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Expert Opinion

Breaking up the band: European regulatory cooperation in a post-Brexit world

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ABSTRACT

Since 1995, the European Medicines Agency (EMA) has progressed from harmonising regulation for human and veterinary medicines across the European Union Member State national competent authorities, to galvanising one of the most successful cooperative initiatives for regulation globally. Although the EMA is the focal point for stakeholders, regulation is delivered through the European medicines regulatory network, in which national authorities, like the UK's Medicines & Healthcare products Regulatory Agency (MHRA), contribute. As with any collaboration, contributions by individual members vary, and the MHRA has been noted as an innovative and highly productive member of the network. Progress in regulation not only in Europe – but also around the world through convergence – can be attributed to this unique European cooperation. The decision by the UK to leave the European Union threatens to mark the end of this cooperation; we argue here that the best decision is to maintain regulatory cooperation under new structures.

REGULATORY HARMONY

In 2015, we celebrated the 20th Anniversary of the European Medicines Agency (EMA), applauding the success of a European collaboration in regulation of human and veterinary medicines that was unique in the world. However, the origins of the European regulatory system go far beyond the 1995 launch date of the EMA. It began in a shared concern, prompted by tragedies around the world, that effective regulation of medicines was essential to deliver effective innovation in treatment and patient safety.

In Europe, harmonisation of regulation for medicines began with an EEC Directive in 1965 (65/65/EEC) and was extended in two further Directives specifying standards, law, regulation and administrative requirements in 1975 (75/318/EEC and 75/319/EEC) (Rägo and Santoso 2008). These Directives provided the basis for the forerunner to the EMA: the Committee on Proprietary Medicinal Products (CPMP). A multistate procedure was established to allow countries to mutually recognise each other's regulatory decisions, to facilitate production and use of medicines across the Community. The decade following, a procedure was further agreed that allowed centralised decision making for regulatory review. All of these features are now fully embodied in the work of the European medicines regulatory network and visible in the EMA as an agency "that protects public and animal health in 28 EU Member States, as well as the countries of the European Economic Area, by

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ensuring that all medicines available on the EU market are safe, effective and of high quality" (EMA 2017a).

The early decades of the European medicines regulatory network were a process of establishing regulatory harmonisation across the European Member States. In regulation, 'harmonisation' has a very particular meaning: that it is a process by which the interpretation and/or application of technical guidelines can be made uniform or mutually compatible (Tominaga 2015). Harmonisation of regulations is a challenging task, and experts have noted that it requires science-based dialogue, consensus and a limited number of players that have a comparable regulatory and technical capability and are committed to implementing the products of harmonisation (Lustig and Weisfeld 2013).

In the 20th anniversary year of the EMA, the focus was on the future, targeting the innovation in regulatory science that would need to accompany the innovations in drug development as well as the growing global health challenges we face. In the Network Strategy to 2020, the agenda was to advance the scientific rigour and effectiveness of regulatory assessment but also to find efficiencies and better ways of working. New medical technologies and breakthroughs in pharmacogenomics challenge existing models for regulation, and the EU regulators mapped out their approach to address these. Also figuring in the Strategy was the desire to optimise the operation of the European medicines regulatory network itself, looking to improve through "efficient and cost-effective procedures" and minimising "as much as possible the administrative burden for the pharmaceutical industry commensurate with public and animal health" (EMA 2015).

Just one year later, the United Kingdom was to take a decision that has threatened to mark the end of this harmonised regulatory system in Europe. Over decades, this regulatory system has enabled markets and production to integrate across the European Member States, and this is particularly true for medicines, where the multi-step process of production and distribution can take a medicine across many country borders until it reaches the patient. Maintaining supply is a critical issue for the immediate future; maintaining regulatory harmonisation is a longer term priority.

