Title: Contingency legislation to establish MHRA as a standalone medicines, medical devices and clinical trials regulator in a result of no-deal on EU exit.

IA No: DHSC IA 4076

RPC Reference No: N/A

Lead department or agency: Medicines and Healthcare Products Regulatory Agency (MHRA)

Other departments or agencies: Department of Health and Social Care (DHSC)

Impact Assessment (IA)

Date: 22/01/2019

Stage: Final

Source of intervention: EU

Type of measure: Secondary legislation

Contact for enquiries: MHRA EU Exit
euexit@mhra.gov.uk

Summary: Intervention and Options

RPC Opinion: Awaiting Scrutiny

Cost of Preferred (or more likely) Option				
Total Net Present Value	**Business Net Present Value**	**Net cost to business per year** (EANDCB in 2014 prices)	**One-In, Three-Out**	**Business Impact Target Status**
			N/A	Out of scope

What is the problem under consideration? Why is government intervention necessary?

The UK is currently part of the European medicines and medical devices regulatory framework. Contingency legislation is needed in order for the MHRA to be able to take on regulatory processes for human medicines and devices that are currently undertaken by the European Medicines Agency (EMA) and other bodies in the event of the UK leaving the EU without a deal by the 29 March 2019. Regulatory continuity would be essential in order to ensure the ongoing safety of medicines and medical devices being placed on the UK market and to avoid disruption to supply chains. This would be necessary to ensure stability amongst patients, practitioners and businesses; providing suppliers with the incentive to innovate in medical products where buyers would not be prepared to pay the prices necessary to cover the costs of innovation.

What are the policy objectives and the intended effects?

The objectives of the policy are to ensure continuity in regulation by ensuring that existing processes are mirrored or implemented by the MHRA where appropriate, in the short term. This will maintain a high level of public health protection when the MHRA is a sovereign regulator outside the EMA. The intended effects are to ensure continuity in the safety of medicines and devices in the UK whilst retaining the UK regulator's ability to take regulatory action to protect public safety. These objectives are intended to be met with minimum disruption and burden on businesses and with minimum disruption to the supply of medicines and devices in the UK. Examples of this approach are converting European Centrally Authorised Products (CAPs) issued before Exit to UK Marketing Authorisations (MAs) and allowing medical devices on the market which comply with EU legislation for a time limited period.

What policy options have been considered, including any alternatives to regulation? Please justify preferred option (further details in Evidence Base)

Options are assessed against a 'dual baseline' of Options 0.1 and 0.2

Option 0.1: Baseline – Static acquis with the UK part of the European medicines and devices regulatory framework. This is the baseline which options are primarily assessed against

Option 0.2: Do nothing – deficient UK law applies

Option 1: Establish MHRA as a standalone UK regulator following a principles-based approach in order to protect public health and to minimise impact and disruption for business

Option 2: UK accepts decisions of cross-European regulatory bodies without any oversight, influence or additional assessment

Option 3: MHRA becomes a standalone regulator requiring full assessment of all products, not taking into account any information already provided to cross-European regulatory bodies.

In the event of no deal, Option 1 is the preferred option.

Will the policy be reviewed? It will not be reviewed. **If applicable, set review date:** /

Does implementation go beyond minimum EU requirements?				
Are any of these organisations in scope?	**Micro**	**Small**	**Medium**	**Large**
What is the CO_2 equivalent change in greenhouse gas emissions? (Million tonnes CO_2 equivalent)		**Traded:**	**Non-traded:**	

I have read the Impact Assessment and I am satisfied that, given the available evidence, it represents a reasonable view of the likely costs, benefits and impact of the leading options.

Signed by the responsible Minister Stephen Hammond Date: 22nd January 2019

Summary: Analysis & Evidence

Policy Option 1

Description:

FULL ECONOMIC ASSESSMENT

Price Base Year	PV Base Year	Time Period Years	Net Benefit (Present Value (PV)) (£m)		
			Low: Optional	High: Optional	Best Estimate:

COSTS (£m)	Total Transition (Constant Price) Years		Average Annual (excl. Transition) (Constant Price)	Total Cost (Present Value)
Low	N/A		Optional	**Optional**
High	N/A		Optional	**Optional**
Best Estimate				

Description and scale of key monetised costs by 'main affected groups'

Although the approach aims to minimise business burden, there would be ongoing costs for businesses currently operating in the UK as they would need to adhere to additional UK only regulatory requirements if they currently sell in the EU/EEA. This includes additional fees, legal and administration costs. There would be familiarisation and set up costs as businesses transition into dealing with both systems. There would be costs to the MHRA of establishing and sustaining new regulatory capabilities; these will be largely recouped through fees.

Other key non-monetised costs by 'main affected groups'

As the UK would become a standalone regulator, only medicines approved through the MHRA would be able to reach the UK market and therefore there is a possibility that some medicines that would have been authorised in the UK because of the UK's involvement in the EMA will not be submitted to the MHRA due to business decisions. This could have an impact on access to certain medicines and therefore to public health. The extra costs of complying with a new UK regulator could be passed onto the purchaser through higher prices of medicines.

BENEFITS (£m)	Total Transition (Constant Price) Years		Average Annual (excl. Transition) (Constant Price)	Total Benefit (Present Value)
Low	Optional		Optional	**Optional**
High	Optional		Optional	**Optional**
Best Estimate				

Description and scale of key monetised benefits by 'main affected groups'

Compared to a situation where there is deficient legislation in the event of no deal being agreed with the EU before 29 March 2019, the preferred option minimises the risk to businesses and offers regulatory continuity. The ability of the MHRA to operate as a trusted and comprehensive UK regulator will allow consumers to have confidence in medicines and devices on the market and allow businesses to innovate.

Other key non-monetised benefits by 'main affected groups'

The UK regulator would have the ability to protect public health and make its own decisions to ensure patients have confidence in the safety of medicines and devices on the UK market. Retaining a comprehensive UK regulator means that the scientific expertise that the MHRA holds would be retained to an extent, reducing a possible flight of scientific knowledge and skills which could have negative spillover effects for the UK's life sciences industry and the UK's ability to regulate medicines and devices. This contingency legislation also aims to benefit business by helping them prepare for a no-deal scenario.

Key assumptions/sensitivities/risks (%)	Discount rate	3.5%

Although this contingency legislation aims to help business in their preparations for a no-deal scenario, there is a risk that due to the requirements set out, businesses will not have sufficient time to prepare. In the event of no deal being agreed with the EU before 29 March 2019, the MHRA will have regulatory processes in place so that businesses will have the relevant information to prepare for this scenario. The MHRA is not able to exactly estimate proportion of businesses that now apply through the European centralised procedure that will apply for an authorisation through the MHRA, only through evidence from third countries can an estimate be reached.

BUSINESS ASSESSMENT (Option 1)

Direct impact on business (Equivalent Annual) £m:			**Score for Business Impact Target (qualifying provisions only) £m:**
Costs:	**Benefits:**	**Net:**	

Contents

Introduction: The UK's withdrawal from the EU and preparations for no-deal

1. The UK will leave the EU on 29th March 2019. The draft Withdrawal Agreement provides for an Implementation Period, lasting until 31st December 2020. While the UK is clear in its commitment to reaching agreement on an agreement with the EU, it is prudent to be prepared for all possible outcomes, and the consultation that accompanies this Impact Assessment forms part of these preparations.

