Cancer Research UK response to MHRA consultation on EU exit no-deal proposals

November 2018

Summary

The consultation looked at how the Medicines and Healthcare products Regulatory Agency's (MHRA) legislation and regulatory processes would have to be modified in the event of the UK not securing a deal with the EU after the UK's exit, with no Implementation Period. **CRUK's priorities for Brexit include clinical trials and access to medicines; hence, our response covers the sections on Medicines, Clinical Trials and Fees.**

In general, the proposals seem pragmatic, but clarity is needed on the approaches outlined, in particular:

- The terminology and responsibilities of UK representatives of clinical trials.
- The capacity of the MHRA to undertake new routes for licensing, and converting existing EMA licenses to UK-specific licenses.
- The process for importing IMPs and providing import licences.
- How fees related to MHRA's processes and services could better incentivise the UK as a launch market.

Background

Following on from the publication of the technical notices, on 23 August 2018, in relation to How medicines, medical devices and clinical trials would be regulated if there's no Brexit deal, Batch testing medicines if there's no Brexit deal, and Submitting regulatory information on medical products if there's no Brexit deal, this consultation also asks questions on the finer detail of how that policy might be best implemented in the event of no deal being reached.

The overall approach in no-deal is for the Secretary of State for Health and Social Care and the Minister for Health, Social Services and Public Safety in Northern Ireland, acting through the **MHRA**, to be a **stand-alone regulator**, taking any decisions and carrying out any functions which are currently taken or carried out at EU-level. This would include decisions on Marketing Authorisation (MA) applications which are currently authorised through the Centralised Procedure, paediatric investigation plans and orphan status, as well as pharmacovigilance responsibilities.

Draft SI legal text

Consultation Impact Assessment

Consultation Annex

MEDICINES

Legal Presence

Summary

As described in the 'How medicines, medical devices and clinical trials would be regulated if there's no Brexit deal' Technical Notice:

1. A Marketing Authorisation Holder (MAH) would have to be established in the UK by the end of 2020. Until a UK MAH is established, the UK would require a contact in the UK. This person (MAH or interim contact person) would be responsible for taking urgent action in the event of a safety concern. The MAH would retain ultimate legal responsibility, during this period.

2. As is the case today, the UK require a Qualified Person for Pharmacovigilance (QPPV) to be responsible for delivery of a pharmacovigilance system that covers UK authorised products. Given that the EU QPPV will not have responsibility towards UK authorised products, a QPPV should be established in the UK from Exit Day. Those without a current UK presence would have until the end of 2020 at the latest to establish a presence, 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, and comply with UK inspection requirements, during this period. Companies may choose to have the EU QPPV take on responsibility for UK MAs until the UK QPPV could be established. A variation should be submitted to the MHRA to change QPPV.

Relevant legal text (page 2-3)

Q: Do you have any views on how the proposed transition period for UK MAH and QPPV establishment should be managed by the MHRA in order to reduce any impact or burden in terms of meeting the requirements?

The outlined transition period for UK MAH and QPPV seems pragmatic, but further clarity is needed to fully understand the possible implications for industry stakeholders and the overall impact on patient access to medicines. We would be interested in learning the number of companies that currently have no legal presence or QPPV in the UK to understand the scale of the problem.

New Marketing Authorisation (MA) assessment routes

Summary

The MHRA would offer the following new assessment procedures for applications for products containing new active substances alongside our existing 210-day national licensing route (which

will continue to operate as now):

1. A targeted assessment of new applications for products containing new active substances or biosimilars which have been submitted to the EMA and received a Committee for Medicinal

Products for Human Use (CHMP) positive opinion, based on submission of all relevant information and the CHMP assessment reports.

2. A full accelerated assessment, for new active substances, with a reduced timeline of no more than 150 days.

We would also offer a 'rolling review', for new active substances, which would allow companies to make an application in stages, throughout the product's development, to better manage development risk.

We would also offer national conditional MAs through the conversion of the existing EU legislative framework into UK law.

This consultation will focus on the targeted assessment route. The targeted assessment of new applications for new chemical or new biological entities and biosimilar medicines would be based on all relevant information already submitted to the EMA and the CHMP assessment report, with a commitment to grant a licence within a timeframe of 67 days from submission of the application following the positive CHMP opinion. The only exception to this would be if the UK identified an objection relating to public health.

