How medicines, medical devices and clinical trials would be regulated if there's no Brexit deal

Summary

Continuing human medicine, device and clinical trial regulation in the UK if we leave the EU with 'no deal'.

Detail

If the UK leaves the EU in March 2019 with 'no deal', this would affect the regulation of:

- medicines
- medical devices
- clinical trials

A scenario in which the UK leaves the EU without agreement (a 'no deal' scenario) remains unlikely given the mutual interests of the UK and the EU in securing a negotiated outcome.

Negotiations are progressing well and both we and the EU continue to work hard to seek a positive deal. However, it's our duty as a responsible government to prepare for all eventualities, including 'no deal', until we can be certain of the outcome of those negotiations.

For two years, the government has been implementing a significant programme of work to ensure the UK will be ready from day 1 in all scenarios, including a potential 'no deal' outcome in March 2019.

It has always been the case that as we get nearer to March 2019, preparations for a 'no deal' scenario would have to be accelerated. Such an acceleration does not reflect an increased likelihood of a 'no deal' outcome. Rather it is about ensuring our plans are in place in the unlikely scenario that they need to be relied upon.

This series of technical notices sets out information to allow businesses and citizens to understand what they would need to do in a 'no deal' scenario, so they can make informed plans and preparations.

This guidance is part of that series.

Also included is an overarching framing notice explaining the government's overarching approach to preparing the UK for this outcome in order to minimise disruption and ensure a smooth and orderly exit in all scenarios.

We are working with the devolved administrations on technical notices and we will continue to do so as plans develop.

Purpose

The purpose of this notice is to update businesses on the arrangements that will come into force for human medicines regulation currently subject to EU rules if we leave the EU on 29 March 2019 with no deal.

The life sciences sector may also wish to consider other relevant notices, including on Batch testing medicines if there's no Brexit deal. Other relevant notices will be signposted as they are published.

The pharmaceutical sector may also wish to be aware that the Medicines and Healthcare products Regulatory Agency (MHRA) is planning a consultation in early autumn, covering the regulation of medicines, medical devices and clinical trials. A more comprehensive technical notice covering the life sciences sector will follow after the consultation.

Before 29 March 2019

Medicines

Under the current EU membership, the UK is integrated in the EU medicines regulatory network (EMRN), including the European Medicines Agency (EMA).

The EU legal framework for human medicines sets standards to protect public health and ensure medicines are safe and effective. The rules for marketing authorisation and monitoring authorised products are primarily laid down in Directive 2001/83/EC and in Regulation (EC) No 726/2004.

In UK law, the Human Medicines Regulations (2012) (HMRs) set out a comprehensive regime for the authorisation of products, including their manufacture, import, distribution, sale and supply, as well as labelling, advertising and pharmacovigilance (monitoring the effects of medicines).

The Medicines and Healthcare products Regulatory Agency (MHRA) is our national regulator for human medicines (as well as medical devices, clinical trials and blood products).

The EMRN manages some aspects of regulation including EU licensing procedures, pharmacovigilance and legal presence requirements.

Medical Devices

In the UK, all medical devices are subject to EU legislation, which use a CE marking to show compliance.

Medical devices are regulated under three EU directives:

- Active Implantable Medical Devices (AIMDD) (1990)
- Medical Devices (MDD) (1993)
- In Vitro Diagnostic Medical Devices (1998).

Higher-risk devices (such as Class IIa, IIb and III medical devices and in vitro diagnostic devices in list A and list B in Annex II of the EU Directive, plus those for self-testing) must be certified by an independent conformity assessment body, called EU Notified Bodies (NB). EU NBs must be designated and overseen by their national authority (the MHRA in the UK), following joint audits by two other national authorities and the European Commission.

Clinical Trials

Clinical trials are managed nationally - in the UK by the MHRA.

Some aspects of clinical trials are shared across the EMRN. For example, a clinical trial sponsor or legal representative for clinical trials in the EU should be based in the EU/EEA.

The requirements and procedures for clinical trials in the UK are set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 (2004 Regulations). These regulations require all interventional clinical trials to be authorised by the MHRA and ethically approved. They also include requirements for the application and assessment, the supply of investigational medicinal products and safety reporting.

The EU is planning to implement new regulations for clinical trials, which will further integrate clinical trial processes and requirements.

After 29 March 2019 if there's no deal

Medicines

If there's no deal, the UK's participation in the European regulatory network would cease. The MHRA would take on the functions currently undertaken by the EU for medicines on the UK market. This would require changes to UK law, via the Human Medicines Regulations 2012 (HMRs). The MHRA is planning a public consultation in early autumn on some of the key proposed legislative changes.