Medicines

2. The UK is currently a member of the European medicines regulatory framework. This means:

- Taking an active role in the activities of the European Medicines Agency (EMA) and its committees.
- Mutual recognition of batch release and Qualified Person (QP) certification for medicines across EU/EEA
- Being a member of the European Heads of Medicines Agencies network.
- Participating in the EMA's 'centralised procedure' (CP) marketing authorisation (MA) process for medicines, which grants a medicine for sale across the EU.
- The UK is also part of the decentralised (DCP) and mutual-recognition (MRP) marketing authorisation procedures, which allows medicines to be brought to market across specific EU27/EEA countries through a procedure involving all relevant member states or a series of procedures via mutual-recognition of regulatory approval decisions.
- Participating in a pan-European GxP inspections process, which grants mutual-recognition of inspections across the EEA, reducing the number of duplicate inspections on the medicines supply chain, and the number of inspections individual national regulators need to carry out. GxP refers to the series of laws, regulations, and guidance that govern various areas of the research, development, testing, manufacturing, and distribution of medicines. Examples of these include: GCP (Good Clinical Practice), GMP (Good Manufacturing Practice), GDP (Good Distribution Practice) and GPvP (Good Pharmacovigilance Practice).
- Being part of the Official Control Authority Batch Release (OCABR) network, which allows for a mutually-recognised batch testing and release of biological medicines, vaccines, blood and plasma products across the EEA by a single Official Medicines Control Laboratory (OMCL), reducing duplicative scientific testing for sensitive or time-critical products.
- Participating in pan-European pharmacovigilance processes, allowing for signal detection and management across the EEA.

- Taking part in the agreement of orphan designation and paediatric investigation plans to ensure that patients experience the benefits of EU incentives for the development of 'orphan' and paediatric medicines, supporting the increased access to medicines for rare clinical conditions and child-specific formulations, including clinical trials for these.
- Sharing of several EU-owned systems that enable sharing and exchange of data, such as EudraVigilance, EudraCT for clinical trials, CESP and the Common Repository.

Clinical Trials

3. Clinical trials are managed nationally in the UK by the MHRA. However, they are relevant to this legislation because:
    - 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. However, these are outside the scope of this Impact Assessment.

Medical Devices

4. The UK is currently a member of the European devices regulatory framework. This means:
    - Being a member of the Medical Devices Coordination Group (MDCG) and its committees.
    - Being a member of the Competent Authorities Medical Devices (CAMD) network (former chair and current member of the elected Executive Group) and its sub-committees.
    - Recognising the CE mark assessment provided by UK notified bodies.
    - Notified Bodies (NBs) based in the UK are able to certify the CE mark on medical devices.
    - Participating in Joint Actions with other member states designed to improve coordination and collaboration across the network in relation to the performance of market surveillance responsibilities.
    - Access to databases (e.g. EUDAMED) providing information on products on the market and pooling information about performance and safety.

Regulation in the context of a no-deal scenario and the EU (Withdrawal) Act

5. As this is contingency legislation, the costs and benefits of the preferred option compared to the static acquis baseline (Option 0.1) are zero. Where there are costs and benefits of the preferred option compared to the static acquis, these described throughout the remainder of this document Without membership of these European medicines and devices frameworks in the event of no deal being agreed with the EU before 29 March 2019, the UK would need to make arrangements for its regulator to take on regulatory processes of medicines, medical devices and clinical trials currently performed at EU level where necessary.

6. The EU (Withdrawal) Act provides the ability to bring EU law into UK law in the event of no deal. The Statutory Instrument (SI) laid under that act is necessary to ensure that medicines and medical devices regulation continues to function in an effective way in such a scenario.

Description of options considered (including status-quo)

7. Options are assessed against a 'dual baseline' of Options 0.1 and 0.2. Given that this is contingency legislation, the costs and benefits of the Option 0.1 baseline are expected to be zero, as

   Option 0.1: Baseline – Static acquis with the UK a member of the European medicines regulatory framework, and pan-European CE marking system for medical devices, and this is the baseline which options are primarily assessed against

   Option 0.2: Do nothing - deficient UK law applies. A full description of what this option would mean is available in Annex A.

   Option 1: The MHRA to become a standalone UK medicines and devices regulator following a principles-based approach to protect public health and to minimise impact and disruption for businesses

   Option 2: The UK accepts decisions of cross-European regulatory bodies without any oversight, influence or additional assessment

   Option 3: The MHRA becomes a standalone regulator requiring full assessment of all products, not taking into account any information already provided to cross-European regulatory bodies.

8. Where there are costs in the preferred option compared to the static acquis in a no deal scenario, these are described throughout the rest of the IA.

9. The benefits of the preferred option compared to the static acquis are expected to be zero in monetary terms. However, the benefits of choosing this option compared to doing nothing, i.e. the rationale for taking the preferred policy approach, are described in narrative terms in this document.

10. The principles determining the preferred option are as follows:

- Pragmatic and proportionate approach in establishing standalone UK regulatory requirements.
- The UK regulator's continued ability to take regulatory action to protect public safety.
- Minimum disruption and burden on business as the UK exits the EU.

11. These principles ensure that:

- Public health is not adversely affected through disruption to the regulation of medicines while at the same time as minimising additional regulatory requirements for businesses need to comply with.
- Businesses have the ability to implement changes and familiarise themselves with regulatory changes within a reasonable timeframe, where possible; this necessitates a pragmatic approach to legislation.
- The UK public continues to have confidence in the safety, quality and efficacy of medicines and medical devices on the UK market through the MHRA continuing to be able to licence medicines and providing relevant safety information about them. This also ensures that businesses are willing to bring new products to market as only medicines and medical devices that meet UK standards would make it to market and would not have to compete with sub-standard products.

12. On this basis, Option 1 is the preferred option in the event of no deal. The other options were not taken to appraisal stage because it was determined that they were unacceptable as they did not fulfil the principles as set out above, particularly in the context of delivering a pragmatic and deliverable solution in the event of a no-deal. Option 2 is not feasible because it does not protect the UK regulator's ability to take regulatory action to protect public safety and is discounted from this analysis. Option 3 is not feasible because it does not minimise burdens on businesses and therefore is likely to delay or deter Marketing Authorisation submissions to the MHRA as the UK exits the EU and is also discounted from this analysis.

Policy objective and overall rationale for intervention

13. The overall approach in the event of no deal being agreed with the EU before 29 March 2019 is for the Secretary of State for Health and Social Care and, acting through the MHRA as a stand-alone medicines and devices regulator, to take any decisions and carry out functions that are currently taken or carried out at EU-level. These would include deciding on applications for marketing authorisations (MAs) which are currently obliged to use the centralised procedure, paediatric matters and orphan status.

14. The MHRA would continue to carry out the wide range of work it currently does on a national basis including medicines licensing, pharmacovigilance, inspections, standards and enforcement. The

MHRA would also take an expanded role in registration, assessment, and post-market surveillance of medical devices.

15. More specific details around how these principles are applied to specific policy decisions are outlined in the costs and benefits sections for each policy issue.

Section 1: Medicines

Batch testing and Qualified Person certification of human medicines

Summary of policy proposal in preferred option

16. As described in the Technical Notice for Batch testing medicines if there's no Brexit deal, in order to continue to protect safety and minimise disruption and protect the medicines supply chain, the UK would recognise batch testing carried out in countries named on a list set out by the MHRA for a limited time. In this scenario, on EU Exit, this list would include EU and EEA countries and those third countries with whom the EU has already made arrangements under article 51(2) of the Directive when the UK leaves the EU.

Benefits and rationale of approach

17. This approach would preserve the status quo and protect the supply chain of medicines in the short term through accepting batch testing, certification and release from trusted countries, including the EU and EEA upon EU Exit.

Costs: Direct Costs

18. As this option preserves the status quo in terms of UK recognition of EU/EEA batch testing, there is no additional cost to industry. Beyond the limited time period mentioned, there would be a cost to industry, however it is unknown when this cost would be incurred.

Data and marketing exclusivity for Marketing Authorisations

Summary of policy proposal in preferred option

19. It is not proposed that there will be any change as a result of EU exit to the data and marketing exclusivity periods enjoyed by the holders of UK national MAs or converted EU MAs.

20. After the UK's withdrawal, the start of data and/or market exclusivity will be the date of authorisation in the EU or UK, whichever is earlier.