New fees for MAs under a new national targeted assessment route of (see Section 4 for other fees):

1. £62,421 for a major application for a MA for a new active substance; and,

2. £17,330 for a complex abridged application for a MA for a biosimilar.

Relevant legal text **(page 4)**

Q: Do you agree with the proposed new targeted assessment process?

Yes

We see the proposed targeted assessment process as a pragmatic way to minimise new barriers and delays to UK patient access to the newest medicines, if no deal is reached between the UK and the EU. However, this will likely not be enough to prevent access to new drugs in the UK being delayed compared to the current situation, or a scenario with a deal featuring a comprehensive agreement on medicines regulation.

We continue to believe that the best outcome for patients would be a deal which ensures the EMA's marketing authorisation decisions continue to apply in the UK, and where the MHRA continues to play a significant role both in those decisions and in shaping a broader shared UK-EU medicines regulatory environment.

However, we recognise the need to prepare for no deal being reached between the UK and the EU. In this event, the targeted process is sensible. The expectation of aligning with the CHMP decision in most cases should help to ensure UK patients can continue to access the newest medicines swiftly by removing the need for a separate UK assessment of a medicine's safety, quality and efficacy.

However, we are concerned that, if the MHRA is no longer able to contribute to the EMA's work post-Exit, this could delay the production of the CHMP reports which will be the basis for future licensing decisions under the targeted process. We note concern about such delays has also been expressed by the Executive Director of the EMA.[1] Between 2008 and 2016 the MHRA acted as the lead assessor on at least 20% of centralised EMA medicines approval processes, demonstrating its contribution to the expertise and capacity of the EMA in assessing new applications.[2]

It is therefore in the interests of patients in both the UK and the EU that the MHRA can continue to participate fully in the EMA's assessment and decision-making processes. Government should look to agree a deal on the UK's future relationship with the EU which secures this, building on its welcome ambition to agree "associate membership" of the EMA for the UK.[3] This will also help to maintain the MHRA's global reputation as a respected, world-leading regulator.

In the short-term, in the interests of transparency and to ensure public and patient trust in the proposed new system, we would welcome examples of envisaged scenarios relating to a public health concern which would lead to the MHRA conducting a separate evaluation of a medicine's safety, quality and efficacy.

In addition, we have heard some companies may be unwilling to commit the additional resources required to submit a licensing application to the MHRA while a final EMA decision on marketing authorisation is still pending, even if the same documentation is being used for both.

This would especially be the case for smaller companies who must prioritise their limited resources, or for larger companies whose global strategies would prioritise the EMA as the gatekeeper to a larger sales market. This would mean the UK could fall behind the EU in terms of timelines for accessing new medicines. Government should continue to work with industry to explore what actions Government or the MHRA can take to mitigate this.

Q: Do you agree with the proposed new fees for targeted assessment?

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[1] https://www.politico.eu/pro/ema-chief-brexit-will-cause-some-shortages-of-medicines/

[2] See our drug licensing statement

[3] See PM speech

Yes

We recognise the need to introduce a fee to cover the cost of the MHRA's work in undertaking the new targeted assessments, but Government must continue to engage with industry to ensure this does not act as a disincentive to companies launching new products in the UK.

The proposed fees for both major new applications and complex abridged applications are equivalent to the existing fees for incoming mutual recognition assessments with the UK as a Concerned Member State and with European reference products. This seems reasonable as this situation is broadly comparable to the proposed targeted assessment process post-Exit, based on the submission of the same dossier to both the MHRA and EMA.

However, we are concerned about the potential implications for patient access to new medicines from the introduction of this new cost for companies to enter the UK market. While the EMA currently covers an area responsible for 25% of global pharmaceutical sales, the UK on its own accounts for just 3%.[4]

There is therefore a risk that the introduction of an independent UK system for licensing medicines, together with its associated costs, will mean the UK market is deprioritised by pharmaceutical companies launching their new drugs.

This risk may be amplified by the proposed introduction of a new fee to renew UK-based marketing authorisations (as set out in section F2), the additional resource which will be required from companies to maintain a separate UK marketing authorisation, and the proposed introduction of cost recovery fees for NICE Technology Appraisals in England from April 2019.[5]

Government should be clear on how it will ensure the introduction of the proposed new fees for targeted assessment, in combination with the other fees across the system noted above, does not discourage companies (especially SMEs) from seeking UK marketing authorisation for their products, and should continue to engage with industry to achieve this.

