the UK and EMA should aim for closer interactions between drug developers and regulators. It is vital that those involved in the discovery and development of medicines can anticipate what the likely future regulatory requirements will be, thus providing the best chance of bringing safer, more efficacious new treatments to market. This will be facilitated by regulatory bodies that constantly exchange information and opinions to maximise consistency in policies. Among possible scenarios are that the UK remains a member of the EMA, by providing appropriate remuneration, or that the EMA devolves selected activities to a new UK regulator. It is also essential that the UK continues to participate in European consortia such as the Innovative Medicines Initiative, which seeks to accelerate access to new medicines, especially those with an unmet need [19]. Negotiators need to remember that ultimately it is the patients *across Europe* that matter.

The current regulatory processes for medicines in Europe and the USA are not perfect and Brexit provides an opportunity for a timely EMA rethink. We posit that whilst Brexit presents many issues to be addressed, these should be eminently manageable if negotiations were more pragmatic and less *de rigueur*. There is an opportunity for all sides to reflect on the European pharmaceutical landscape, but let's not dismantle what is fundamentally great and good. We see the goal as working towards an efficient and productive new relationship between the UK and the rest of Europe, always putting the needs of the patient first, and discarding narrow sectional interests. Discourse and cooperation between European scientists and medical practitioners has been a prominent feature since the early 19th Century, if not long before, and it is ridiculous to think that Brexit will stifle that [13].

Several of the issues discussed here parallel those advanced for other sectors and many of the matters that need to be addressed are generic. There is a risk that concerns relating to the pharmaceutical industry will be of low priority in negotiations, relative to say financial services. However, the wider negotiations will hopefully offer early solutions, or at least set a precedent and provide reassurance as to how the future terrain for the regulation of drug development might evolve. Our opinion is that there must a synergistic relationship between the EMA and future UK regulator, if the latter is what transpires, thus avoiding duplication of effort and unnecessary costs. Ultimately, will common-sense prevail? Given the crisis of the emergence of resistant pathogens, abrogating many current treatments [20], unabated drug discovery in Europe is too important to fall on the sword of political infighting. The Brexit negotiating teams must realise that all European citizens will suffer without the UK continuing to be being intimately involved in every aspect of drug discovery, evaluation and regulation. Hopefully, we can look back in say 5 years' time and marvel how the myriad of current issues were equitably resolved.

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