UNITED KINGDOM EXIT FROM THE EUROPEAN UNION "BREXIT"

Life Science Industry Coalition

Position paper

AESGP

abpi
Bringing medicines to life

BIA
UK BioIndustry Association

BRITISH GENERIC MANUFACTURERS ASSOCIATION

ebe
european biopharmaceutical enterprises

efpia
European Federation of Pharmaceutical Industries and Associations

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

EuropaBio
The European Association for Bioindustries

medicines for europe
better access. better health.

PAGB
Representing the Consumer Healthcare Industry since 1919

Vaccines Europe
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Abstract

The life science industry is highly integrated across Europe and regulated under EU law through a sophisticated system of legal and regulatory arrangements involving EU Institutions, Member States and national competent authorities.

The products of the human life science sector are unique. Access to medicines support patients in the UK and across the EU to live longer and more productive lives. The UK leaving the European Union presents a significant challenge to the way that medicines are developed, trialled, regulated and supplied to patients, which may have a direct impact on patient health. It is critical that negotiators understand this challenge, and prioritise patients in the Article 50 negotiations. The objective of this **joint paper** is to present a common UK-EU life science position on key challenges that lie ahead in the Brexit negotiations and proposed solutions to safeguard public health.

The paper covers four areas:

- People and Patients;
- Intellectual property and legal framework;
- Regulation;
- Trade and supply.

Life science priorities should cover the following:

* **Prioritising patients in second phase of Article 50 negotiations.** Patient access to medicines must be a primary consideration for phase two of the Article 50 negotiations.
* **People.** The life sciences workforce, including their families and spouses, should be protected by a solid citizens' rights agreement.
* **Intellectual property.** Provided the UK remains in the single market or in a new legal arrangement with the EU based on consistency of regulatory frameworks, the EU and the UK IP systems should remain aligned in order to avoid uncertainties for industry.
* **Regulatory cooperation.** Close cooperation in the regulation of medicines, including mutual recognition of regulatory activities and quality testing, is essential in ensuring that patients in the EU and the UK can continue to access medicines.
* **Trade.** Trade between the UK and EU must ensure that medicines are able to continue to move between both regions, ensuring that both UK and EU patients can continue to access medicines.
* **Transition period.** A period of transition beyond March 2019 will be critical to ensuring that companies, national competent authorities and the EMA can deliver the necessary changes so that patients can continue to access their medicines after the UK leaves the EU.

I. Potential impact on people and access to medicines

Introduction

Medicines are able to reach patients thanks to the legal and regulatory cooperation between numerous stakeholders in the UK and the EU, guided by the relevant EU legislation on pharmaceuticals. This cooperation has significantly reduced the regulatory and approval process for national authorities and ensured access to safe medicines for patients.

This life science industry coalition is fully committed to working with European and national regulators to meet and maintain Europe's stringent regulatory standards and to promote these standards globally. Millions of European patients today have benefited from better access to gold standard therapies as a result of comprehensive collaboration between national authorities in the EU member states and the European Medicines Agency.

This paper outlines the potential implications of the UK's prospective withdrawal from the EU, focusing on implications for people. Given the uncertainty in this area, as well as the urgent need to safeguard patient access to medicines, this life science industry coalition urges negotiators to address these issues expeditiously, to ensure patients, companies and regulators have time to adequately prepare and adapt, ensuring that access to these critical medicines is not disrupted or compromised.

Changes in the process of UK withdrawal from the EU should not affect the supply of medicines for patients

Access to medicines

Securing patient access to medicines should be paramount when negotiating cooperation arrangements for pharmaceuticals between the EU and the UK. Safeguards should be put in place to ensure certainty in the supply of safe and quality medicines for patients for existing medicines and ensure timely access to new medicines. Patients should not suffer any disruption in the provision of their medicines as a result of the negotiations or future agreement between the UK and EU.

This has wide ranging implications, from scientific research, manufacturing processes, development of medicines including participation in clinical trials, and trade. Trade barriers, for example, could lead to a delay or shortage of supply of medicines for patients, thus causing a disruption in their treatment and potential risk to public health as may be the case for vaccines and antibiotics. Shortages of supply will increase costs both to

the patients and costs to Governmental Health Budgets both in the UK and EU Member States. In the case of an unorderly withdrawal there is a risk that all goods due to be moved between the UK and EU could be held either at border checks, in warehouses or manufacturing sites and/or be subject to extensive retesting requirements. The time and costs associated with technical transfer of test methods required to retest medicines within the supply chain will drive up the cost of medicines and cause potential delay in the availability of medicines for patients. Substantial delays in the supply chain would have an adverse effect on essential medicines with a limited shelf life (e.g. radio pharmaceuticals).

This could lead to a severe disruption of companies' supply chains, which would lead to potential supply disruptions of life-saving medicines. Due to the long co-operation between the UK and EU member states inspecting bodies there should be an immediate recognition of equivalent Good Manufacturing Practice (GMP) standards applied and therefore no requirement to retest product crossing the borders between UK and the rest of Europe.

Life science industry coalition ask

The life science industry coalition calls for an agreement which would facilitate a sure and certain supply of medicines for patients by underlining a maximum level of cooperation on pharmaceutical regulation and cooperation in a future UK and EU agreement. Citizens have the right to expect to receive speedily the safest possible medicines.

Safeguards for healthcare workforce and life science professionals

Healthcare provision in the UK across the spectrum includes professionals from EU countries. Brain circulation between the UK and EU27 is mutually beneficial and should continue. EU migrants make up a significant proportion of life science staff in the UK, often in roles that are highly specialised, and where expertise may be limited. According to the English Health Service's Electronic Staff Record, 55,000 out of the 1.2 million staff in the English NHS are citizens of other EU countries[1]. This includes doctors, nurses, pharmacists, paramedics, and care and support staff as well as highly specialised professions such as medical researchers, pharmacovigilance experts and qualified persons. The spouses and families of workers equally need to be able to work in their chosen profession both in the UK and EU27.