In particular, in the event of no deal, it should keep under review the impact of any newly-introduced fees, and be prepared to amend the fee structure if evidence emerges that this is harming patient access to new medicines in the UK.

Converting centrally authorised products (CAPs) to UK MAs – commonly referred to as 'grandfathering' of licences

Summary

CAPs would be converted automatically into UK MAs and issued with a UK MA number on Exit day. MAHs would be given the opportunity to opt out of conversion prior to Exit. No fee would be charged for the grandfathering process.

MAHs would have one year from Exit day to provide the MHRA with baseline data for CAPs that are converted to UK MAs. Baseline data should be submitted before any variations can be accepted by the MHRA. Under exceptional circumstances, the MHRA would allow variations to be submitted prior to baseline data.

Relevant legal text (page 5-10)

Q: Do you agree with the requirements for data provision for grandfathered CAPs?

Yes

[4] See our drug licensing statement

[5] https://www.gov.uk/government/consultations/nice-recommendations-charging-and-appeal-panels

We agree with the proposed requirements, but would welcome further clarity from Government and the MHRA on the circumstances in which it will be possible to make alterations to existing medicines' marketing authorisations while the grandfathering process remains ongoing.

We agree it is appropriate for the MHRA to hold baseline data on all drugs with a converted UK marketing authorisation. However, in a no deal scenario, the MHRA must ensure it has sufficient capacity to be able to undertake the grandfathering process, without knock-on delays to its work reviewing applications for new marketing authorisations. This will be a particular concern if there is high demand from industry for applications under the "accelerated" or "rolling" assessment processes, which appear to be more resource-intensive for the MHRA than the "targeted" process.

In addition, we are concerned that the requirement for companies to submit baseline data to the MHRA prior to any variations in marketing authorisation being approved may result in delays in patients accessing existing medicines in new indications.

For example, many new oncology drugs can "target" cancer cells with specific molecular characteristics (such as those expressing a specific genetic mutation), and can be used in multiple different tumour sites. As evidence emerges of their effectiveness in different sites, it is vital their marketing authorisation can be altered to reflect this.

Government and the MHRA must ensure patients do not miss out on treatment with such medicines if the MAH has not completed the grandfathering process for those medicines' existing indications. Otherwise, there is a risk of a gap in access to such medicines opening up between new patient populations in the EU and the UK.

We would therefore welcome clarity on the definition of the "exceptional circumstances" under which the MHRA would allow variations to be submitted prior to baseline data.

Paediatric investigation plans (PIPs) and studies

Summary

MA applications for new medicinal products (new global MAs) and applications for new indications, including paediatric indications, routes of administration and new pharmaceutical forms for products with supplementary patent protection should demonstrate compliance or partial compliance with a UK PIP or have a waiver.

Paediatric Use Marketing Authorisations (PUMAs) in compliance with a PIP may be granted through any appropriate national licensing route and would be eligible for the usual 8 years data exclusivity and further two years' market exclusivity protection.

Class waivers, product-specific waivers and deferrals would be possible as per existing EU system.

Reward of a 6-month extension for a UK Supplementary Protection Certificate (SPC) (which extends the patent period) based on a UK MA that complies with a PIP and paediatric information in the Summary of Product Characteristics (SmPC)/Patient Information Leaflet (PIL) would be granted in the UK on the same basis as it is currently granted in the EU.

There would be 2 years additional market exclusivity for orphans complying with a PIP, as at present.

Newly completed paediatric studies would need to be submitted by UK MA holders for assessment.

Relevant legal text **(page 13-20)**

Q: Do you agree with the proposal for UK paediatric investigation plans (PIPs) and newly completed paediatric studies?

No

The outlined proposal to initially adopt any ongoing positive PDCO opinion and to subsequently have a UK system of paediatric obligations and incentives as currently set in the EU Paediatric Regulation could put UK children's access to innovative medicines at risk. The 10-year report on the EU Paediatric Regulation showed that while it is successful for many paediatric diseases, it is less effective for paediatric oncology. There is currently an on-going review to see how the system can be amended to improve paediatric drug development in such areas. It is crucial that UK stakeholders, including the MHRA, remain part of these discussions and aligns with legislation that could incentivise the creation of innovative medicines for children.

A critical flaw in the regulation permits companies to abandon agreed PIPs if they decide to abort the adult development programme. The result is that new medicines showing promise for children are not adequately researched after a drug fails to show potential in an adult indication. Better regulatory requirements and rewards for early PIP completion is needed to establish an evidence base for the paediatric population even if the adult development program is aborted.