INDUSTRY RESPONDS

The global pharmaceutical industry is used to having to balance very long term and high risk investments in the discovery, development, manufacture, regulation and provision of its medicines in an uncertain world. In that respect, the UK's decision to leave the EU was certainly a novel and considerable challenge for our industry to plan, but dealing with uncertainty and change is not new. Our response was to undertake a detailed situation analysis and review, much of which was already in draft as companies anticipated the risks of the Referendum. We also began the considerable work of exploring and discussing the details across companies and across the wider life sciences sector. The Association of the British Pharmaceutical Industry (ABPI) joined with the BioIndustries Association (BIA) to lead this process, at the request of the UK Ministerial Industry Strategy Group (GovUK 2017).

We worked over the summer of 2016 to set out the priorities for the life sciences sector that the UK and EU Governments must consider in order to ensure that patients and public health continue to be well served by our medicines, and that in the future, the UK can continue to build on its thriving life sciences sector for the benefit of innovation and the economy. ABPI and BIA reached out to the other trade organisations, representing medical technologies (devices), diagnostics, clinical research, consumer healthcare and animal health (as animal medicines are also regulated through the European medicines regulatory network). Our work identified four key priorities which was set out in a Ministerial Report in early September (see Figure 1):

1. *Long-term, predictable funding for scientific research, and continued ability to collaborate at scale*
2. *Ability to trade and move goods and capital across borders*
3. *A common regulatory framework with Europe*
4. *Access to the best talent.*

Behind these headings lies a considerable wealth of detail and analysis, exploring these requirements for our industry under different scenarios and timing challenges. This was not the end of the planning.

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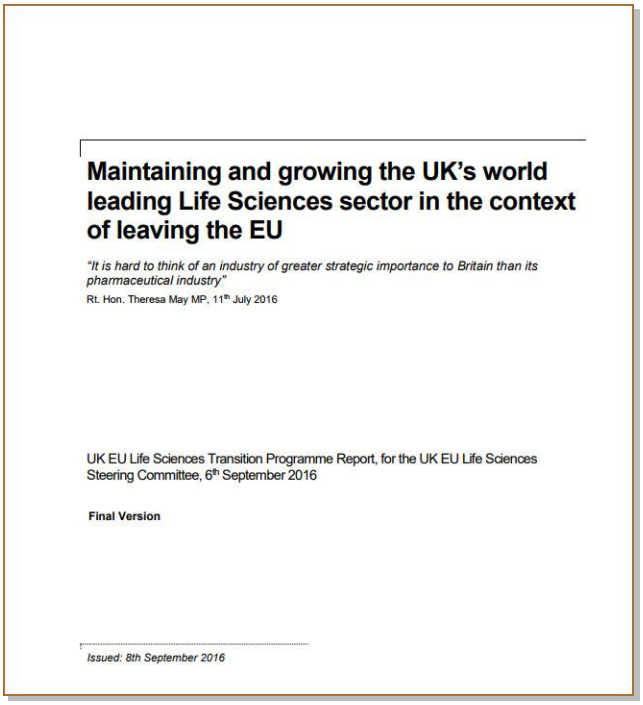
We have continued to work through these matters in partnership with government and other stakeholders ever since and will continue to do so until we have clarity on the changes to come.

The next step in the process has been to engage with our European representative organisations to take this alignment across the European Member States.


Maintaining and growing the UK's world leading Life Sciences sector in the context of leaving the EU

"It is hard to think of an industry of greater strategic importance to Britain than its pharmaceutical industry"

Rt. Hon. Theresa May MP, 11th July 2016

UK EU Life Sciences Transition Programme Report, for the UK EU Life Sciences Steering Committee, 6th September 2016

Final Version

Issued: 8th September 2016

Fig. 1. *Life Sciences industry, led by ABPI and BIA, report to Ministers to set out the needs for medicines and public health (ABPI 2016).*

Engagement across Europe is fundamental to consider a new future for medicines discovery, development and manufacture and the new markets and regulatory systems that will emerge. Certainly the "Day 1" impacts of Brexit are at the forefront of our work and discussions today to ensure that, at least for the supply of medicines, the day of departure for the UK does not impact upon the patient. However, engagement across Europe is also needed to define how regulation will be pursued. As discussed earlier, a series of crises (in the case of thalidomide in the 1960s) prompted the development of the world's most successful cooperation for harmonised regulation in medicines; the question now is what will Brexit evoke next in the evolution of this regulatory system?