Benefits of preferred approach

21. This approach does not represent a change to the status quo. It has been adopted to encourage companies to submit applications for innovative products to the UK as soon as possible (see the wider impacts section a full description of the issue of possible delays) and therefore is beneficial in protecting public health in the UK.

Costs: Direct costs

22. There will be no additional cost to industry unless individual businesses decide to delay their UK market authorisation applications. In this case, they will lose any additional revenue in the UK as a

result of a shortened UK exclusivity period and earlier possible generic entry, there would also be a social cost for society from delayed access to medicines.

Pharmacovigilance

Summary of policy proposal in preferred option

23. 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.

24. 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.

25. 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)) directly to the MHRA. 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.

Benefits of preferred approach

26. This approach maintains the UK's ability to conduct pharmacovigilance activity in the UK, ensuring the safety and efficacy of medicines is monitored once they have entered the market.

Costs: Direct costs

27. There will be the administrative cost to business providing the information to the MHRA for those who market medicines in UK and the EU 27 as they will now have to provide information to the UK and EU systems.

Parallel Imports

28. Parallel import of medicinal products is an important route of supply for medicinal products in the United Kingdom and provides cost savings to the NHS across the UK, as well as alleviating supply issues.

29. Medicinal products that hold a marketing authorisation in another Member State, or which have a central marketing authorisation, and are essentially similar to a product that has been granted a UK marketing authorisation, will still be able to be imported under a parallel import licence. This is

subject to the MHRA being able to obtain the information it needs on the product to be imported to determine if it is essentially similar to the UK reference product, and remain satisfied that the product is essentially similar and thus with safety assured. The parallel import regime will remain limited to EEA States. The MHRA will be able to vary, suspend or revoke a parallel import licence if the UK reference product is suspended, revoked or varied. It will also be able to do likewise if it can no longer be satisfied that a product to be imported remains essentially similar to the UK product: that power will not be exercised before 1 April 2020 and nor will it be exercised in respect of products that were certified by a qualified person in the EEA before Exit.

30. Parallel import licence holders will in future need to be established in the United Kingdom. Those holding licences will have until 31st December 2020 to effect this change if currently established elsewhere in the EEA.

31. Holders of parallel distribution notices, issued by the EMA, in respect of medicinal products that hold a central marketing authorisation will, where the UK is listed in that notice as a destination country, be automatically, and with no fee, issued with a parallel import licence, subject to providing specified information on the products to be imported to the MHRA by 21st April 2019.

Benefits of preferred approach

32. This approach maintains the UK's ability to ensure the safety of products imported for resale in the UK.

Costs: Direct costs

33. There will be the additional cost for parallel importers of paying the annual fee to the MHRA for their new parallel import licenses (for those converted from European Medicines Agency Parallel Distribution notices) and associated variations for packaging as a result of these licenses.

Serious shortage powers

34. This contingency legislation enables regulations to be made to modify the application of the Human Medicines Regulations 2012 to deal with serious shortages of medicinal products. This would replace the regulation making power in the European Communities Act (ECA) for certain limited purposes and would ensure the Government continues to have the power to make temporary changes to the Human Medicines Regulations 2012 to deal with shortages in a No-Deal scenario when we can no longer rely on the ECA to make regulations (because the UK will no longer be in the EU and therefore the ECA will no longer apply). No impact assessment has been undertaken as this is an enabling power and it is not known whether the powers will eventually be used.

Change M1: Legal presence

Summary of policy proposal in preferred option

35. At present, the UK as part of the EU medicines regulatory network, requires a marketing authorisation holder to be located in the EU/EEA. In the event of a deal not being agreed with the EU before 29 March 2019, a Marketing Authorisation Holder (MAH) would have to be established in the UK by the end of 2020. Until a UK MAH is established, a contact in the UK would be required. 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.

36. As is the case today, the UK will require a Qualified Person for Pharmacovigilance (QPPV) to be responsible for delivery of a pharmacovigilance system that covers UK authorised products. In the event of no deal, given that the EU QPPV would not have legal responsibility towards UK authorised products, a QPPV would need to be established in the UK by EU Exit. Those without a current UK presence would have until the end of 2020 at the latest to establish a UK 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 that interim 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 the QPPV.

Benefits of this option (rationale for approach)

37. Legal presence is important in protecting public health by giving the ability to prosecute in enforcement cases. In the event of an adverse incident, MHRA needs to be able to contact companies at any time. The ability to prosecute a MAH in appropriate circumstances is important to deter unsafe practice.

38. The requirement for a QPPV that resides in the UK allows the MHRA to gain access to the pharmacovigilance system data and documentation applied to UK MAs, in order to maintain MHRA's supervisory role over MAH compliance with pharmacovigilance.

Costs: Direct Costs

39. From EU Exit, there would be a cost to industry in establishing a contact person, MAH and QPPV presence in the UK for those who do not already have a UK presence, compared to the static acquis baseline, including a direct cost to change the MAH to a UK MAH. This would include the costs of establishing any premises, familiarisation and administration for the interim contact person or MAH, and QPPV to comply with the new legal requirements, and labour costs for these representatives.

Change M2: New marketing authorisation (MA) assessment routes

Summary of approach in preferred option

40. As the UK would no longer be part of the European medicines regulatory framework in the event of no deal , the MHRA would offer the following new assessment procedures for applications for products containing new active substances alongside the existing 210-day national licensing route (which would continue to operate as now). This would represent additional costs to those firms who currently apply to the EMA for authorisation in all member countries. This would include:

    a) 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. New fees for marketing authorisations under a new national targeted assessment route would be: £62,421 for a new active substance; and £17,330 for a biosimilar.

    b) A full accelerated assessment, for new active substances, with a reduced timeline of no more than 150 days. The fee for this would be the same as the current national assessment route major fee of £92,753.

41. The MHRA would also offer a 'rolling review', for new active substances, which would allow companies to make an application in stages.

42. The existing (210-day) national assessment route would also remain available for MA applications. This route would continue to be available for all MAs, including all new active substances and those that would have gone through the centralised procedure. The existing MHRA national fees for such applications would apply (see gov.uk: https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees).

Benefits of option (rationale for approach)

43. This approach is proposed to ensure that the principle of the UK's ability to protect public safety is upheld while still minimising burdens and processes on business.

44. For targeted assessment, the MHRA would not be seeking to repeat questions or work - it would be focusing its contribution on ensuring the quality, safety and efficacy of the product in the context of clinical use in the UK. The UK decision would only differ from EU in the situations where there is a significant public health concern about the risk/benefit of the product.

45. The proposed targeted assessment fees are based on the incoming mutual recognition (IMR) fee for a marketing authorisation for major application for a new active substance (£62,421) and for a complex abridged application (£17,330) for a biosimilar. The MHRA considers that basing the proposed fees for targeted assessment on existing fees for IMR is merited as targeted assessment requires a similar amount of work by the assessment team as IMR assessment, and therefore the

costs to MHRA are similar. Two fees are required to reflect the different amount of assessment work required for applications involving a new active substance and a biosimilar.

46. The accelerated assessment route would be made available for those products containing a new active substance in order to support the quickest route to the UK market.

47. The 'rolling review' would allow for companies to better manage development risk.

Costs: Direct Costs

48. This would represent an additional direct cost to industry for each application for a new active substance or biosimilar compared to the status quo of applying through the European centralised procedure at the EMA and receiving approval across all EU countries. The level of cost would depend on the UK route selected.

49. For those marketing authorisation holders who previously used the decentralised (DCP) or mutual recognition (MRP) procedures, these routes would no longer exist to obtain a UK MA, and they would now have to apply for a UK MA separately. MHRA fee income changes and costs to business would depend on which proportion of firms selected the UK as a Reference Member State (whereby the MHRA lead the assessment) and how many selected the UK as a Concerned Member State (CMS) (whereby the MHRA decide whether to accept the decision of the RMS), and also on the level of the CMS and RMS fees in other countries.