EU migrants make a significant contribution to life sciences in the UK, including research and development, manufacturing and distribution. A potential cessation in the rights of these professionals to work in the UK may cause a staffing crisis within the NHS and lead to disruption in the life science sector more broadly, leading to longer waiting times for patients. Equally, the UK is a key contributor of the European life sciences ecosystem. The UK contributes to life science internationally including leading universities, a developed technology transfer system, funds to support the commercialisation of science and institutes and research charities.

[1] http://www.electronicstaffrecord.nhs.uk/

The UK and EU are home to numerous multinational companies, with international functions. Companies seek to have a multinational workforce to reflect their multinational nature. Both UK and EU based companies should ensure that inter-company transfers remain simple post Brexit. The intra-company transfer process should facilitate movement into the UK of people employed overseas by pharmaceutical companies and for UK nationals to spend time in other company sites in the EU27.

Spin-outs and SMEs should also be able to employ an international workforce. Medium sized member companies in the UK tell us that up to 30% of their research & development staff are non-UK EU nationals. Multinational companies' research & development facilities in the UK have a non-UK EU national workforce of about 20%. We are aware of university spin-outs where 60%+ of their researchers are non-UK EU workers.

Life science industry coalition ask

An agreement on citizens' rights at an early point in the negotiating process between the UK and the EU is crucial to provide an element of certainty for EU citizens working in the UK. An early agreement would also ensure that healthcare providers and life science professionals, including their families and spouses are able to prepare and adapt to a future agreement. International collaboration and multi-national working environments should continue to be fostered to facilitate exchange of expertise between life-science professionals.

Access to high quality information for patients

The EU infrastructure is uniquely positioned to gather and act as a central point for exchange of best practices, many of which may be of benefit for patients. Continued co-operation and exchange of information on drug safety is critical to ensure that patients are aware of the current safety information for their medicines to ensure their safe and effective use. Managing separate systems for exchange of information on safety of medicines within the UK and EU creates further complexity is ensuring patient safety, diverts capacity and capability and increases costs and stifles innovation. As patients are increasingly empowered and take a leading and participatory role in decisions concerning their own treatment, the dissemination of high-quality information has become of primary importance. As patient empowerment increases, patients should continue to have access to high quality information materials concerning their medicines and treatment.

Life science industry coalition ask

The life science industry coalition calls for a high level of collaboration on the development of information for patients and exchange of best practices after the UK leaves the EU.

Conclusion

The life science industry coalition calls for people and patients to be of primary consideration when negotiating an agreement between the UK and the EU in the pharmaceutical sector. The importance and real life implications of medicines shortages or disruptions to a patient's treatment and associated risk to public health cannot be under estimated. EU migrants who contribute to the UK health workforce and life science sectors, including their families and spouses, should be protected by a solid citizen's rights agreement. Patients should also continue to benefit from high quality information concerning their medical treatment and be empowered to participate in such decisions. In this regard, the life science industry coalition calls for early discussion on these points to increase certainty for patients. An early agreement would safeguard public health and patient safety in the UK and the EU, and ensure a stable healthcare environment for people across the region.

II. Intellectual Property and Legal Framework

Introduction

The exit of the UK from the EU has the potential to create significant uncertainties related to the framework regulating intellectual property (IP) and regulatory exclusivity rights as well as generic/biosimilar competition in the pharmaceutical and life science sector.

The life science industry coalition underlines the importance of ensuring continuity of existing IP rights at the moment of Brexit.

The pharmaceutical industry needs clarity about the transition to the post-Brexit landscape, in particular with regard to the Unitary Patent system.

Maintaining certainty when the UK leaves the EU

Pharmaceutical products can be covered by different IPs and other regulatory exclusivity rights and rewards (patents, Supplementary Protection Certificates (SPCs), trademarks, regulatory data protection, orphan exclusivity, paediatric extension, etc.). These derive primarily from EU law and seek to ensure sustained investments in researching and developing innovative treatments and related rewards and compensations.

For the sake of continuity and certainty, immediately upon Brexit, IP rights, incentives and rewards already obtained or available in the UK under EU law, or applications therefor, should continue to be in force as a matter of UK law. In addition, such rights should be available to be granted immediately upon Brexit for new products.

Provided the UK remains in the single market or in a new legal arrangement with the EU based on consistency of regulatory frameworks, the EU and the UK IP systems should remain aligned in order to avoid uncertainties for industry.

The Unitary Patent (UP) system

While the UK has indicated its intention to ratify the Unified Patent Court (UPC) Agreement, participating EU Members States should explore possible ways for the UK to remain in the scope of the UP/UPC Agreement. Further clarity in this regard would ensure more predictability for the industry when it is deciding whether to use the new system.

Any transitional measure that may be necessary to ensure the above should be as simple and the least burdensome possible.

The life science industry coalition is ready to further engage in order to facilitate cooperation between the EU and the UK on these important matters.

III. Manufacturing and supply, regulatory, clinical trials and pharmacovigilance and proposed solutions

Introduction

Continuous patient access to medicines is paramount and is the main objective for the health authorities and pharmaceutical industry. Access to treatment for patients must not be disrupted as a consequence of the UK leaving the EU. In view of the importance of a continuous supply of medicines from a public health perspective, all necessary measures must be put in place to avoid any shortages or other difficulties in patient access to treatment.

Based on the assessment made by the pharmaceutical industry, the need for an **implementation period** beyond March 2019 is considered critical. This transitional period will be necessary for national competent authorities and the EMA who need to ensure they can deliver these regulatory procedures while ensuring that other regulatory licensing, maintenance and supervision activities are continued without disruption.