HARMONISATION OR CONVERGENCE?

Looking to the future for European regulation, we have argued as an industry that cooperation should continue. By cooperation, we are really calling for a continuation of the harmonisation in regulation that has been established over the previous decades. Such harmonisation allows for a free flow in research, manufacturing and supply that will ensure that European patients – both EU and UK – will continue to benefit from innovation in the most straightforward way, that industry will benefit from streamlined regulation and that European regulation itself will continue to move in a progressive and innovative way with full capabilities and capacity.

The question is, what will happen to European regulation if cooperation is not possible? How will UK regulation and European Union regulation evolve from the closely harmonised and even unified (centralised) structures we have today?

One possibility is that in future, the British and EU regulatory systems move to a process of regulatory convergence. Regulatory convergence is a "process whereby regulatory requirements across economies become more similar or aligned over time as a result of gradual adoption of internationally recognised technical guidance documents and standards" (Tominaga 2015). Generally speaking, the process of regulatory convergence is one that countries go to on a path towards harmonisation; however, regulatory harmonisation may not be an ultimate goal for some countries as they may not be able to engage in the legal harmonisation that underpins these technical requirements.

There is little precedent for countries to re-establish convergence, after they have been unified/harmonised in regulatory policies and shared the regulatory work across their systems. For the UK and for the EU medicines regulatory network, this is a novel challenge. We may anticipate that both the UK and the EU regulatory systems will continue to align to the standards and the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Certainly, the EMA and the EU medicines regulatory network will continue to participate as Founding Regulatory Members of ICH. The UK's regulator, the MHRA,

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will need to apply to become a Regulatory Member upon the UK's departure of the EU, when it will no longer be directly represented by the European Commission.

We also know that the regulation as established through standing European law (EU acquis) will be brought into UK law through the Great Repeal Bill. (Davis and May 2017). In that regard, we expect the UK regulatory policies to remain harmonised with EU regulations, at least in the short term. The conduct and practice of those policies – e.g. the UK regulatory system – should largely mirror what is undertaken in Europe, but within the UK agencies, including MHRA, the Health Research Authority (HRA), the Human Tissue Authority (HTA) and others. The details of these arrangements are greatly anticipated, and industry has urged the UK Government to clarify its arrangements as soon as possible. The EU and the European Medicines Agency have already started to set out the requirements for marketing authorisation holders to be prepared to operate in the EU/EEA following the UK exit and status thereafter as a third country (CMDh 2017a,b; EMA 2017b,c).

CONCLUSIONS

This article is titled "Breaking up the band" because it reflects both (1) the unique and productive cooperation that has been established over decades in the European medicines regulatory network and (2) the view that it has been the diversity and combination of areas of scientific expertise and creative approach to regulatory science that has really made this a unique partnership. Finally, it also reflects a concern that both the UK and the EU medicines regulatory system may be diminished – at least for a while – because of this sort of upheaval, and that this is clearly to the detriment of supporting innovation in medicines and benefit for all European patients.

As any good music fan, therefore, the author is still hopeful that the "band will not break up" after all. We believe that there is a clear imperative to pursue continued regulatory cooperation across the UK and the EU, and that there is also a means of doing so, if the will is there.

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CONFLICT OF INTEREST

The author is an Executive Director for Research, Medical & Innovation at the Association of the British Pharmaceutical Industry (London, UK), which is playing an important role in understanding the impact of leaving the EU on the UK's world leading Life Sciences sector for the UK Government.

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