50. There would also be the administrative cost of the additional application and maintenance of the marketing authorisation, and also the cost of the additional periodic fees associated with keeping the marketing authorisation (for centralised products). For DCP and MRP procedures, there would be the additional cost of national fees.

Change M3: Converting centrally authorised products (CAPs) to UK MAs (grandfathering)

Summary of policy proposal in preferred standalone option

51. Currently the UK is part of the European Medicines Agency, where products can be authorised centrally through a single application. To protect medicines supply, existing CAPs at the EMA would be converted automatically into UK MAs and issued with a UK marketing authorisation (MA) number upon EU Exit. Marketing Authorisation Holders (MAHs) would be given the opportunity to opt out of conversion prior to EU Exit. No fee would be charged for the grandfathering process.

52. MAHs will have one year from EU Exit to provide MHRA with baseline data for CAPs that are converted into UK MAs.

53. In order to process any variations, MHRA will require the baseline data to have been submitted.

54. MHRA will accept a 'basic' baseline data set initially which will enable variation to be processed. The full baseline data requirements will still need to be met within one year of EU Exit.

55. Any product that is holds a UK licence as of 1st April 2019 would be charged a periodic fee almost immediately under existing periodic fee rules (see gov.uk:

https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees)

Benefits of this option (rationale for approach)

56. The rationale of this option is to provide continuity of licences and the medicines supply chain. The proposed approach aims to have the minimum possible additional burden on industry.

Costs: Direct Costs

Industry

57. In terms of transition costs, the MHRA anticipates there would be additional administrative costs to industry who currently sell in the UK and EU27 of providing MHRA with the baseline data in terms of staff time. There are also costs to these businesses of maintaining their UK MA, including the Periodic Fee, legal costs, and administrative costs. This is the same as the recurring costs for new marketing authorisations as outlined in the fees section.

MHRA (HM Government)

58. There would be one-off costs to the MHRA for staffing and IT in order to convert CAPs and variations from EMA to UK MAs. As MHRA is a trading fund, it must operate on a cost recovery basis. In order to incentivise conversion, cost recovery would not be front loaded through a conversion fee. Rather, costs would be recovered by periodic fees on those converted, to reduce burden on industry.

Change M4: Packaging

A) Amending packaging and leaflets for a product on the market

Summary of policy proposal in preferred option

59. Packaging of medicines in the UK currently reflects the UK's status as part of the European medicines regulatory network and would therefore need to be amended to reflect regulatory changes implemented in a no-deal scenario. The MHRA would give industry until end of 2021 (i.e. an additional year after the time required to change MAH) to amend packaging and leaflets for a product already on the market. The amendments should be necessary to include UK administrative information such as UK MAH name and address, UK PL number and details of the batch release site. However, any regulatory intervention that impacts on public health, and would require a change to the public facing information as a result, should be accompanied by amended packaging components reflecting those changes along with the necessary administrative updates as above.

60. The UK would continue to approve shared packs that include administrative information from other jurisdictions, so long as the entirety of the information complies with UK requirements.

Benefits of preferred option (rationale for approach)

61. This approach balances the need to protect public health through the provision of UK-required administrative information with a proportionate and pragmatic response which should allow business sufficient time to provide this informatio

Costs: Direct Costs

62. There would be the administrative and manufacturing cost to industry of amending packaging to include their UK information, however this is likely to be minimised as the UK would accept shared packs which share information from other jurisdiction(s), so long as the entirety of the information complies with UK requirements. This means that although there would be the cost of changing the packaging itself initially, in terms of administration, it should be possible to use the same pack in more than one territory if that is acceptable to the other jurisdiction(s). There would also be cost of variation fees to change the packaging.

B) Falsified Medicines Directive (FMD)

Summary of policy proposal in preferred option

63. The UK is expected to implement the 'safety features' element of the Falsified Medicines Directive in February 2019. In the event that the UK leaves the EU without a deal, UK stakeholders would no longer be able to comply with the EU's requirements to upload, verify and decommission the unique identifier on packs of medicines. Therefore, the legal obligation related to this would be removed for actors in the UK supply chain. Packs containing the FMD safety features would still be accepted in the UK, provided that they are in line with other UK packaging requirements. In the interests of public safety, the MHRA will evaluate the options around a future national falsified medicines framework, taking into account the investment already made.

Benefits of preferred option (rationale for approach)

64. By accepting packs containing EU FMD safety features in the UK, provided that they are in line with other UK packaging requirements, this approach minimises burden on business and protects the medicines supply chain.

Costs: Direct costs

65. This approach has no future additional costs on industry in the event of no deal, provided that manufacturers are in line with other UK packaging requirements. This does not include the previous costs to manufacturers of preparing for the FMD safety features.

Change M5: Paediatric investigation plans (PIPs) and studies

Summary of policy proposal in preferred option

66. MA applications for new medicinal products and applications for new indications, including paediatric indications, routes of administration and new pharmaceutical forms for products with supplementary patent protection would need to demonstrate compliance or partial compliance with a UK Paediatric Investigation Plan (PIP) or have a waiver.

67. Paediatric Use Marketing Authorisations (PUMAs) maybe granted through any appropriate national licensing route and are eligible for 8+2 years data exclusivity/market protection.

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

69. 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.

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

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

72. Where an application has already been made to the EMA and a positive Paediatric Committee (PDCO) opinion has been given, the EU PIP may be adopted as the UK PIP on provision of the same information already submitted to the EMA including the EMA Paediatric Committee (PDCO) summary reports and PDCO opinion.

73. An exception to this would be in cases relating to UK public health where a focussed assessment would be conducted. This would be particularly considered for products covering rare paediatric conditions, including medicines with paediatric only development, or medicinal products to be developed in therapeutic areas that have been identified in the UK as unmet needs. The focussed assessment would include consultation with expert advisory groups and/or Commission on Human Medicines to ensure the proposed drug development plan agreed in the PIP for the product covers the needs and context of clinical use in the UK.

Benefits of preferred option (rationale for approach)

74. In the event of no deal, where the UK chooses to take a ‘standalone’ approach to medicines regulation, the MHRA would seek to provide incentives for marketing authorisation holders (MAHs) of paediatric medicines to bring these medicines to the UK.

75. If an incentive structure is not in place to incentivise MAHs to carry out this work following EU Exit, public health in the UK could face one of two possible scenarios:

    1. New paediatric medicines may come to the UK later than to EMA members, or;

2. New paediatric medicines may not come to the UK at all.

76. An additional consequence is the potential loss of participation of UK paediatric patients in ground-breaking research aiming to support the development of therapeutic options in areas of unmet clinical needs.

77. The introduction of a UK PIP would assist in ensuring the UK public health system has access to new medicines for paediatric use, by having processes and procedures in place so that the MHRA can continue to carry out licensing assessment work for this category of medicine and that MAHs and developers of paediatric medicines have incentives to bring these medicines to the UK. UK has played a significant role in increasing research in medicines for children in Europe; since 2006, the percentage of paediatric clinical trials has risen, and the UK government has supported the development of research infrastructure through the National Institute for Health Research (NIHR), an investment that could be lost if the pharmaceutical industry chooses to conduct studies in jurisdictions only where they have regulatory obligations.

78. Adopting the EU PIP as the UK PIP, given a positive Paediatric Committee (PDCO) opinion and provision of the relevant documents, supports the UK's global collaboration in drug development within the limited paediatric population and thus avoids unnecessary duplication of paediatric clinical trials.

79. The rationale for focussed assessment is to provide the option to ensure that the proposed drug development and paediatric clinical trial(s) meets unmet paediatric needs in the UK, for example in rare conditions or medicines requiring paediatric only development. It would also provide the option to take action if there is a strong objection to the proposed paediatric investigation plan on public health grounds – further strengthening the UK's capabilities to promote ethical and scientifically robust paediatric drug development.