Detailed information on manufacturer batch testing and certification can be found in the separate technical notice on this subject.

Medical Devices

The UK will recognise medical devices approved for the EU market and CE-marked. Should this change in future adequate time will be provided for businesses to implement any changed new requirements.

The UK will comply with all key elements of the Medical Devices Regulation (MDR) and the in vitro diagnostic Regulations (IVDR), which will apply in the EU from May 2020 and 2022 respectively.

Formal UK presence at EU committees in respect of devices will cease.

Clinical Trials

The 2004 Regulations will remain in force, modified using powers under the EU (Withdrawal) Act (EUWA) to make sure they still work in the UK after exit.

The new EU Clinical Trials Regulation (CTR) 536/2014 will not be in force in the EU at the time that the UK exits the EU and so will not be incorporated into UK law on Exit day under the terms of EUWA.

However, we'll align where possible with the CTR without delay when it does come into force in the EU, subject to usual parliamentary approvals. This alignment will happen after 29 March 2019 so it's not addressed in this guidance.

Implications

The EU (Withdrawal) Act will ensure that existing EU rules are converted into UK law at the moment of exit, with changes where necessary to make sure the rules work in the UK. Where this is needed, we'll give adequate time for business to implement any new requirements. Additionally, where possible, we'll be making use of the information we already have to complete administrative tasks for continuity of work and licences.

There are a number of changes where a UK approach will be required. Some of these are set out below. Other areas and further detail on some of the areas included here will be covered by consultation in the early autumn.

Medicines

Converting centrally authorised products to UK Marketing Authorisations

Most medicines on the UK market already have a UK Marketing Authorisation (MA), and this will be unaffected by our exit from the EU. However, most new medicines come to market via a licencing route overseen by the EMA. These are collectively known as Centrally Authorised Products (CAPs).

To ensure such medicines will continue to be authorised for use in the UK, all CAP MAs will automatically be converted into UK MAs on 29 March 2019. MHRA will write to all CAP Marketing Authorisation Holders (MAHs) prior to 29 March 2019 to inform them of the conversion process (known as “grandfathering”) and to provide them with the opportunity to opt out of receiving a UK MA.

MAHs will have a period of time from exit day to provide MHRA with baseline data for CAPs that are converted into UK MAs. The exact requirements will be communicated at a later date as this is subject to consultation.

Initial Marketing Authorisation applications

After EU Exit, to market a product in the UK, an initial MA application will need to be submitted to the MHRA and will go through a national assessment. MHRA will take a streamlined approach to approving UKMA applications that places no greater burden on industry and ensures that patients can access new and innovative medicines at the same time as EU patients.

The UK will no longer be a part of the EU centralised, mutual recognition and decentralised procedures.

Medicines licensed via Mutual Recognition and Decentralised Procedures

The mutual recognition and decentralised procedures (MR/DC) are two EU routes to obtaining a MA to market a medicine within multiple EU and EEA countries.

Existing medicines that received a MA for the UK via the MR or DC routes prior to 29 March 2019 will be unaffected as they already hold a national UK MA.

In-progress licensing procedures at time of exit

If there’s ‘no deal’, the outcome of EU procedures (including mutual recognition, decentralised and centralised procedures) that have not reached the decision phase at the time that the UK exits the EU, will not be valid in the UK. However, the MHRA will take EU decisions into account where possible.

For centralised procedures in progress at time of EU exit:

- The application, as submitted to the EMA, will need to be submitted to the MHRA
- If the Committee for Medicinal Products for Human Use (CHMP) has issued an opinion by exit day, MHRA will make its decision taking into account the CHMP opinion
- If not yet at the opinion phase, the MHRA will continue to assess the application as a national procedure. MHRA will take into account any CHMP assessment that had already taken place.

For MR or DC procedures in progress at time of EU Exit it's proposed that a transitional provision will be made for MRP and DCP procedures in progress immediately before Exit day. These procedures currently already result in a national MA. We'll complete the assessment (the transitional process for this will depend on how far the procedure has got immediately before Exit day) but if successful, they will be approved as a national (UK) MA.

Data and market exclusivity for Marketing Authorisations

We're not proposing any changes to the data and market exclusivity periods for UK MAs.

After the UK's exit from the EU, the start of data or market exclusivity will be the date of authorisation in the EU or UK, whichever is earlier.

'Generic' MAs – reference products

The MHRA will not have access to the data provided in support of EU approved products. Therefore, new generic applications would need to be based on reference products that have been authorised in the UK.

Existing MAs for generic products which are based on a reference product authorised in the EU would remain valid.