Through organisations such as EFPIA, there is an understanding and willingness for industry to engage with paediatric drug development. However, fragmenting the approach from the future EU PDCO PIP approvals process could disadvantage children's access to innovative medicines. With the UK's smaller market, especially for paediatric cancer and potentially different regulation process, some may not choose to undertake trials and license drugs outside of the EU, unless the UK completely aligns with what is required. Further detail and consultation is therefore needed to establish how the regulation will be adapted to UK law.

Orphan designation

Summary

The EU orphan criteria would be amended so that there are UK-specific criteria (in relation to the prevalence of the rare disease in the UK and the availability of satisfactory methods in the UK and significant benefit). Overall, the orphan criteria would still be based around EU regulatory concepts and should not be overly burdensome to industry (e.g. many prevalence calculations include data from the UK in the current EU system).

The MHRA proposes to explore retention of the most important orphan incentive – namely 10 years market exclusivity from competition from similar products in the approved orphan indication. This incentive would be conferred at the time of MA approval and the evaluation of compliance with orphan criteria would be conducted in parallel with the review of quality, safety and efficacy at the time of the MA application.

The MHRA proposes that it would not duplicate the EU pre-approval orphan designation, rather orphan status would only be assessed at the MA application stage.

Relevant legal text (page 21-26)

Q: Do you agree with the proposal to explore incentivising submission of MA applications for products intended to treat rare diseases in UK?

Yes

We agree that incentives are required for companies to bring their orphan drugs to the UK and additional proposals to those outlined could be considered. With such small patient populations in the UK alone, there is a concern that the costs to file for approval will outweigh any potential returns for organisations.

Clarity is needed on the process. If orphan designation is to be addressed at the marketing authorisation stage this could be additional burden for companies, and submission to the UK could therefore be delayed.

If the 10-year market exclusivity applies from the EU MA approval date, then a period of time will be lost while seeking MHRA approval. To incentivise this initiative, any applications made to the MHRA within 1 year of the EMA approval should have market exclusivity from the date of UK approval.

Abridged applications

Summary

It is proposed that the various abridged procedures to getting an MA (generic applications/hybrid abridged/biosimilars/well-established use and new combinations of existing

products/consent) would remain in place, but with modifications to reflect the UK's exit from the EU. The legal basis for these applications is currently described in Articles 10 – 10c of the

Directive 2001/83/EC, which in turn cross-refer to Article 6. There would be amendments to the HMRs to transpose these requirements.

It is proposed that amendments would be made to the effect that it would not be possible to rely on a European reference product post-Exit, the reference product would have to have been

authorised in the UK (this would include products which have a UK MA because they are converted EU MAs). However, for applications relying on well-established use (Article 10a), the use

could continue in the UK or the EU / EEA post-Exit.

Comparators used in bioequivalence studies for the purpose of approval of generic medicines should be authorised for the UK market, if not then the batch(es) selected for use in

bioequivalence study(ies) should be shown to be representative of the product(s) authorised in the UK.

Relevant legal text **(page 27-30)**

Q: Do you agree with the proposal for abridged applications?

Yes

We agree that existing EMA procedures for abridged applications should be carried over as far as possible into the UK post-Exit. The proposed change is appropriate to ensure products undergoing this assessment route can continue to be quickly and safely introduced onto the UK market.

Biosimilars and generics in particular have a crucial role in freeing up financial headroom to pay for new and innovative medicines. Yet financial margins for these products can be tighter than for branded and/or originator medicines, so it is important to ensure that the pathways to market access remain as smooth and inexpensive as possible. The proposed change will help to accomplish this.

In the event of no deal, the MHRA should keep under review the proposal to disallow products without a UK marketing authorisation to serve as reference products. It will be important to ensure this restriction does not negatively impact UK patients' access to products which might otherwise be available.

Recognition of prescriptions

Summary

EU and EEA countries currently mutually recognise prescriptions issued by qualified professionals in any other EU / EEA country.

The HMRs define who is eligible to issue prescriptions that can be dispensed in the UK.

The proposal is to continue to recognise prescriptions from countries on a designated country list post-exit. This list will initially include EU and EEA countries.

Relevant legal text (page 35)

Q: Do you agree with the proposal to enable continued recognition of prescriptions issued in an EU / EEA country?