The life science industry coalition underlines the **importance of a future cooperation model between the UK and EU** on medicines as part of the negotiations to agree a new relationship between the UK and the EU as soon as possible.

The **shared EU regulatory network** is a robust regulatory system which is a result of decades of development between Member States and relevant stakeholders and benefits from consistency and scale. Future ongoing cooperation is critical in delivering safe, effective medicines. Without agreement on cooperation, even if there is initial harmonisation, ultimately there will be **divergent requirements and safety assessment as well as duplication of processes**, potentially adversely affecting the timely availability of safe and effective medicines.

Compliance with regulatory and legal requirements is a key element in ensuring continued patient access to medicines. In the light of the anticipated high volume of regulatory activity to address changes required as a result of Brexit and the significant amount of time needed to complete and implement these changes, the pharmaceutical industry urges the negotiators to address these issues expeditiously, to ensure industry and regulators have time to adequately prepare and adapt, to ensure that patient access to medicines is not disrupted.

On 31 May 2017, EMA, CMDh and the European Commission published a **question-and-answer (Q&A)** document concerning the location of the establishment of a company in the context of European licensing procedures and certain activities, including the location of orphan designation holders, qualified persons for pharmacovigilance (QPPVs) and company manufacturing and batch release sites[2][3].

The basis for the Q&A is that the **United Kingdom will become a third country** from 30 March 2019. Unless the withdrawal agreement establishes another date or the period is extended by the European Council in accordance with Article 50(3) of the Treaty on European Union, all Union primary and secondary law ceases to apply in the UK.

In general, the guidance from EU is based on the assumption that there will be no negotiated agreement between the UK and the EU27 ('no deal'), and so activities must be completed by end of March 2019. Whilst this might be understandable, as the **outcome of negotiations cannot be predicted**, striving for stakeholders to initiate actions now potentially might divert agency resources away from certain of its activities and is a potentially unnecessary use of public and industry resources.

Given the unique nature of Brexit, it is imperative for both regulators and industry to **agree on a flexible and pragmatic approach** to making Brexit-related changes, in compliance with legislation, particularly as many required changes are administrative in nature and will not impact public health or patient safety.

Life science industry coalition asks

A transitional period beyond March 2019 is considered critical, to ensure that companies, national competent authorities and the EMA can deliver any changes necessary as a result of Brexit, while ensuring that other regulatory licensing, maintenance and supervision activities and supply to patients are continued without disruption.

An agreement between the UK and the EU enabling close cooperation and mutual recognition of regulatory activities is instrumental in preventing duplication of effort and maintain consistency and convergence. Such an arrangement would be minimally disruptive to all parties and ensure continued, timely and consistent decision-making relating to the safety of medicines and ultimately preventing any disruption in the supply of medicines to patients.

[2] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228739.pdf
[3] http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/BREXIT/CMDh_361_2017.pdf

In the next sections we have alluded to identified issues and suggested forms of solutions / pragmatism that we believe should be pursued. We look forward to continuing dialogue on where this pragmatism is best exercised for the benefit of patients.

Manufacturing and Supply

Currently **quality testing and Qualified Person (QP) release** is performed in the EU, for the whole of the EU. In the event of 'no deal' or a mutual recognition agreement (MRA), medicines currently exported from the UK to the EU27 or vice versa, will be subject to additional requirements that will delay supply to patients and lead to costly changes. These include additional quality testing, import testing, QP release into the market, as well as changes to supply chains. This is a significant problem, both for commercial and investigational medicinal products (IMPs).

In the event that there is no mutual recognition agreement (MRA) in these areas, it will result in a **repeat of batch release testing** in the UK and the EU27, eventually putting further and unnecessary burden on Health Care Systems in Europe, with no patient benefit. From a regulatory perspective, this will result in many variations being submitted.

The **technical transfer** required for an additional testing site can take 12–24 months or in some cases even longer, depending on the complexity of the product. This must be followed by regulatory approval, which can take an up to an additional 12 months. In addition, it is unclear if there are sufficient laboratories with sufficient capacity to conduct any additional testing required.

The costs related to the changes mentioned above are significant, companies may consider **relocation of supply routes** in the EU/UK as well as reconsider sustainability of a product in certain markets. This will result in the possible withdrawal of products from the markets, thus impacting the availability of some medicines to patients.

If there is no **GMP (GxP) MRA** between the UK and EU, inspections performed by either the EU27 or the UK may need to be duplicated, which will add no value and contribute to further costs and burden. As inspections can already take time to undertake during the regulatory process, duplications will only result in further delays, resulting in tardy availability of medicines to patients. Long term, requirements from different agencies may diverge adding additional complexity to those receiving inspections and managing complex regulatory regimes.

Urgent clarity is needed on the **expected import and batch release testing requirements** and the GMP recognition intentions. Given the time needed for transfer and approval of analytical sites for most products, decisions must be made now or very soon for an orderly implementation to be feasible, in case of no political agreement is reached by March 2019. For some products, it will not be possible to complete the required changes before March 2019.

For vaccines and biologicals, manufactured lots have to be controlled by an independent **Official Medicines Control Laboratory (OMCL)** before they can be placed on the market. Several manufacturers collaborate with

NIBSC (part of MHRA) for this independent testing so that products can be distributed in all 31 EEA countries. For vaccines manufactured in the EU, the control performed by NIBSC also supports the distribution in many countries outside the EU.

If current OMCL arrangements (including NIBSC's role for the EU) are not maintained, companies will have to undertake significant activity in terms of test transfer and future duplication of control testing. The time requirements for such changes are similar to, if not greater than, those mentioned above.

