Decideum Briefing: The Future UK Medicines Regulation Landscape and Project Orbis

Objective: This document overviews the future UK regulatory landscape, the future role of the Medicines and Healthcare products Regulatory Agency (MHRA), and possible opportunities with Project Orbis.

Future of the UK Regulatory Landscape

Overview of the UK Medicine's Regulatory Landscape: The UK is currently in a transition period with a shared regulatory framework, but is now considered a 'third country' by the European Union. On 1st January 2021, the UK will be a stand-alone country, with its own regulatory framework for medicines, medical devices and trials.

Following the transition period, the UK can align to European regulation, but also has the freedom to diverge. Legislation will be transposed as of 1st January 2021. As of late October 2020, the Government's Medicines and Medical Devices Bill has reached committee stage in the House of Lords, where it will be scrutinised line by line. This is the political and legal tool to allow for amendments of specific aspects of medicines and medical devices regulation. The Bill can ensure alignment with EU, but also the opportunity to amend various aspects. Applications for a marketing authorisation in the UK will, from the 1st January 2021, need to be submitted directly to the MHRA.

What does the future hold for the MHRA?: The exact role, structure, and strategic direction of the MHRA is yet to be finalised as the UK nears the end of the transition period. The Medicines and Medical Devices Bill will go some way towards dictating what a post-Brexit MHRA might look like. Interested stakeholders are already suggesting potential opportunities for the MHRA and the accompanying medicines regulation, to hasten patient access to innovative therapies.

It is evident that the MHRA is undertaking policy work to sketch out its future post-Brexit. At a recent APPG on Access to Medicines and Medical Devices event, Dr Richard Torbett, Chief Executive of the ABPI stated that the industry body was working with the MHRA on the future role of the Agency. Torbett spoke particularly about the UK's ability to become a global leader in regulation, Intellectual Property (IP) protection and innovation. Further, NICE has signalled that it is working with the MHRA and other bodies to input into future regulatory arrangements. At the September NICE board meeting, it was announced that timelines for the process review proposals have been revised to allow additional time to consider the impact of leaving the EU for regulatory arrangements[i].

Potential areas of development: Although there is ongoing policy work to finalise the future role of the MHRA, and it is likely that its role will develop over the course of the next few years, the MHRA's 2020/21 business plan lists 7 priority areas[ii]:

1. "Set the foundations for longer-term strategic and cultural change to refocus the Agency to become

patient-centred, involving patients in proportionate decision-making and becoming a trusted source of information to support patient and health professional decision-making"

2. "Build on our science capability and unique data to develop **a new compelling innovation offer**, thus encouraging research and development of innovative new products in the UK to the benefit of patients, and the wider health and care system"
3. **"Develop and deliver an enhanced safety surveillance system** across medicines and medical devices"
4. "Drive forward the Agency's **efficiency agenda**, cutting costs and focusing our resources – not least our world-leading science and clinical expertise – on actions which will most benefit patients and patient safety"
5. "Support DHSC in its preparations for the **end of the transition period and future relationships with the EU and rest of world.** This includes leading the delivery of an EU and Trade legislative programme to effectively perform our statutory functions and support the health of patients"
6. "Be ready for 1 January 2021 with **new routes to market for medicines and medical devices**"
7. "As a regulator, working with the National Institute for Biological Standards and Control (NIBSC), play a full part in the national public health challenge caused by **COVID-19**"

What do external stakeholders predict?: Meanwhile, other stakeholders have contributed to the discussion about the future regulatory framework. Some, such as Sir John Bell, have spoken about the opportunity for the UK to lead the way in relation to regulation of genomics, digital health and early diagnosis. Speaking at the MHRA's annual lecture, Sir John stated that, *"The challenge is to develop an ambitious strategy which builds on the UK's unique assets of basic science, real world evidence and innovative regulation; a strategy which will enable innovative products to reach patients safely and much more quickly".*

As a mechanism to innovate international regulation, Deloitte has suggested that technologies such as AI, robotic process automation and natural language generation, could become commonplace in trials. This would allow for the streamlining of processes, allow regulators to undertake faster review and feedback, and focus more on decisions and action where needed.[iv] Similar methods may be adopted by the MHRA in the future.

Many believe that the extent to which the MHRA diverges from EMA style regulation will depend on the success of the current UK/EU trade negotiations. For example, should trade negotiations collapse with the EU, MHRA could be completely cut off from the EU regulatory network, forcing it to handle more tasks itself but also giving it the freedom to create new policies[iii]. Some stakeholders would see this as disastrous, believing that global regulatory alignment and robust data sharing arrangements is key to hastening regulatory approvals – *see Project Orbis*[iv].

An audit of trade media publications suggests many make similar predictions. That is, the future UK regulatory landscape could look to balance regulatory flexibility to speed up innovation access, whilst ensuring patient safety through improved surveillance and monitoring systems.

What are stakeholders still concerned about? There are both short and long-term regulatory challenges that Brexit poses to the MHRA.

The ABPI and European Federation of Pharmaceutical Industries and Associations (EFPIA), have called for proposed regulatory changes to medicines in Northern Ireland to be phased in over the course of a year.[v] As we approach the end of the transition period the Northern Ireland protocol still remains unclear. This hinges on a mutual recognition agreement for medicines being agreed between the UK and EU negotiators. At the time of writing, such an agreement has not been made, nor is there an indication that it has been prioritised. The potentially damaging outcome of no agreement would immediately risk introducing additional delay, complexity and cost to supply chains. Currently, it's not clear whether medicines entering Northern Ireland from the EU would have to be tested – something which Northern Ireland does not currently have the required facilities to be able to do.