Yes

The proposal to enable continued recognition of prescriptions issued in EEA countries seems sensible. Consultation on how this initial list may change will be necessary.

CLINICAL TRIALS

Legal presence – clinical trials

Summary

For clinical trials, the UK would require the sponsor or legal representative to be in the UK or country on a designated country list from Exit day. This list would initially include the EU and EEA countries.

Where the sponsor or legal representative are not based in the UK, we propose introducing a duty on the sponsor to ensure that the chief investigator (CI) in the UK is contactable, and UK based to provide real assistance and facilitate action if needed.

Relevant legal text (page 36-37)

Q: Do you agree with the approach proposed, for a sponsor or legal representative to be established in the UK or a designated country?

Yes

We agree with the proposal to preserve the position of a sponsor or legal representative being established in the UK, EU or EEA. This position seems sensible and should cause minimal disruption to on-going multi-national trials where the sponsors or legal representatives are not based in the UK. The proposal fits well with Cancer Research UK's current hub-and-spoke model, with Sponsors contracting with national coordinating countries in each member state.

However, the EU position outlined in the European Commission's no deal notice to stakeholders does not reciprocate this position, stating that UK-based Sponsors of cross-national clinical trials would require legal representation in an EU member state for ongoing trials in the event of a no deal[6]. This would be a considerable burden, and a potentially prohibitively costly step for smaller, non-commercial Sponsors and could mean that UK-based organisations will be less likely to lead multi-national trials, undermining the UK's position as a global leader in clinical research. The UK and EU must come to an agreement that enables legal representatives of UK-EU trials to be established in the UK.

[6] European Commission (2018). *Notice to Stakeholders: Withdrawal of the United Kingdom and EU rules in the field of clinical trials*, European Commission, September 2018. Available at: https://bit.ly/2NVRTSM

The current EU Clinical Trial Directive does not provide clear responsibilities of a legal representative and we would therefore welcome a clearer definition from UK Government to avoid risk-averse practices that would result in overly costly solutions being put in place.

We welcome the commitment made by UK Government to adopting all the of the relevant legislation from the incoming EU Clinical Trial Regulation (CTR). The issue of sponsorship and legal representation under the CTR is clearer, with the understanding that some Member States may require the UK to have a legal representative in the EU. This may therefore limit the UK's ability to collaborate with those EU member states. Greater clarity is needed for researchers to understand the implications of the CTR on their requirements for establishing a legal representative in the EU.

In addition, access to the portal and database underpinning the CTR is subject to negotiations with the EU. In the absence of an agreement with the European Union, the UK would not have access to this digital infrastructure, reducing the efficacy in setting up and patient safety reporting of UK-EU trials.

Q: Do you agree with the additional requirement on the sponsor to ensure that, where both the sponsor and legal representative are not UK-based, a CI is continuously available to assist with the actioning of any relevant licensing authority or sponsor required changes to the conduct of the trial?

Yes

Establishing a contactable, UK-based investigator in cases where there is neither a sponsor nor a legal representative in the UK seems sensible. However, there are elements of the proposal that need further clarity and consideration.

The terminology of a 'UK-based chief investigator' is not appropriate. At present there can be only one CI per clinical trial. If the Sponsor is based in a non-UK country appearing on the list, the CI is likely to be based in the country of the Sponsor i.e. not UK. The definition of a CI is established clearly as:

"chief investigator" means—

1. *(a) in relation to a clinical trial conducted at a single trial site, the investigator for that site, or*
2. *(b) in relation to a clinical trial conducted at more than one trial site, the authorised health professional, whether or not he is an investigator at any particular site, who takes primary responsibility for the conduct of the trial;*

It would therefore be more appropriate to change the terminology to 'UK lead investigator', which is already widely used for non-commercial trials, and can be included in the definitions in Regulation 2 outlined above. The role of this UK lead investigator would require a clear scope. Currently, the Sponsor is responsible for implementing any operational changes relating to trials, including temporary halts and informing sites, with the CI having influence over decisions, particularly for non-commercial trials. Further clarification on how this role would 'assist with actioning of Sponsor required changes to the conduct of the trial' is therefore crucial given they may not have primary responsibility for the trial.

An option for delegation of responsibility from the UK lead investigator to a CTU must also be included. For academic-led trials using non-commercial Sponsors, the role of the CI and/or the UK lead investigator is often supported by a CTU based in a University or NHS site, which would therefore be suitable to support trial decisions. This would also help to manage expectations regarding the UK lead investigator being 'continuously available', which also requires further clarification.