Industry Proposals/Solutions

There should be an extensive MRA between the UK and the EU 27 to recognize as much as possible the assessment/ work done in or by the UK and EU 27, including: adequate implementation period required to transfer to new requirements and remain in compliance, testing/ batch release sites, QP certification and release, OMCL controls, GMP inspections performed by MHRA/ or the future EU 27 and API manufacturers (or at least, to add the UK quickly to the list of acceptable third countries for FMD API importation).

The MRA needs to be in force immediately at the date of UKs withdrawal from the EU, to avoid any risk of disruption in the supply chain and ensure business continuity. If this cannot be reached in time in relation to a broader EU-UK trade agreement, it should be handled separately, like the MRA with the United States.

Regulatory

Marketing authorization (license)

The **marketing authorization (licence)**, needs to be amended to implement the Brexit-related changes as outlined in the referenced Brexit Q&As.
A marketing authorization holder (MAH) established in the UK must be changed to a MAH in the EEA (European Economic Area) for products placed on the EEA market, to comply with Article 2 of Regulation (EC) No 726/2004 which states that the marketing authorization holder must be established in the Union.
The holders of **thousands of marketing authorization (MAs) will need to be changed** (this applies for both centralized and nationally authorized products). If these changes are not completed on time, a Brexit with a no-deal scenario will cause supply disruption and products may not be available for patients.

Under current MA transfer requirements, one application has to be prepared for each MA, including administrative **documentation and related product information changes.** It can take months to prepare and to obtain regulatory approval (to reflect the name and address of the new holder of the licence).

In most cases, the MA will stay within the **same group of companies**, and the change will be **purely administrative**. Therefore, considering the high volume of changes necessary, industry proposes to have

further discussions to simplify this change, and to have a simplified one-off administrative change which can be conducted in parallel or combine with ongoing regulatory procedures.

Product information

Brexit changes to the product information are needed, such as a change in MAH, changes in QP release site and changes to multi-country packs (see below). The required changes to the labelling and Patient Information Leaflets can take several months, and will require extensive resources. This is further complicated by the requirements of the Falsified Medicines Directive, which will have to he be implemented in parallel;

Many companies have **multi-country packs** where the UK is combined with other EU countries, particularly with Ireland and Malta. In both the short and long terms it would be advantageous to find a way of maintaining joint packs for these markets unless they need to diverge due to different regulatory labelling text in the future.

Industry Proposals/Solutions

Industry believes that it is possible to interpret the MA transfer regulation, the Variations Regulation and Variations Guideline, in a way that allows for a simpler, more pragmatic approach to be taken.

The recitals to the MA transfer regulation[4] indicate that it applies "*where the new holder of the authorisation is not the previous holder*". For these Brexit-related changes, the new holder of the authorisation will remain within the same group of companies as the UK-based holder.

Chapter 1 of Volume 2A of the Notice to Applicants[5] states in section 2.8 that: "*marketing authorisation holders belonging to the same company group or that are controlled by the same physical or legal entity are to be considered as one entity*". The Notice to Applicants gives examples of contexts in which this notion applies, but does not preclude its application in other contexts.
Therefore, it should be possible for a Brexit-related change of the Marketing Authorisation Holder within the same group of companies to be submitted as a Type IAIN variation.

In order to ensure a minimal impact on supply, it should be permitted for implementation of any Brexit-related changes on product information to be done in a flexible way at a suitable time.

Products that have already been released into the distribution chain prior to 30 March 2019 can continue to be used after 30 March 2019.

[4] https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_1996_2141/reg_1996_2141_en.pdf
[5] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/vol2a_chap1_rev6_201612.pd

Reference member states

For the EU procedures, centralized procedure (CP)/mutual recognition procedure (MRP)/decentralized procedure (DCP), a **Reference Member State (RMS)/(co-)rapporteur, as appropriate, will need to be assigned** in cases where the UK is either (Co)Rapporteur or RMS.

MRP/DCP: Change of RMS, as the UK is the Reference Member State (RMS) for approximately 3400 [6] EU procedures, it is imperative that regulators develop a realistic action plan to help smooth the RMS transition**.**

A complicating factor is that, in principle, **a change of RMS cannot take place during a pending regulatory procedure**. With the current situation where we are facing delays in starting and finalizing variations and renewals, this will create serious delays in submission of RMS transfers.

CP: Regulatory procedures for which the **UK MHRA is the (co-)rapporteur** will need to be reassigned to an EU MS agency. Further clarity is needed on the **re-distribution of UK (Co)-Rapporteurships**; involvement of a MAH early-on would facilitate further alignment on future life cycle management activities and further knowledge transfer.

Some **ongoing MRP/DCP procedures with the UK as RMS/ CMS will probably not be concluded by the date of UK withdrawal from the EU**. A process needs to be put in place on how to handle such cases. Applicants must be aware of the risks they might be accepting in choosing the UK as a RMS for future procedures.

Existing art 126a marketing authorisations[7], referring to UK marketing authorisations. In order to increase availability of medicinal products, in particular on smaller markets, Article 126a of Directive 2001/83/EC provides that, in the absence of a marketing authorisation or of a pending application for authorisation for a medicinal product, which has already been authorised in another Member State, a Member State may, for justified public health reasons, authorise the placing on the market of that medicinal product. Some Member States make use of Article 126 a by referring to UK MAs to allow availability of products in their Markets such as Malta, Cyprus and the Baltic States. It is essential for patients in these smaller markets that there is continuity of supply of these medicines.