Some academics still question whether the MHRA could fill the gap left by the EMA in the near term, given that the UK has outsourced technical responsibilities to the EMA for decades[vi]. These challenges, the academics argue, are exacerbated by the fact that the MHRA previously derived a sizable share of its funding from the EU, both from contract work for the EMA and from other EU research funds. Government investment will be needed over the long-term to compensate for this loss.

Project Orbis

Context: Project Orbis is an initiative of the Food and Drug Administration's (FDA) Oncology Center of Excellence (OCE). It provides a framework for concurrent submission and review of oncology products among international partners.

The first Project Orbis action occurred in September 2019, in conjunction with the Australian Therapeutic Goods Administration (TGA) and Health Canada. Under this project, the FDA, TGA and Health Canada collaboratively reviewed applications for two oncology drugs, allowing for simultaneous decisions in all three countries[1]. The aim is for collaboration among international regulators to allow patients with cancer to receive earlier access to products in other countries, where there may be delays in regulatory submissions. Health Canada stated that the collaboration helped it to reduce its normal review process from 200 to 90 days[vii].

How does this work in practice? On submitting an application to Project Orbis, associate director for medical policy at the FDA's OCE, Patricia Keegan, said:

"We don't have a formalized process, typically the review team will, in their discussions before the application comes in, ask about the timing of submission of an application to other agencies … and invite the sponsor to consider participation in Orbis, but there's no reason that the sponsor couldn't bring it up as well."

With the example of Lenvima, three regulatory agencies collaboratively reviewed the application, allowing for

[1] In conjunction with decisions by TGA and Health Canada, the FDA granted accelerated approval to Lenvima (lenvatinib) in combination with Keytruda (pembrolizumab) for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation.

simultaneous decisions in all three countries. The exercise was used to identify any regulatory divergence across the review team. Each international regulator still has its own format for the drug label. The regulators exchanged drug labels to learn about any potential differences and in practice, only minor differences were noted. Further, the collaborative review is not a process guided by consensus. For example, if one country decided to diverge from the consensus, it could do so, if it wishes.

Opportunities for the UK and Project Orbis: The UK's announcement that it has joined Orbis signals the MHRA's ability now to make autonomous regulatory decisions undeterred by the EMA[viii]. Time will tell, however it seems likely that other international regulators involved in Orbis would benefit from UK involvement, particularly as the UK is often a primary launch pad for life sciences companies looking to invest in Europe.

Given countries can decide not to follow the consensus, there is little risk involved with Project Orbis. If review times can be reduced, as was the case in Canada for Lenvima, there may be advantages for patients, payers and industry. However, that will also depend on the existence of simultaneous reviews from other regulators at the same time as the UK. A less stringent regulatory system such as the FDA's could stand to benefit the UK access landscape. Indeed, the MHRA may look towards alignment with the FDA, where there has been a move from quality control to quality assurance.

The benefit for industry centres around reducing the need for duplication of work, in effect, gaining regulatory approval through a central route. This could potentially grant marketing authorisation across several markets simultaneously. From a market access perspective, faster regulatory approval may be attractive, however this doesn't guarantee reimbursement. It is therefore encouraging, specifically from an oncology perspective now the UK has joined Project Orbis, to see bodies such as NICE and NHS England collaborating with the MHRA during ongoing policy discussions.

Conclusion

Whilst a level of concern about Brexit exists, the MHRA and its stakeholders appear to be considering the opportunity it presents. It is also worth noting that COVID-19 has perhaps bolstered this ambition – particularly in relation to the need for regulatory flexibilities, faster clinical trial approvals and greater use of virtual meetings, telehealth and artificial intelligence[ix].

Whilst the UK has an opportunity to consolidate its own regulatory landscape, and the broader medicines and medical devices system, there is also appetite to develop relationships internationally. As such, the pending shift of the UK's medicines regulatory landscape provides ample opportunity for the UK to collaborate with other regulators involved in Project Orbis. Companies who are interested in this prospect would be advised to liaise with the MHRA and the ABPI, as well as patient organisations, to understand the appetite, feasibility, opportunities and risks of such a move.

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i https://www.nice.org.uk/Media/Default/Get-involved/Meetings-In-Public/Public-board-meetings/agenda-and-papers-sep-20.pdf
iihttps://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/889864/MHRA_Business_Plan_2020_to_2021.pdf
iii https://www.raps.org/news-and-articles/news-articles/2020/6/eu-regulatory-roundup-mhra-puts-speed-to-market-at
iv https://www2.deloitte.com/uk/en/pages/life-sciences-and-healthcare/articles/life-sciences-predictions-2025.html
v https://amp-ft-com.cdn.ampproject.org/c/s/amp.ft.com/content/2879e5ef-bdd3-4f49-9b67-ff32071a3633
vi https://jamanetwork.com/channels/health-forum/fullarticle/2761757
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viii https://www.gov.uk/government/news/cutting-edge-treatments-to-be-fast-tracked-to-patients-through-international-collaborations
ix https://pink.pharmaintelligence.informa.com/PS142888/The-UKs-Future-As-Innovator-In-A-PostBrexit-PostCoronavirus-World