The appointment of a UK lead investigator with additional responsibilities would not remove the need for regular, clear communication between MHRA and EEA based sponsors or legal representatives. In the interest of patient safety, formal communication channels between the MHRA and other national competent authorities in EU member states must also be preserved.

Transparency

Summary

To ensure continued transparency of clinical trials, in keeping with the current situation, a change would be made for there to be a provision for MHRA to publish information on UK trials, in line with what is currently published about them in the EU clinical trials register.

Relevant legal text (page 38)

Q: Do you agree with this approach?

Yes

Transparency is a key element of clinical trial conduct and must be preserved. We welcome the intention to align UK clinical trials transparency requirements in the event of a no-deal with those currently used and agree further consultation on how this would work is vital.

Any future system would require effective communication with the EU held databases, including the incoming CTR database, to preserve transparency and minimise duplication of effort. It would also require the ability to search and download information, while linking trial registration with trial data publication. We await the consultation for this process and require clarity on the situation on Exit day should the UK and EU not reach a deal, since any process will not be in place by then. This consultation should address the timeframe for any new system, what happens with regards to UK REC approval and registration, and the implications for ongoing trials and patients on those trials.

Use of designated country lists, including for legal presence and importation of investigational medicinal products (IMPs)

Summary

The MHRA would develop lists of countries where activities relating to clinical trials can be performed. There would be three such designated country lists:

1. A designated country list where a sponsor or legal representative could be established.

2. A designated country list from which:

The UK would accept the summary of product characteristics (SmPC) (in English) as an alternative to the investigators' brochure in an ethics application, where the IMP has a MA in that country.

Products such as advanced therapy medicinal products (ATMPs) that have an MA in the designated country would not be subject to usual special provisions when used in trials in the UK.

3. Countries from which a UK MIA (IMP) holder could import IMPs that have already been certified by a QP, for which further certification would not be required in the UK (for IMPs both manufactured in or imported to that designated country).

Relevant legal text (page 39-40)

Q: Do you agree with the proposed designated country lists?

Yes

We welcome the pragmatic approach taken by UK Government to preserve activities related to clinical trials by using designated country lists, and agree that EU and EEA countries should be on each of these lists.

Further information on the criteria used to determine which countries will be excluded from the designated list after the initial transition period is vital. This should include examples of types of issues that would lead to a country within the EEA being excluded from the list. Furthermore, clarification is needed on the process of adding countries to these lists, including countries with which the EU has Mutual Recognition Agreements.

It is vital that the availability and movement of IMPs to and from the UK is not disrupted. For designated country list 3, clarity on the terminology used regarding the import of IMPs is necessary. Currently, IMPs can be manufactured and QP released in the EU and shipped directly to the clinical sites in the UK. We understood from the technical guidance issued earlier this year by UK Government, that this would still be the case in a no deal scenario.

This consultation, including the transitional arrangements in the annex, refer to the import of IMPs and implies that there is a receiving organisation holding a manufacturing or import license in the UK. It therefore suggests that while QP certification in EU member states will still be accepted, it is expected that the IMP will be imported into the UK through a manufacturing organisation with a licence. Clarity is needed for organisations that do not hold this type of licence.

In addition, clarification on the process for importing IMPs to the EU from the UK is needed. 70% of IMPs used in ongoing EU clinical trials are QP released in the UK. We understand from the European Commission's notice to stakeholders that UK IMP manufacturing sites will no longer be recognised by EMA. Disrupting the process for IMP supply to EU partners risks damaging trials involving the UK. Clarity on how UK Government intends to minimise this disruption is vital.

Impact Assessment - Clinical Trials

Q: If you have evidence to help quantify the costs to business of these proposed changes, please respond below

We will continue to research the potential impacts on clinical research and will share this information once complete.

Q: If you have any additional costs that you think have not been included, or would like to challenge the cost analysis included in the Clinical Trials Impact Assessment, please give your views below

The Clinical Trials Impact Assessment is largely focused on industry trials and takes less consideration of academic sponsored trials. The requirement of putting into place a legal representative and processes associated with QP release will incur considerable and potentially prohibitive costs for academic trials and must be considered in the Impact Assessment.

In addition, the Clinical Trials Impact Assessment suggests that there are no direct costs in relation to CT3. However, if import into the UK is required, there would be a considerable cost associated with setting up a central UK manufacturing hub and must also be considered.