[6] Number derived from verbal communication in CMD meeting October 2017
[7] http://ec.europa.eu/health/documents/community-register/html/except_index.htm

Industry Proposals/Solutions

To guarantee a timely transfer of RMS from the UK to the EU 27, it should be an agreed exception that the RMS transfer can start even if another regulatory procedure is still pending. These changes can then be handled in parallel.
To put in place a process of finalising ongoing MRP/DCP procedures with the UK as RMS/ CMS if this is not concluded by the Brexit date.
To confirm that to separate the UK MA from the EU procedure, there is no need for any additional activities and the existing MA in the UK will stay unchanged.

To avoid duplication in the future, maintenance procedures (i.e. variation categorization, data requirements and in particular implementation times) should remain aligned going forward.

Clinical trials and comparability / bioequivalence studies

A 'no-deal' scenario will mean that clinical trial supplies from the UK/EU27 will be subject to an **extra Qualified Person (QP) release** on import into the other territory, in addition to the QP release already done in the country of origin.

An additional QP release will cause **unnecessary delays in getting IMPs to trial sites**. This could have an impact on the conduct of ongoing trials with the potential to interrupt treatment for patients participating in those trials.

Industry Proposals/Solutions

A transitional MRA for the release of IMPs should be put in place even in the event of 'no deal', to ensure continuity of supply and trials. This agreement would help to remove the unnecessary duplication of resources and reduce some of the delay in transporting IMPs to clinical trial sites.

Clinical trials being conducted in the EU must be sponsored by an **EU-based legal entity or the sponsor should have a legal representative established in the EU**. UK-based sponsors or ex-EU sponsors using a UK-based legal representative would therefore need to establish a legal representative in the EU (if not already existing) in order to continue to conduct trials in the EU.

The UK conducts numerous **GCP inspections** on behalf of the EU. When the UK leaves the EU, GCP inspections conducted by the UK may be duplicated by the EU, and vice versa. As GCP standards are common, this would create extra regulatory burden with no benefit to patients.

Industry Proposals/Solutions

To avoid duplicative inspection activities, an agreement should be reached so that the EU will recognise GCP inspections conducted by the UK and vice versa.

Consideration also needs to be given as to how clinical trials ongoing under the **European Clinical Trial Directive** 2001/20/EC will be managed post-Brexit, including the use of EU clinical trial databases for trials and sites in the UK.

Related to clinical trials are the **bioequivalence/ comparability studies**. The reliance on the reference product is the key principle of generic/ biosimilar medicines application after expiry of the exclusivity period.

Brexit should not undermine the possibility to refer to the reference product authorised in the UK/ EU for up-coming generic/ biosimilar applications. We would therefore propose that any medicine authorised in the UK before March 2019 can be utilised as an EU reference product after withdrawal of the UK from the EU.

The obligations of the generic products MAH is to monitor the product information of the reference product and submit related variations continuously. If the generic product refers to the reference product from the UK (based on the European Reference Product principle) it is not clear how this link will be maintained after Brexit.

Industry Proposals/Solutions

We trust that the use of a reference product should not be an issue in accordance with Directive 2001/83: "reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community". The approval of the UK reference product has been given under these conditions. However, it needs to be a clearly communicated to avoid unnecessary misinterpretation. It can also be proposed that the UK to transpose this to national law.

It should also be possible to source the reference product from both jurisdictions to perform bioequivalence/ clinical trials (as long as the requirement remains at the same high level of comparable standard).

Pharmacovigilance

EU legislation has become increasingly harmonised following amendment in 2012, with numerous efficient **shared work activities/databases across EU member states** (e.g. Eudravigilance database, evaluation of periodic safety reports and pharmacovigilance inspections).

Removal of the UK from this established and effective EU regulatory system could result in **divergent regulatory requirements with the resultant duplication of efforts** on behalf of industry. This could also result in divergent safety assessment and safety related decisions, with divergent information and recommendations to patients and HCP.

Industry Proposals/Solutions

An agreement between the UK and the EU enabling close cooperation and mutual recognition of activities is required to prevent duplication of effort and maintain regulatory requirement consistency and convergence. Such an arrangement would be minimally disruptive to all parties and ensure continued timely and consistent decision-making relating to the safety of medicines.

People: Roles as defined in pharmaceutical legislation

According to Article 8 of Directive 2001/83/EC and Article 74 of Directive 2001/82/EC, the **qualified person responsible for pharmacovigilance** must reside and carry out his/her tasks in the Member State of the Union (EEA).

Approximately 150 QPPVs are located in the UK. Post Brexit these QPPVs will have to relocate to one of the EU 27 Member States or another QPPV will have to be hired. The QPPV role is unique and challenging and requires a specialised skill set and these roles are therefore difficult to fill.

Uncertainty remains about the location requirements for UK based **Deputy QPPVs**. The legislation makes no mention of further location requirements of a Deputy QPPV, merely the need for back-up procedures in the event of an absence of a QPPV, further clarity is needed.

According to Article 51(1) of Directive 2001/83/EC and Article 55(1) of Directive 2001/82/EC, the **qualified person of the manufacturing and importation authorisation holder** responsible for certifying that each batch of medicinal product intended to be placed on the EEA market was manufactured in accordance with EU GMP requirements and marketing authorization, must reside and carry out his/her tasks in the Member State of the Union (EEA).

Industry Proposals/Solutions

In order to fulfil the requirements described above, an implementation period that extends beyond 30 March 2019 is needed to allow all parties to hire and train new staff and establish new processes where necessary to manage the post Brexit requirements.

Environmental Health

The UK chemicals sector is the second largest contributor to the REACH registration process. The pharmaceutical industry may also have made registrations in the UK of chemicals subject to the REACH Regulation requirements. Consideration must also be given to ways of working as documented in the legislation which means the legislation is only operable in the EU.