Costs: Direct Costs

80. As with current paediatric work that the UK undertakes on behalf of the EMA, this would be covered by the periodic fee, therefore there is no additional cost to industry beyond the administration costs associated with the additional submission of the PIP to the UK.

Change M6: Orphan designation

Orphan products

81. An orphan drug is one developed for the treatment of a rare condition. In the event of no deal, where the UK chooses to take a 'standalone' approach to medicines regulation, in order to incentivise medicines in a similar way as the EMA does at present, the MHRA would seek to provide incentives for marketing authorisation holders (MAHs) of orphan drugs (following the EMA definition and amending where necessary) to bring these medicines to the UK.

Summary of policy proposal in preferred option:

82. The EU orphan criteria would be amended so that they have UK-specific criteria (in relation to the prevalence of the rare disease in the UK and the satisfactory methods of treatment in the UK and significant benefit).

83. 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.

84. However, the MHRA does not propose to duplicate the EU pre-approval orphan designation, given that this will be available at EU level and that a separate UK only designation is to further incentivise industry to warrant the investment required to resource a separate system. As it is proposed to have UK specific criteria, it would not be possible to simply copy the EU designation for these high value drugs.

Benefits of this option (rationale for approach)

85. In the event of no deal, where the UK chooses to take a 'standalone' approach to medicines regulation, the MHRA would seek to provide incentives for MAHs of orphan drugs to bring these medicines to the UK.

86. If an incentive structure is not in place to incentivise MAHs to carry out this work following EU Exit, public health in the UK could face one of two possible scenarios:

    - New orphan drugs may come to the UK later than to EMA members, or;
    - New orphan drugs may not come to the UK at all.

87. The exclusivity award has been highlighted by stakeholders as being very important to MAHs who develop orphan drugs, and this should be preserved.

Costs: Direct Costs

88. As this option preserves the status quo, there is no additional cost to industry, except for the fee waiver as described in the fees section, change F1.

Change M7: Abridged applications

Summary of policy proposal in preferred option:

89. In the event of no deal, the MHRA would 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, including CAPs that have been converted in UK MAs.

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

91. 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, which in turn cross-refer to Article 6. There would be amendments to the HMRs to transpose these requirements.

92. 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).

Benefits of option (rationale for approach)

93. This option allows for a pragmatic approach to abridged applications, preserving the status quo as far as possible, given that MHRA would not have access to the data provided in support of EU approved products.

Costs: Direct Costs

94. The MHRA expects the impact of this requirement to be minimal because the overwhelming majority of new active substances are approved through the EU centralised procedure and the already approved products would be grandfathered by the UK. Additionally, the MHRA's experience is that there are very few applications made in the UK relying on an EU reference product.

Change M8: Licensing regime for wholesalers importing QP certified medicines

Summary of policy proposal in preferred option

95. As previously announced in a Technical Notice [insert link], the UK will continue to recognise QP certification from EU / EEA countries after EU Exit.
96. However, to ensure public safety, there will be a need to distinguish between those medicines that have been QP certified in the EU / EEA and those which are passing through the EU / EEA in transit to the UK (known as 'introduced medicines').
97. To enable this, all existing holders of UK Wholesalers Licences who import from the EEA will have their wholesale dealer's licence automatically varied to include the operation of import from an approved country for import, subject to providing certain information to the MHRA – if this information is not provided it will be assumed that the wholesale dealer does not wish to have this operation included in their wholesale dealing licence and they will not be able to undertake this type of activity under the licence. The Wholesalers Licence for Import will allow UK wholesalers to import medicines from approved countries for import, which are countries for which the UK recognises QP certification: initially those countries will be EU and EEA countries.

98. Holders of this new licence will be required to put in place an assurance system to ensure any medicines they import have been QP certified. **This will not require any QP re-certification**. The assurance system will be overseen by a new role of Responsible Person for Import (RP-I), for which guidance will follow. Wholesalers will have a 2-year period after EU Exit to be fully compliant, but will be expected from EU Exit to have in place assurance systems to avoid introduced medicines entering the UK supply chain without QP certification.
99. A Manufacturers Licence (MIA) for Import will continue to be required for all other forms of import of human medicines being supplied onto the UK market, in line with the existing regime.

Benefits of preferred option (rationale for approach)

100. This approach is vital in helping to protect the medicines supply chain in the event of no deal with the EU. Upon the UK exiting the EU, EU/EEA countries would become third countries and measures put in place to distinguish between those medicines that have been QP certified in the EU / EEA and those which are passing through the EU / EEA in transit to the UK (known as 'introduced medicines') will ensure safety and confidence in medicines is protected as the necessary regulatory checks will be made.

Costs: Direct Costs

101. The new Responsible Person for Import would have increased expertise requirements in some circumstances compared to the previous Responsible Person, therefore may command a higher salary, however the number of people who were Responsible Persons who will be able to hold this role is uncertain.

Change M9: Recognition of prescriptions

Summary of policy proposal in preferred option

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

103. Human Medicines Regulations 2012 define who is eligible to issue prescriptions that can be dispensed in the UK.

104. The regulations would be amended so that the UK recognises prescriptions from those countries on a designated country list from day one. This list would initially include EU and EEA countries.

105. For a prescription to be eligible, the prescriber must be of equivalent professional status to a profession that is eligible to prescribe in the UK. This is to ensure that the UK will be able to monitor the standard of the professions which can prescribe outside the UK to be dispensed in the UK.

Benefits of preferred option (rationale for approach)

106. At present the EU cross border healthcare directive means that prescriptions issued in any member (or EEA) state can be dispensed across the EU. This would cease to apply to the UK after

the end of the implementation period or from March 2019 in the case of no-deal. By recognising EU and EEA states in the legislation, the status quo is preserved, and the UK continues to take a pragmatic approach to safety while enabling business continuity.

Costs: Direct Costs

107. This option largely preserves the status quo in the UK. The EU does not maintain a central list of professions who may prescribe so this could mean that some professions will no longer be covered. Data is not collected on the number of EU/EEA prescriptions currently received from different professions. However we believe the impact of this will be negligible as the key country for whom recognition of prescriptions is used is the Republic of Ireland and all eligible prescribers in the Republic of Ireland are of equivalent professional status to a profession eligible to prescribe in the UK. These prescriptions are all dispensed privately at no cost to the NHS.

Section 2: Clinical Trials

Change CT1: Use of designated country lists, including for legal presence and importation of investigational medicinal products

Summary of policy proposals in preferred option

108. The MHRA has developed lists of countries where activities relating to clinical trials can be performed. There would be three such designated country lists in a no deal scenario:

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.
    - advanced therapy medicinal products (ATMPs) and products with 'special characteristics' that have an MA in the designated country would not be subject to usual special provisions for ATMPs 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).

109. For the supply of IMPs from EEA, sponsors will have 12 months to comply with this.

110. Upon EU Exit, all EU/EEA states would be on all three lists. ICH countries would be included in the second list.

Publishing trial results

Summary of policy proposals in preferred option

111. In the short term, those running trials should continue to use existing and established international registries such as EudraCT (EU), ISRCTN (International Standard Randomised Controlled Trial Number) registry, ISRCTN (UK), and ClinicalTrials.gov (USA) to ensure that UK patients are aware of any clinical trials. The UK will continue to make information about trials being conducted in the UK available to patients and clinicians via the UK Clinical Trials Gateway.

112. By the time the EU's new portal goes live (as part of the new CTR), the UK will have its own specific hub that would give both the UK patients and researchers a single reference point for all UK trials.

Benefits of preferred option (rationale for approach)

113. The UK's overall intention is to align transparency provisions with those currently operating in the EU, in order to eliminate the need for companies to duplicate efforts.