Legal presence requirements

At present, the MHRA requires a named individual who can be contacted in the event of a safety issue, and has the ability to require independent re-testing of medicines and also the ability to withdraw a product from the market. This will continue if there's no deal.

The requirement for this would include:

- a MAH should be established in the UK by the end of 2020. Until then, the MHRA will require a contact in the UK. A Change of Ownership will need to be submitted to MHRA to change from an EU MAH to a UK MAH for UK MAs
- the Qualified Person for Pharmacovigilance (QPPV) should be established in the UK on day one, although those without a current UK presence will have until the end of 2020 at the latest to do so, but would nevertheless be required to make arrangements for providing the MHRA with access to the relevant safety data related to UK Marketing Authorisations (MAs) at any time. Companies may choose to have the EU QPPV take on responsibility for UK MAs until the UK QPPV can be established. A variation should be submitted to the MHRA to change QPPV. Exact details of this will be consulted upon
- a Qualified Person (QP) for products manufactured in the UK or directly imported into the UK from outside a country on a designated country list (whitelist) must reside and operate in the UK. A QP for products manufactured in a country on a whitelist or manufactured in a third country and imported into the UK from a country on a whitelist can reside in a country on the whitelist.

Paediatric medicines

Human medicines for children are known as paediatric medicines. In a ‘no deal’, there will be a UK system for regulation of paediatric medicines in which the UK will ensure incentives remain to encourage such medicines onto the UK market. We will make provisions for a UK Paediatric Investigation Plan (PIP), including the deferral and/or waiver of the requirement for studies where appropriate as currently provided for in EU legislation. Details of this will be subject to consultation.

Orphan medicines

Medicines that have been developed to treat rare diseases are known as orphan medicines. We will be consulting on the proposed UK approach to the regulation of orphan medicines post-exit, including on incentives to encourage such medicines onto the UK market.

Packaging and leaflets

The MHRA would continue to accept proposals for packaging and leaflets in the English language that include information from other jurisdictions (such as Ireland), as long as information complies with UK requirements.

The MHRA would be pragmatic in changing UK requirements and would provide time for companies to comply with any changed requirements, including updates to packaging and leaflets. Any changes will be subject to consultation.

Advanced Therapy Medicinal Products (ATMPs)

An ATMP is a medicinal product which is either: a gene therapy medicinal product, a somatic cell therapy medicinal product or a tissue engineered product.

MA applications for ATMPs to be marketed in the UK, whether for an initial, variation or in progress application, or a conversion from a CAP, would be treated as set out above.

Pharmacovigilance

Currently pharmacovigilance, which is the monitoring of the safety of medicines on the market, is co-ordinated at EU level. If there's 'no deal', the MHRA will have primary responsibility for the conduct and oversight of all pharmacovigilance activities in relation to UK MAs, certificates of registration and traditional herbal registrations. The details of our approach will be subject to consultation.

Sharing of common systems, and formal exchange and recognition of data submitted for regulatory activities between the UK and EU countries would cease. The MHRA already holds its own database of Individual Case Safety Reports (ICSRs), so will not require historical information from MAHs.

In future, for medicines sold in the UK, MAHs will be required to submit pharmacovigilance data (UK and non-UK ICSRs and PSURs (Periodic Safety Update Report)[1]) directly to the MHRA.

Online sellers

The EU common logo for online sellers currently allows sale of medicines throughout EU countries and can be issued by the MHRA and other EU competent authorities.

In order to sell into the EU, EU-based online sellers have to register, comply with relevant requirements and display an EU common logo linked to the competent authority in which they are based. As they would be outside of the EU, UK-based online sellers would no longer be required to do this. For the UK market, we propose to explore requiring the use of new 'UK logo' for UK-based online sellers from 2021.

Good X Practice (GxP) Guidelines

[1] An Individual Case Safety Report (ICSR) is an adverse event report for an individual patient and is a source of data in pharmacovigilance. A Periodic Safety Update Report (PSUR) is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined points in time post-authorisation.

GxP refers to guidelines established to ensure that businesses working in regulated industries, such as pharmaceuticals, make products that are safe, fit for use, and which have met strict quality standards throughout the entire process of production. The “x” stands for the particular field, for example manufacturing (GMP) or distribution (GDP) and so on.

In the event of a no deal scenario the UK proposes to continue using, until further notice, the EU Good Manufacturing Practice and Good Distribution Practice guidelines, as issued under Article 47 and 84 of the 2001 Directive.

Parallel Distribution and Parallel Imports

Parallel imports are goods produced genuinely under protection of a trademark, patent, or copyright, placed into circulation in one market, and then imported into a second market without the authorisation of the local owner of the intellectual property right.