UK businesses have already made several thousands of REACH registrations and this number is expected to increase significantly with the final REACH registration deadline in May 2018. The costs of such registrations are typically in the range of several hundred thousand €/per registration. Many registrations of chemicals imported into the EU have been done via only representatives/companies in the UK. The immediate need to change the location of the registering legal entity to a remaining EU member state does not only add costs but equally critical may lead to interruption of EU member states' supply chains. Registrations made from UK prior to Brexit should remain valid. Failing that, some form of transitional arrangement to allow an orderly transfer of registrations would be essential.

Confirmation is needed on whether UK REACH registrations will remain valid for the continuous supply of chemicals from the UK to the EU in the event of a 'no deal' Brexit. Expectations and any arrangements for implementation will need to be clarified as early as possible to facilitate business planning.

Existing data sharing agreements may not allow access to and the use of EU data for UK REACH compliance purposes resulting in companies having to pay twice for EU REACH and UK REACH registrations.

Notifications to the **Classification and Labelling Inventory and compliance** under the Biocidal Products Regulation (BPR) will need consideration in order to continue to facilitate EU-UK trade. The impact of wider environmental and public health legislation such as packaging and waste or environmental liability will also need to be clarified.

Medical Devices

A number of **medicinal products contain a device component for delivery or use** of the medicinal product and therefore the pharmaceutical sector has a number of questions concerning medical devices when impacting medicinal products submission or authorisation.

To include a CE mark device in a pharmaceutical dossier, **a certificate of conformity** is usually provided. The CE mark is granted by notifying a body located in the EU. It is unclear how the CE mark granted by a UK notified body will be managed after March 30th.

Clarification is required whether a **CE certificate delivered by a UK notified body will remain valid** for its certificate duration beyond March 30th 2019. If the CE certificate is invalid after March 30th 2019, it is understood that impacted devices will have to re-apply for a CE certificate to another notified body located within EU.

Planning related to medical devices is particularly challenging, as the **implementation of the EU Medical Device and In Vitro Diagnostic Medical Devices Regulations** (May 2020 and 2022 respectively) run in parallel with the Brexit negotiations. The uncertainty surrounding the rules which will apply after April 2019 may create major disruption in the availability of medical devices.

Industry Proposals/Solutions

Short term:

To ensure that there will be no disruption of patient access to necessary treatments, a transitional period is needed to implement secondary legislation for medical devices and in vitro diagnostic MD. The 4 digit notified body number is usually described in module 3 of the MA application file. If no change is made to the device during the switch from one notified body to another one, we consider that this change can be considered as administrative in nature (no risk for the patient), and we propose to consider such dossier update as an editorial change and to notify the Health Authority at the next opportunity.

Long term:

In the interest of patients and industry alike, EU and UK negotiators should work together to ensure that legislation relevant to the regulation of medical devices is as cohesive as possible for the sake of continued access to these products in the EU-27 and UK.

In line with the MedTech Europe Position Paper on Article 50, negotiations between the European Union and the United Kingdom (Brexit)[8], the pharmaceutical sector agrees that a complete adoption of the EU MD regulations would be a desirable and comprehensive agreement between the EU and the UK post-Brexit.

There is already a very well-functioning arrangement in place between the EU and Switzerland, allowing a close collaboration on, and the free movement of, medical devices between both partners (Mutual Recognition Agreement 0.946.526.81). An approach following the example of this agreement could also work well for the EU-27 and UK in a post-Brexit scenario. However, in order to achieve this, the rules being introduced in the EU will also have to be fully transposed into U.K. law and may require an appropriate transitional period in order to avoid disruption of patient access to effective medical technology until such an agreement would become effective.

[8] http://www.medtecheurope.org/MTE-position-paper-Brexit

IV. Trade

Introduction

- In the event of withdrawal from the EU without agreement ahead of March 29, 2019, UK-EU trade falls back to WTO terms. It is vital that tariffs are not put in place between the EU and the UK, and that no non-tariff barriers are imposed between the two sides;
- Customs controls at UK-EU borders will be imposed if the UK is not within the Customs Union or the Single Market. These controls will be costly and time-consuming, with serious risks of limiting and delaying patients' access to medicines; to avoid this, the parties will need to find a solution to deliver frictionless trade after Brexit;
- Value Added Tax (VAT) will be one of the most complex and challenging areas after the exit of the UK. VAT will need to be pre-funded by pharmaceutical companies. This will have a significant cash-flow impact on pharmaceutical companies.
- In the context of the Free Trade Agreements (FTAs) concluded by the EU with third countries, which include preferential measures for goods developed in EU member states, the exclusion of the UK from FTAs would automatically exclude all operations undertaken in the UK from this preferential treatment, and have an impact on EU exports. The UK also risks losing the benefits of Mutual Recognition Agreements (MRAs) between the EU and third countries.
- In the short term, given the range of issues which present a major risk to continuity of supply of medicines to patients, and ability for businesses to operate effectively, it will be critical to provide an adequate transition period.

Tariff and non-tariff issues

EU tariffs on pharmaceutical products

Between January and October 2016, UK pharmaceutical finished product exports to the EU were valued at £9.4bn. The UK imported pharmaceutical finished products at a value of £14.7bn.[9] This trade is currently tariff-free. The current EU schedule of concessions on tariffs for finished pharmaceutical products are 0%, Active Pharmaceutical Ingredients (APIs) and intermediates are 0% if included within the Annex, and biologic products are typically 0%; raw materials and R&D materials are however often subject to positive rates of duty. These

[9] Statistics on UK-EU trade, 7: http://researchbriefings.parliament.uk/ResearchBriefing/Summary/CBP-7851

rates apply whether the products are shipped for commercial or research purposes.[10] This is in line with the global reduction of tariffs on certain pharmaceutical products, started during the Uruguay Round of trade talks in the early 1990s, which remain close to zero in developed countries and have been markedly reduced in developing countries and Least Developed Countries (LDCs).[11] However and critically for trade in medicines, the APIs and intermediates in the Annex reflects only a subset of materials which we would expect to trade, and this Annex has not been updated since 2010.