Costs: Direct Costs

114. There would be no immediate cost to business as those running trials can continue to use existing registries.

Safety reporting

Summary of policy proposals in preferred option

115. As now, the UK will require sponsors to submit all UK relevant suspected unexpected serious adverse reactions (SUSAR) reports to the MHRA. The only difference is that these would need to be submitted via UK based IT systems (as the option to report via EMA systems will no longer exist).

116. Annual safety reports will continue to be required to be submitted to the MHRA for all UK trials as they are now.

Benefits of preferred option (rationale for approach)

117. This option allows for continuity of clinical trials regulation as the UK will continue to be able to receive unexpected serious adverse reaction reports.

Costs: Direct Costs

118. There would be the additional administrative cost to business of submitting via UK based IT systems.

Assurance of IMPs being imported into the UK

Summary of policy proposals in preferred option

119. For IMP coming into the UK, the UK will recognise testing and QP certification done in an approved country (which would initially include all EU/EEA countries, but would be subject to review).

120. All importers of IMPs into the UK will require a Manufacturers Licence (MIA) (IMP). For IMPs coming from countries on the approved country list (initially all EU / EEA countries) the MIA(IMP) holder will required to put in place an assurance system to check these IMPs have been QP certified in the EU or EEA. This assurance system must be overseen by a QP. Note, such IMPs would not require re-certification. IMPs coming from other countries would, as today, require QP certification in the UK by the MIA(IMP) holder.

121. Third party MIA(IMP) holders already exist, who act as the importer for IMPs from existing third countries to UK Clinical Trials site.

Benefits of preferred option (rationale for approach)

122. The designated country list would minimise burden on business by allowing certain activities relating to clinical trials to be performed in countries where the UK deems this safe to do so due to regulatory equivalence, thus maintaining the status quo where possible. The requirement for a UK(IMP) holder to verify that the necessary testing and QP certification has taken place in the EU/ EEA is important to ensure the quality of investigational medicines used in the UK. This proposal would also protect public health by excluding countries where it is not deemed safe to carry out these activities.

Costs: Direct Costs

123. There would be the cost to clinical trial sponsors of engaging the services of an MIA(IMP) for assurance to check IMPs have been certified in the EU or EEA.

Section 3: Medical Devices

Summary of policy proposal in preferred option

124. In the UK, all medical devices are subject to EU legislation, which requires a manufacturer to place a CE mark on their product to attest compliance to applicable standards. Manufacturers of low risk devices (Class I medical devices, Self-certified IVDs) can self-declare conformity to the legislation before affixing the CE mark.

125. Higher-risk devices (such as Class IIa, IIb and III medical devices and in vitro diagnostic devices (IVDs) must be certified by an independent conformity assessment body, called a Notified Body (NB), before the CE mark can be affixed. NBs are monitored by their national authority (the MHRA in the UK), following a process of designation which involves joint audits by two other national authorities and the European Commission.

126. If the manufacturer is based outside of the EU they appoint and 'Authorised Representative' to do this, their responsibilities are:

a. Informing the competent authorities of their registered place of business, and of the devices and certificates (for the devices listed above)
b. Keeping certain information at the disposal of the national authorities, such as declarations of conformity and technical documentation
c. They may have further responsibilities (such as checking labelling and instructions for use for compliance), but these depend on the mandate between the manufacturer and the authorised representative.

127. In a no deal scenario, the UK's current participation in the European regulatory network for medical devices would end, and the MHRA would take on the responsibilities for the UK market that are currently undertaken through the EU system.

Conformity of Products

128. For a time-limited period, the MHRA will continue to allow devices to be placed on the UK market that are in conformity with the applicable EU legislation. Relevant labelling requirements will continue to apply including the requirement for products to carry a CE mark and devices which currently require conformity assessment by a Notified Body must have a valid CE certificate.

129. If there's no deal, UK-based NBs will no longer be recognised by the EU after 29 March 2019, meaning the devices they have certified will no longer be in conformity with the applicable EU Directive. As such these products will not be able to be placed on the EU market.

130. To support the continuity of supply of products to the UK market, the MHRA will give UK-based NBs an ongoing legal status and continue to recognise the validity of certificates that they issued prior

to 29 March 2019. This will allow products covered by certificates issued by UK-based notified bodies to continue to be placed on the UK market after 29 March 2019.

Market Surveillance of Devices

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

Registration of Medical Devices on the UK Market

132. After 29 March 2019, all medical devices, active implantable medical devices, in vitro diagnostic medical devices (IVDs) and custom-made devices will need to be registered with the MHRA prior to being placed on the UK market.

133. These registrations will have a grace period to allow for time for compliance with the new registration processes set out below:

4 months	Class III medical devices Class IIb implantable medical devices Active implantable medical devices IVD List A
8 months	Class IIb non-implantable medical devices Class IIa medical devices IVD List B Self-test IVDs
12 months	Class I medical devices Self-certified IVDs Class A IVDs

134. For manufacturers based outside of the UK, they must appoint a 'UK Responsible Person' to register devices with the MHRA. This includes manufacturers who were previously based outside of the EU and had appointed an Authorised Representative. In a no deal scenario, 'Authorised Representatives' based in the UK will no longer be recognised by the EU after 29 March 2019. The 'UK Responsible Person' must:

a. Verify the declaration of conformity and technical documentation have been drawn up, and where applicable ensure that a conformity assessment has been carried out by the manufacturer.
b. Keep available copies of technical information for the Secretary of State and provide them with information and documentation necessary to demonstrate conformity.
c. Forward to the manufacturer any request by the Secretary of State for samples or access to a device.
d. Co-operate with the competent authorities to mitigate risks posed by devices.
e. Immediately inform the manufacturer of issues and complaints with the device.
f. Terminate the legal relationship with the manufacturer if the manufacturer acts contrary to its obligations under the Regulations

Costs: Direct costs

135. There will be the direct cost to business of applying to register medical devices on the UK market, which includes fees and administration costs.

Benefits

136. If there's no deal, the UK's current participation in the European regulatory network for medical devices would end, and the MHRA would take on the responsibilities for the UK market that are currently undertaken through the EU system to ensure the continued safety of patients. The changes are being made to strengthen the MHRA's market surveillance and assurance role allowing it to take on roles formerly conducted by the wider EU regulatory network, ensuring patient safety.

Section 4: Fees

Change F1: Fee waivers for orphan products

Summary of policy proposal in preferred option

137. The EMA currently offers waivers for orphan pharmaceutical products. The MHRA, as a standalone regulator in the event of no deal, 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. This would include:

- 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).

Benefits of preferred option (rationale for approach)

138. Incentives are important to ensure that MAHs continue to carry out this work and bring orphan products to the UK market. The fee waivers help to incentivise bringing orphan products to the UK.

Costs: Direct Costs

HM Government

139. The preferred option would introduce additional costs to HM Government.

Change F2: New/amended MHRA fees for six processes/services previously provided centrally by EU/EMA

Summary of policy proposal in preferred option

140. In the event of no deal, six other processes/services currently undertaken by the EU / EMA would need to be carried out in the UK in order to protect medicines supply and provide regulatory continuity. The MHRA is therefore proposing new MHRA fees for those existing EU/EMA processes for introduction upon Exit. 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. These are additional costs for businesses who currently sell in the UK and the EU27.

141. MHRA would charge fees for this work, which includes:

142. A fee of £8,309 for certification of a new Plasma Master File (PMF); a fee of £277 for a certified annual update of a PMF involving epidemiology updates only; and a new fee of £734 for a certified annual update of a PMF where there are significant changes to safety-related information.

143. A fee of £8,309 for certification of a new Vaccine Antigen Master File (VAMF).

144. Fees of £8,309 to undertake assessment of a Pharmacovigilance Post-Authorisation Safety Study (PASS) protocol, and £8,309 to undertake assessment of a PASS results.