EU exit does not mean that parallel imports of medicines will cease. Under the TRIPS agreement - the Agreement on Trade-Related Aspects of Intellectual Property Rights, an international legal agreement which governs international rules around intellectual property and trade - countries may choose their own exhaustion regime (for products that have been sold by an intellectual property owner) which means they can determine whether or not to allow parallel imports.

If there’s ‘no deal’, the UK will unilaterally align to the EU/EEA exhaustion regime from Exit day to provide continuity in the immediate term for businesses and consumers and ensure that parallel imports of goods, such as pharmaceuticals, can continue from the EU/EEA.

We’re currently considering all options for how the exhaustion regime should operate after this temporary fix. Any substantial changes to the exhaustion regime will occur only after a full research programme and consultation.

Our intention is to convert all currently approved Parallel Distribution Authorisations of CAPs into parallel import licences. In order to grant parallel import licences after exit day the MHRA would also require full product information from the source country competent authority in order to verify the safety of the medicine and that the product is essentially the same as the reference product on the UK market.

Devices

Medical devices on the UK market

For a time-limited period, we would continue to recognise the CE Mark on medical devices, which demonstrates their conformity with EU regulatory requirements. During this period, devices would be accepted on the UK market if they meet all EU requirements, which for all but the lowest-risk devices would include certification by EU Notified Bodies.

Further detail on the future process after this temporary situation of bringing a medical device onto the UK market will be subject to consultation in due course.

Notified Bodies

UK-based Notified Bodies would, in a 'no-deal' scenario, no longer be able to assess the conformity of medical devices for devices to receive the CE mark and enter the EU market.

Therefore, the MHRA will no longer be able to oversee Notified Bodies in the way that it does now.

Post market surveillance of devices

Currently, post-market safety data is shared across all members of the European regulatory network for devices (EU, EEA, Turkey and Switzerland), and any disagreement over the marketing of a device can be escalated through regulator forums such as the Medical Devices Coordination Group, and potentially through the European Commission and Court of Justice of the European Union.

If there's 'no deal', the MHRA would continue to perform national post-market surveillance of medical devices on the UK market, and able to take a national decision over the marketing of a device in the UK, regardless of the position of the European regulatory network, or any decision of the CJEU.

Clinical Trials

Clinical Trial applications

As clinical trials are currently managed nationally, UK clinical trial applications will continue to be authorised by the MHRA and ethics committees as they are now. The UK ability to participate in multinational trials will also not change.

MHRA will be improving processes to enable closer working with ethics bodies and allowing a single application and a single national decision in the UK. The initial pilot work has started and would continue to be developed post-exit.

Legal presence

At present, a sponsor or their ‘legal representative’ should be based in the EU or EEA; we’re seeking to preserve this position if there’s ‘no deal’. While the legal representative will only need to be based in the EU or EEA we anticipate it will be necessary to have an individual based in the UK who has overall responsibility for the trial and can be contacted to discuss urgent issues arising in connection with a trial, for example urgent safety matters or trial suspensions. We’ll provide more information in due course.

Transparency

Our intention is to align UK transparency provisions with those currently operating in the EU. Information on how a UK system would be developed will be the subject of consultation.

More information

We’ll publish more information in the coming months. We aim to give businesses and individuals as much certainty as possible as soon as we can, and to ensure that any new requirements are not unduly burdensome.

This notice is meant for guidance only. You should consider whether you need separate professional advice before making specific preparations.

It is part of the government’s ongoing programme of planning for all possible outcomes. We expect to negotiate a successful deal with the EU.

The UK government is clear that in this scenario we must respect our unique relationship with Ireland, with whom we share a land border and who are co-signatories of the Belfast Agreement. The UK government has consistently placed upholding the Agreement and its successors at the heart of our approach. It enshrines the consent principle on which Northern Ireland's constitutional status rests. We recognise the basis it has provided for the deep economic and social cooperation on the island of Ireland. This includes North-South cooperation between Northern Ireland and Ireland, which we're committed to protecting in line with the letter and spirit of Strand two of the Agreement.

The Irish government have indicated they would need to discuss arrangements in the event of no deal with the European Commission and EU Member States. The UK would stand ready in this scenario to engage constructively to meet our commitments and act in the best interests of the people of Northern Ireland, recognising the very significant challenges that the lack of a UK-EU legal agreement would pose in this unique and highly sensitive context.

It remains, though, the responsibility of the UK government, as the sovereign government in Northern Ireland, to continue preparations for the full range of potential outcomes, including no deal. As we do, and as decisions are made, we'll take full account of the unique circumstances of Northern Ireland.