The UK should sign and implement the WTO Pharmaceutical Tariff Elimination Agreement[12]. However, this is not a blanket arrangement, but relates to a schedule of active ingredients and intermediate products which was last updated in 2010. It is not a comprehensive list.[13]

In the event of a WTO trade position, the UK-EU medicines trade may be affected by duty requirements at several stages of the supply chain. Complicated supply chain arrangements may involve crossing borders more than once. Given this, the UK should implement similar relief procedures to those of the EU[14]. Moreover, there are several other reliefs which should also be considered, including relief on R&D products, products tested to destruction and extension of inward processing to cover the old processing under customs control. However, authorisation to utilise these reliefs is not simple and UK importers/exporters should not be unduly penalised by needing to set these burdensome reliefs up for an interim period. Transitional measures need to be kept to a practical number and approach.

Non-tariff barriers

To ensure that trade is maintained, it is imperative that non-tariff barriers are not put in place in either the UK or EU.

Export controls and licenses are another factor of trade regulation for pharmaceuticals. It would be valuable for the UK to retain access to the EU general export license regime.

[10] EU Schedule of Concessions, available to download here: http://tariffdata.wto.org/

[11] WTO, Intellectual Property, Chapter 4: Medical technologies: the access dimension, D.1(b): https://www.wto.org/english/tratop_e/trips_e/trilatweb_e/ch4d_trilat_web_13_e.htm

[12] The Pharmaceutical Tariff Elimination Agreement was agreed by 22 countries[(1)] during the Uruguay Trade Round and entered into force on 1 January 1995. Signatories to the WTO Pharmaceutical Agreement are Canada, the European Union and its 28 Member States, Japan, Norway, Switzerland, the United States, and Macao (China).

[13] 2010 list is available here: https://www.usitc.gov/publications/332/pub4181.pdf

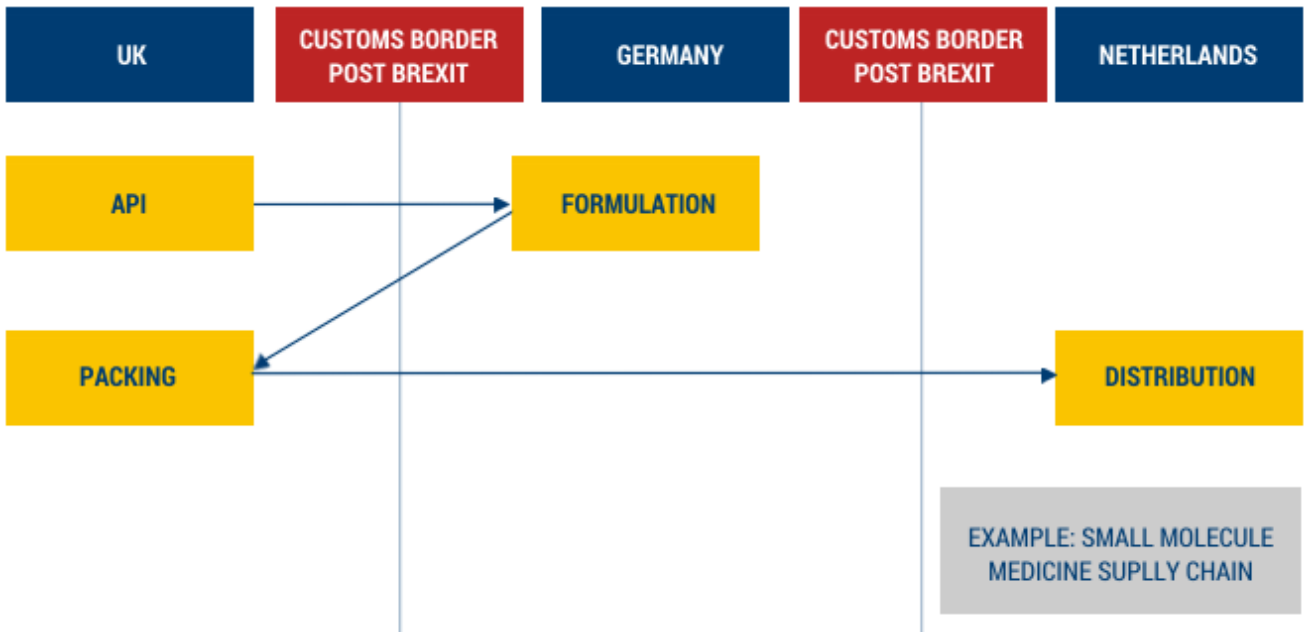
[14] For example EU inward processing relief (relief from customs duties and import VAT on goods imported into the EU for processing before being consumed in the EU or exported back outside of the EU), and EU outward processing relief (relief from import duty on goods re-imported to the EU after being sent to a third country for processing or repair).

UK-EU customs border and pharmaceutical supply chains

The production of medicines involves complicated supply chains in which goods used in the research, development, manufacture and packing are transported between facilities in different countries. There are currently no declarations on movements of goods between EU member states. Once goods from outside the EU have been cleared in customs at the EU border, they are in free circulation within the EU. Many UK biotechnology and pharmaceutical companies rely on this free movement of goods within the EU in their supply chains and vice versa.

If the UK were to operate under a WTO framework, customs declarations would be required for exported and imported goods to and from the EU, as well as from non-EU states. This includes investigational medicinal products, intermediate goods, finished goods, research goods and services. To indicate the scale of trade just in finished products, a recent survey of EFPIA member companies showed that every month, 45 million packets of medicines are supplied from UK to the EU; going the other way, 37 million medicines packs go from the EU to the UK.[15]

The example below follows a chemically-processed medicine as it is manufactured and distributed in Europe, and where the introduction of trade borders will impact and impede supply.