145. A fee of £51,286 to undertake a Pharmacovigilance Major Safety Review.

146. A fee of £890 to undertake a single assessment of Pharmacovigilance Periodic Safety Update Reports (PSURs).

147. Amend Renewals fees so that all new medicinal products (new active substances), whether authorised nationally, or through a centralised procedure that will become a national licensed medicine from EU Exit, are subject to a renewal fee of £9,682 five years after the licence was first granted

148. Additionally, the MHRA would explore the possibility of offering fee waivers for MA applications for medicines considered to be orphan products to encourage such products on to the UK market (see Orphans section above).

Benefits of this option (rationale for approach)

149. By charging fees to industry, the MHRA is able to continue protecting UK public health by bringing regulation of medicines currently assessed by the EMA in-house. The implications of this option are that:

a) The MHRA is able to take on work in the above areas, as the Agency would be able to recover its costs – in compliance with Trading Fund rules against cross-subsidy.

b) The MHRA recovers its costs when undertaking work in the above areas, avoiding the need for the Department of Health and Social Care (DHSC) or HM Treasury (HMT) to subsidise MHRA activities – in violation of Trading Fund rules – which would have implications for other public spending priorities.

150. Charging these fees would allow consumers of medicines in the UK to continue to have confidence of the safety and efficacy of medicines on the UK market and incentivise manufacturers to place them on the UK market.

Costs: Direct Costs

151. These fees represent an additional cost to industry per product for the services listed in order to stay eligible for sale on the UK market in addition to the remaining EU27 countries. This analysis does not take into account that EMA fees could change following the UK's departure from the EU.

Section 5: NIBSC

Change N1: Independent UK batch testing of biological medicines and associated fees

Summary of policy proposal in preferred option

152. The UK is currently part of the EU Official Control Authority Batch Release (OCABR) network. In the event of no deal, where the UK is not part of this network, a new power in the Human Medicines Regulation HMRs would enable the licensing authority to require UK certification of batches (immunological medicinal products or a medicinal product derived from human blood or plasma) by the National Institute for Biological Standards and Control (NIBSC), and a prohibition on sale or supply until such testing takes place, unless the batches have been certificated in line with the terms of a Mutual Recognition Agreement (MRA) agreed with the UK. Where no MRA is in place, the UK will decide on a risk-based approach whether to waive the associated laboratory testing for some products/batches and replace it with a paper-based assessment of data.

153. EU Official Control Authority Batch Release (OCABR) certificates issued prior to 29 March 2019 would be accepted by the UK, whether they have been issued by the UK or another EU OCABR laboratory.

154. There would be a new statutory fee to enable NIBSC as the UK Official Medicines Control Laboratory (OMCL) to charge for OCABR certification and testing in the UK, broadly the same as the current fees charged by NIBSC in its role as an EU OCABR laboratory. Proposed fees are shown below, based on the existing fees tariff.

Price Bands	Proposed Certification Fee (£)	Proposed Laboratory Testing Fee (£)	Proposed Combined certificate/lab testing fee	Current NIBSC batch testing fee
Plasma pools, 3, 5 and 6 tests only	£90	£90 for 3 tests £135 for 5 tests £140 for 6 tests	£180 for 3 tests £225 for 5 tests £230 for 6 tests	£180 for 3 tests; £215 for 5 tests; £230 for 6 tests
Band A	£305	£1,355	£1,660	£1,660
Band B		£1,605	£1,910	£1,910
Band C		£2,035	£2,340	£2,340
Band D	£677	£3,013	£3,690	£3,690
Band E		£5,733	£6,410	£6,410
Band F		£9,673	£10,350	£10,350
Authorised Copies	n/a	n/a	£50	£50

Benefits of this option (rationale for approach)

155. Introducing a fee tariff for NIBSC that enables the UK competent authority to continue its critical role in protecting public health. This would allow NIBSC to certify or re-test products to ensure their safety and efficacy for use in the UK.

Costs: Direct Costs

Industry

156. The preferred option would in some cases bring about increased costs to industry, as batch-release activities carried out in the EU27 for batches to be used in the UK and elsewhere in EEA countries would now require either certification or re-testing and certification for use on the UK market. Where batches are tested and used in the UK only, there will be no increase in costs to industry.

Section 6: Rationale and evidence that justify the level of analysis used in the IA (proportionality approach)

Context in terms of EU Exit

157. This impact assessment relies on costs and benefits identified through policy development, research and meetings with industry, in addition to further responses from the no deal consultation.

Section 7: Risks and assumptions

Risk that industry is not sufficiently prepared for the additional requirements of a no-deal EU Exit under a standalone UK regulator in the proposed preferred option

158. Overall, this contingency legislation is aimed to be of benefit to businesses and help them to prepare for the possibility of the UK leaving the EU without a deal on 29 March 2019. In the event of no deal the preferred option is to minimise burden on business while protecting public health. There is a risk, however, that some businesses would not be prepared in time for these changes in legislation, in particular those changes which are resource intensive and where time is limited. This could risk disruption to the medicines supply chain. There is also a risk that medical device manufacturers may not be re-certified by an EU27 Notified Body in time. This could have an impact on the supply of medical devices in the UK.

159. Action is underway to communicate to business and support preparations. There is some evidence that businesses are taking steps to prepare for EU exit in a July 2018 report - the EMA[1] contacted over 180 marketing authorisation holders (MAHs) of 694 human and veterinary centrally authorised medicinal products that are based in or have control procedures undertaken in the UK and found that overall, MAHs of centrally authorised medicines are taking steps to make the necessary changes to their marketing authorisations to prepare for the withdrawal of the UK from the EU.

160. However, one of the principles of MHRA's approach to this contingency legislation is to take a pragmatic and proportionate approach to regulation and ensure where possible that businesses have adequate time to implement changes. As outlined in the preferred policy option, transitional arrangements for the majority of changes have been provided to mitigate these impacts.

161. The government has published technical notices relating to certain elements of EU exit and medicines and devices regulation in order to assist business in preparing for the possibility of no deal being agreed with the EU before 29 March 2019 and to minimise this risk. These are available here. A further guidance notice was published on 3 January 2019 outlining the government position

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/07/WC500251842.pdf

following DHSC and MHRA's public consultation, in order to provide further guidance to business, this is available here.

162. The MHRA has notified CAPs license holders of the decision to convert CAPs licenses and requesting them to notify the Agency whether they are opting out of conversion.

163. MHRA and DHSC will continue to review business preparedness for a no deal being agreed with the EU before 29 March 2019 and act accordingly.

Other risks and assumptions

164. There is some uncertainty around the desirability for businesses in applying to a UK regulator and how this would affect public health and access to medicines.

165. Specifically, there is uncertainty on what proportion of businesses that would continue to pay the periodic fee for grandfathered CAPs. Also, as discussed in the public health impacts section which follows in the next section of this document, there is uncertainty around when companies would submit applications for new and innovative medicines to the UK as a standalone regulator and to what extent this would impact on public health. MHRA will continue to review the evidence in this area.

Section 8: Wider impacts

Medicines prices and trade effects

166. In the event of no deal, duplicating regulatory processes between the EU could have a number of effects on pharmaceutical businesses and other organisations. For manufacturing authorisation holders (MAHs) of generics, biosimilars, and established new medicines authorised through the centralised procedure, there would be duplication of MA maintenance for CAPs and other additional processes to comply with as outlined in this Impact Assessment. It is likely manufacturers would seek to recoup these additional regulatory costs through price increases, which would affect NHS budgeting and spending choices, however the exact effects are uncertain.

167. For prospective manufacturing authorisation holders of these medicines, duplicated licensing procedures may act as a disincentive to apply for marketing authorisation in the UK, delaying patient access to new treatments and biosimilars. In this instance there is the possibility of NHS cost savings due to the high price of innovative medicines, however the wider economic costs of any public health impacts from inferior treatment options could cancel out any financial savings made.