We will continue to research the impacts on clinical research and will share this information once complete.

FEES

<u>Fee waivers for orphan products</u>

Summary

MHRA propose to offer fee waivers for orphan products for initial marketing authorisation (MA) applications, and variations in the first year after the initial marketing MA is granted.

100% fee waiver for small-medium enterprises (SMEs) (for initial MA applications, and for variations in the first year after the initial MA is granted); 10% fee waiver for all other manufacturers (for initial MA applications only)

Q: Do you agree with the proposal to consider offering new fee waivers for orphan products?

Yes

We agree with the proposal to replicate existing EU incentives.

37% of orphan drug designations granted by the EU have been for cancer drugs.[7] It will be crucial to protect existing incentives to bring these drugs to market post-Exit. See also our answer to Q15 of this consultation for more detail on the incentives we would like to see the MHRA put in place to incentivise applications for marketing authorisation for orphan drugs.

We would welcome clarity on whether the waivers would also apply to the new "rolling" and "accelerated" assessment procedures. We would also encourage the MHRA to keep under review the incentives it offers to encourage marketing authorisation applications for orphan drugs post-Exit, and consider expanding these if it becomes clear that access to new orphan medicines is slowing in the UK relative to the EU.

New/amended MHRA fees for six processes/services previously provided centrally by EC or EMA

Summary

In a no-deal scenario, six other processes/services currently undertaken by the EU / EMA would need to be carried out in the UK. The MHRA is therefore proposing new MHRA fees for those existing EU/EMA processes for introduction on Exit day. The proposed MHRA fee levels are based on analogous existing products/services in the MHRA's existing statutory fees tariff, and are competitive when set against the associated fees for the comparable existing EU/EMA processes/services.

Q: Do you agree with the proposed new/amended MHRA fees for six processes/services previously provided centrally by EC/EMA?

Yes

We believe the proposal to charge a renewal fee for all new medicinal products is broadly reasonable. We note this expands the fee currently charged by the MHRA for the renewal of a license granted under mutual recognition where UK is the Reference Member State.

However, we remain concerned that this, in addition to the initial fees it is proposed to introduce for the new assessment routes post-Exit, will add further to the cost companies will have to pay in a no deal scenario to access the UK market. Government should be clear on how it will ensure this does not discourage companies (especially SMEs) from seeking UK marketing authorisation for their new products, which would negatively impact on UK patient access to new medicines.

[7] https://www.pharmaceutical-technology.com/research-reports/researchreportorphan-cancer-drugs-take-up-37-of-market-share-5825834/

As stated in our answer to Q8 of this consultation, the MHRA should keep under review the impact of any newly-introduced fees, and be prepared to amend the fee structure if evidence emerges that this is harming patient access to new medicines in the UK.

Further questions or comments on this consultation

Q: Please give any comments or questions below

We welcome the Government's intention to ensure minimal disruption to science and research, including the publication of No Deal Notices and this consultation. Further clarity is needed on elements not included in this consultation, including the pharmacovigilance and safety reporting in clinical trials in the event of a no deal.

This consultation response was informed by a range of stakeholders, including representatives from our Centre for Drug Development, Experimental Cancer Medicines Centres and core funded Clinical Trials Units. Cancer Research UK (CRUK) directly funds nearly 200 clinical trials, over one quarter (28%) involve at least one other EU country.

The UK's departure from the EU has introduced uncertainty to the European clinical trials environment. Of immediate concern is the UK's ability to participate in the future regulatory framework for clinical trials testing new medicines being rolled out in the EU. Action is also needed to ensure: minimal interruption to the supply of trial products; continuation of sufficient collaborative funding initiatives for clinical trials; the ability for researchers to be mobile across borders to support collaborative working; and ability to safely share patient data used in research.

CRUK is the largest charitable funder of cancer research in the world. In 2017/18 we invested £423 million in research to improve the prevention, diagnosis and treatment of cancer. We are the only charity funding research into over 200 types of cancer and we receive no Government funding, depending on the public for support.

In the 1970s, 1 in 4 people survived their cancer for ten years or more. Today, thanks to research, 2 in 4 people survive. CRUK's ambition is to accelerate progress so that 3 in 4 people survive their cancer by 2034. This is even more important given the increasing incidence of cancer, which will grow from 350,000 a year in 2015 to over 500,000 by 2035 across the UK.