Example of how customs controls will slow down a small molecule medicine supply chain.

[15] https://efpia.eu/media/288531/brexit-survey-outcome-08112017.pdf

Increasingly time-consuming customs controls in medicine supply chains will have an economic impact of medicines trade. More importantly, however, customs controls and additional administrative burdens on companies to seek any form of additional authorisation would increase burdens on both the HMRC and European authorities as well as businesses, meaning that patients will have to wait longer to receive important medication; more acutely some medicines require cold chain storage or have short shelf lives, and thus cannot sit at borders. From a UK perspective, HMRC and EU27 competent authorities should cooperate to avoid an increase of the administrative burden on companies seeking any form of additional authorisation in order to achieve the Prime Minister's goal of "as frictionless trade as possible". If companies are required to obtain Authorised Economic Operator status, the concern is that neither HMRC nor business would be able to handle the additional workload in the short term.

In terms of administrative requirements, importers and exporters will be required to file Customs Declarations with the EU and UK. Traders will also need to hold additional data to support the correct completion of these declarations. The costs and time required to complete these declarations (including fees paid to customs agents) will be substantial.

It is estimated that export declarations to the EU amount to around 497 and import declarations into the UK to around 777 between January and October 2016. For each declaration, pharmaceutical companies have to bear significant costs.

The Union Customs Code (UCC) was implemented across the EU in May 2016 and it has introduced changes in movement of goods across EU borders, including IT systems development and requirements. In particular, the UCC requires all exchanges of information (including declarations) to be electronic. Looking to the future scenario in the UK, there are complications in the requirements of the UCC that would be an advantage for the UK to resolve when it leaves the European Union. Moreover, given the overwhelming increase in the volume of import/export declarations that will need to be processed for trade, there is a concern whether the HMRC's IT systems will be able to absorb this new volume; directing resources to this need rather than the UCC plan should be considered. For example, implementing the same or a similar system as the one used in EU27 countries would definitely reduce some of the IT burdens companies are going to face.

Value Added Tax in Trade

Value Added Tax (VAT) liability and treatment will be complicated in a cross-border trade setting. Many UK companies have multiple VAT registrations and VAT filing requirements across the EU. Import VAT will be payable on all non-UK sourced goods before they can be brought into free circulation within the UK.

Triangulation[16] procedures will no longer apply. Intra EU trade declarations (Intrastat declarations, EC sales lists) will also no longer be necessary, but replaced by customs declarations.

Businesses will have to make advanced payment of import VAT to HMRC (although a deferment account can allow payment to be delayed to the following month). Depending on how the UK establishes tax requirements, this could have considerable cashflow impacts for many pharmaceutical businesses. For example, some countries (e.g. the Netherlands) have established a mechanism for simultaneous payment and recovery of import VAT for fully taxable businesses, which yields no cashflow impact. Enhanced import VAT relief could be applied to areas of strategic value to the UK, such as pharmaceutical research, clinical trials, manufacture and packaging, whereby the processor (rather than the owner or future owner of imported goods) can recover the tax paid.

The impact on existing FTAs

The EU has signed around 35 free trade agreements (FTAs) with non-EU countries. Several trade agreements are currently under negotiation or nearing implementation. While the UK currently trades with non-EU states via these 35 FTAs, this will cease to apply to the UK once it leaves the EU. If the UK leaves the EU without an agreement on trade and no adequate transitional arrangements, the trade regulated by these FTAs will also revert to WTO rules.

An eventual exclusion of the UK from the terms of these FTAs might create potential barriers to access markets and also lead to additional duty costs in these specific countries for pharmaceuticals exported from the UK. Indeed, the existing FTAs include preferential measures for goods developed in EU member states. The exclusion of the UK from the covered member states would automatically exclude all operations undertaken in the UK by pharmaceutical companies from this preferential treatment.

It would also be particularly important to better understand what rules of origin would be applied in the UK, also given the impact for EU exports to third countries and for integrated supply chains.

Were the UK to remain party to EU FTAs, this would benefit the UK (reduced duty costs, improved market access) but also the EU (maintains number of EU exports covered by relief, improves EU negotiation position for future FTAs). From a regulatory viewpoint, maintaining UK access to other trade related agreements such

[16] For details on triangulation, see: https://www.gov.uk/government/publications/vat-notice-725-the-single-market/vat-notice-726-the-single-market#triangulation

as EU Mutual Recognition Agreements with a number of third countries (e.g. those with US, Japan, Canada on GMP) will be critical[17].

Noting the strong value that our sector sees in FTAs in defining strong and consistent rules at global level (e.g. in the regulatory space), it will be imperative that under any future trade policy the UK would co-operate strongly with other parties, including the EU, on issues related to third countries (e.g. driving regulatory convergence, tackling protectionist measures).

The way forward

Given major uncertainties in the road ahead, there are multiple different outcomes possible; these will have different implications on the challenges mentioned above. Nonetheless, given the range of major risks and impacts that these entail, not only on the industry, but also on patient access to medicines, the EU and the UK should immediately start working on an ambitious agreement to frame relations between the two parties.

In the scenario where a final agreement cannot be reached before 29 March 2019, an interim agreement should apply in order to limit to the highest possible extent the impact of Brexit on trade between the two parties and ultimately on patients access to medicines. Given the complexities involved, this should be at least 2 years.

[17] Underpinning this, it is also critical that an MRA is in place between the EU and UK to cover a number of key regulatory areas such as testing/batch release, GMP/GCP inspections, and APIs manufacture.