168. It is also important to note that this IA only examines the impacts on business in terms of UK fees and does not examine any possible changes in EMA fees if the UK was to leave the EMA, and how this could impact businesses.

169. As some measures in this contingency legislation constitute non-tariff barriers to trade, this could have an impact on exports of medicines from the UK. The long-term effects would be uncertain due to future trade policy decisions in a scenario in which the UK leaves the EU without a deal.

Public health impacts

170. In the event of the UK leaving the EU without a deal, some third-party analysis has suggested that there could be delays in new innovative medicines coming to the UK market, once the UK has legislated to become a standalone regulator.

171. The evidence base for this area of concern is summarised below.

172. Centre for Innovation in Regulatory Science (CIRS) data analysed by the Office for Health Economics[2] for authorisations in the years 2013-2015 shows a 2-3 month median submission lag between applying to the EMA versus selected third country authorities, namely Health Canada, SwissMedic, and Australia's Therapeutic Goods Agency (TGA).

173. Using the same dataset, between 5% and 15% of submissions were submitted one year after the EMA.

[2] https://www.ohe.org/sites/default/files/Technical%20Annex%20-%20final.pdf p.24

174. Using the same dataset, 45% of submissions to EMA were not submitted to all three of the above comparators – SwissMedic did not receive 22%, TGA did not receive 29%, Health Canada did not receive 38%.

175. Separate CIRS analysis[3] showed that the size of the submitting company could also be a key factor – companies with a 2016 R&D budget under $3bn were shown to have larger submission gaps between the EMA and the US Food and Drug Administration (FDA), and third countries.

176. As the circumstances of EU Exit are without precedent, the CIRS figures have used proxy data from comparable national regulators outside the EMA network. However, this does not consider ways in which the UK may be a more attractive market than these proxies, or ways in which the UK can make itself a more attractive market, or the regulatory alignment of these proxy countries.

177. The pragmatic and proportionate approach to targeted assessment as outlined in this document is designed to mitigate the risk outlined above. Furthermore, the UK is also offering a new accelerated assessment route for innovative products with an overall shorter timeframe of 150 days than the EMA standard timeframe of 210 days.

Small and micro business assessment (SaMBA)

178. The number of small and medium businesses in the UK according the Office for Life Sciences, which will likely fall under the scope of parts of this legislation is set out below. It would be disproportionate to outline how many SMEs are affected by each individual proposal in the IA.

BioPharma Core	SME		NON-SME		Total
Number of businesses	523	78%	150	22%	673
Turnover (£bn)	0.8	2%	32.5	98%	33.3
Employment	4,805	7%	59,315	93%	64,120

BioPharma Service & Supply Chain	SME		NON-SME		Total
Number of businesses	1,221	88%	172	12%	1,393
Turnover (£bn)	1.7	11%	13.2	89%	14.9
Employment	13,561	25%	41,343	75%	54,904

Med Tech Core	SME		NON-SME		Total
Number of businesses	2,264	87%	340	13%	2,604
Turnover (£bn)	3.8	21%	14	79%	17.8
Employment	31,153	32%	66,159	68%	97,312

[3] Bujar M, McAuslane N, Liberti L. 2018. *R&D Briefing 67: New drug approvals in six major authorities 2008 – 2017: Focus on the availability of medicines and company size*. Centre for Innovation in Regulatory Science. London, UK. p.14

Med Tech Service & Supply Chain	SME		NON-SME		Total
Number of businesses	858	88%	121	12%	979
Turnover (£bn)	1.3	29%	3.1	71%	4.4
Employment	8,721	36%	15,829	64%	24,550

179. The EMA Small and Medium Enterprises (SME) waiver for orphan medicines would be mirrored in legislation (excluding pre-approval designation stage). MHRA notes the importance of financial assistance for small and medium businesses and the UK would continue to provide incentives that it currently provides domestically, including the current 'Payment Easements for Small Companies' scheme. In order to ensure public health spending is protected initially on exit other EMA SME waiver incentives, or any other incentives would not be brought into UK law immediately, however they would be reviewed as part of the overall fees policy cycle, with data gathered on the application levels of SMEs to the MHRA. (See post-implementation review section at the end of this document.)

Section 9: Summary and preferred option, with description of implementation plan and review

Preferred option

180. In the event of the UK leaving the EU without a deal, the preferred option, in the context of this impact assessment, is for the MHRA to become a standalone medicines and devices regulator and implement the changes as outlined in this impact assessment and in more detail in the main consultation document.

181. The MHRA and DHSC will continue to communicate with stakeholders on contingency plans for a no deal exit and issue guidance when appropriate.

Post implementation Review

182. This contingency legislation would not be regularly reviewed under a statutory review clause. However, as part of its internal processes, the MHRA regularly reviews its fee levels internally and this will be the case with fees introduced as a result of EU Exit. The MHRA, with support from DHSC, will also be producing a review of the incentives introduced as part of the EU Paediatric Regulation which will inform any future policy decisions in that area. The MHRA would conduct internal monitoring of application volumes for various services post-Brexit in a no-deal scenario to inform future policy decisions in the area of medicines regulation.

Annex A: Explanation of what 'do nothing' means for the regulation of medicines, medical devices and clinical trials

Medicines

The practical implications of not proceeding with contingency legislation would be the UK's medicines regulation system becoming unable to properly protect public health, with immediate effect from our departure from the EU. It would mean the UK would have little control over those medicines authorised through the EMA processes including the higher risk biological medicines on the UK market, which would bring public health risks, unless mitigated by other means. In this scenario new medicines that are licensed by the EMA would be allowed on the UK market, despite the UK having had no involvement in the assessment of these new medicines. It would, as a minimum, hinder the UK's ability to resolve any safety problem, indeed it is unclear that the UK would have the power to make an urgent public health suspension of an EU authorised medicine, as this power is only available to Member States. The UK's ability to make urgent safety variations to medicines would be compromised, due to lack of clarity in the legislation once the UK is no longer a Member state. The SI will also continue to enable the MHRA to authorise parallel imports so far as possible when no longer a Member State. Such imports save the NHS millions of pounds annually.

Medical Devices

This SI will make provision for the Secretary of State to register all classes of medical device placed on the market in the UK. If the SI is not brought forward and there is no legislative power to require registration of high-risk medical devices with the relevant UK authority, there could be very real risks to patient safety, particularly with regards to product safety notices and the recall of unsafe products. Additionally, this SI would remove numerous references to the Commission, the EU and Member States. This is necessary because in a no deal scenario there will be no UK notified bodies operating as they do now in the medical devices sphere and to protect public health; the Secretary of State will need to be in a position take on some of the vigilance work which those bodies would otherwise have undertaken. Apart from the potential to have serious consequences on access and patient safety, large pharmaceutical companies and suppliers would lose their confidence in continued operation and so impact the life sciences sector in general. Implementing this legislation is an opportunity for the MHRA to position itself as an international regulator for medical devices.

In addition, if this SI did not proceed, it is possible that many medical devices would no longer be valid in the UK at the point of Exit. This is due to these devices having CE Marks from UK-based Notified Bodies; once we leave the EU these CE Marks would no longer be valid, and so unless these have been transferred to EU-based Notified Bodies (and without any provision being made in UK law for their continued lawfulness) these could not lawfully remain on the UK market due to the lack of a valid CE Mark.

Clinical Trials

If the current Clinical Trials Regulations were not fixed, then the most important risks are to patient safety as adverse reactions would not be reported to the UK, unless mitigated by other means. There would be a lack of oversight of the importation of IMPs from the EU which may also have safety implications. The existing UK legislation would also contain many senseless references to the EU/EEA, which may create confusion within the research community and discourage researchers from conducting trials in the UK. Therefore, the agency may no longer be perceived as a leader in this area or involved in key decision-making processes.