



## **ABPI-BIA submission to MHRA consultation on EU Exit no-deal contingency legislation for the regulation of medicines and medical devices**

**1 November 2018**

*The ABPI and BIA have worked together to develop this joint submission to the MHRA consultation. We have provided our members' views on how the MHRA's 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. This consultation covers no-deal proposals on medicines, clinical trials and medical devices.*

*The full questions list and consultation documents published on 4 October can be downloaded here: <https://consultations.dh.gov.uk/mhra/mhra-no-deal-contingency-legislation-for-the-regul/>*

### **Summary**

The ABPI and BIA position is and remains that close cooperation with the EU in the regulation of medicines, including mutual recognition of regulatory activities and quality testing, is essential in ensuring that patients in the EU and the UK can continue to access safe and effective medicines.

The ABPI and BIA believe that a no-deal Brexit would significantly damage public health and the UK life sciences sector and that this must be avoided at all costs. We continue to advocate this position.

We welcome the opportunity to contribute to the MHRA and DHSC consultation on the future of the UK medicines and medical device regulation in case of a no-deal Brexit. We acknowledge the MHRA's commitment to ensuring continuity in medicines regulation despite the uncertainty surrounding Brexit and would like to thank the Agency for its engagement with us to date. We welcome the opportunity to respond to the consultation and to comment on the future of medicines and medical device regulation in the event the UK and EU do not reach agreement on the Withdrawal Agreement.

Should the UK and the EU-27 agree the terms of a structured withdrawal, with an associated implementation/transition period, we trust that the MHRA will again engage with stakeholders on the best approach to medicines and medical device regulation in those circumstances.

Before setting out our detailed responses to the consultation questions below, we would like to make some general remarks on the consultation.

We acknowledge that the proposed legal text is indicative only and that the wording might change in the final draft. Therefore, we have not commented in detail on the proposed drafting in our responses. We also appreciate that section 8 of the European Union (Withdrawal) Act 2018 limits the MHRA's ability to go beyond the legislative changes "*appropriate to prevent, remedy or mitigate –(a) any failure of retained EU law to operate effectively, or (b) any other deficiency in retained EU law*" arising from Brexit. This means there is inevitably scope for greater detail and clarity in a number of areas, including on the regulatory procedures to implement the changes contemplated by the statutory instruments.

Much of this detail will inevitably find its way into further legislation, policies and guidance that will provide greater clarity. We trust that the Agency will consult and engage with the life sciences industry on all relevant measures going forward. An ongoing constructive dialogue over the coming months will help to ensure the proper functioning of the pharmaceutical regulatory regime for the benefit of patients.

While a no-deal scenario is of course one we hope we can avoid, this consultation and the proposed statutory instruments address many of the consequences of a no-deal Brexit. The ABPI and the BIA are therefore generally supportive of the proposals made in the consultation. However, we have some key concerns about the suggested approach in the following areas, as described in more detail in our responses to the consultation questions:

- The potential impact on public safety of removing certain legal obligations under the Falsified Medicines Directive;
- The lack of incentives linked to research and development of orphan medicines;
- The proposal for UK paediatric investigation plans;
- The practical details of the proposed new targeted assessment route;
- The proposed requirements for data provision for grandfathered centrally-authorised products; and
- The challenges of the proposed approach on packaging.

Moreover, we are also concerned that the proposal for data and market exclusivity for marketing authorisations is not being consulted on. Data exclusivity is a critical incentive for innovation and therefore highly important to the life sciences industry. For this protection to fulfil its intended function in recognising the enormous investment lying behind clinical trials for new medicines, it is vital that the term should be connected to the actual date of grant of a marketing authorisation in the UK which enables its holder to place the medicine on the UK market. The terms of data exclusivity and other protection (SPCs

and orphan exclusivity) may influence the choices made by companies and therefore the activities of the regulatory authority.

The ABPI and the BIA trust that the MHRA and Government will consider and address these concerns as they work towards the final statutory instruments. We would like to stress our ongoing commitment to work with the MHRA to ensure that patients in the UK continue to benefit from the UK's world-leading medicines regulatory regime.

## **Section 1 Medicines – Changes M1–M9**

### **Change M1: Legal presence**

#### **Summary of proposal**

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.

**Q6:** *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?*

We agree that a transition period is required to ensure legal presence in the UK. However, there is inconsistency in the time frame of the transition period and certain aspects need further clarification.

Further guidance is required from the MHRA on the scope of legal accountability for the new UK QPPV role in order to understand what type of person is required for the role. The accountabilities should be limited to those that are critical to protecting the safety of UK patients and should be clearly defined.

It would be beneficial if the transition period for appointing a UK QPPV could be applied to all companies whether or not they currently have a UK presence as they may not have suitable staff to fulfil the role of UK QPPV from day one. This transition period is vital to allow enough time to identify and appoint a suitable person as UK QPPV and also operationalise the role of the UK QPPV into MAH procedures.

The requirement to register a UK QPPV via a variation means that companies will first need to submit a baseline eCTD for all grandfathered CAPs prior to registering the QPPV, if the proposed process for grandfathering CAPs (Change M3) is implemented; this presents significant challenges (see responses to Questions 9 and 10). This will affect not only grandfathered CAPs, but all other UK MAs held by the MAH, as maintaining 2 QPPVs (UK and EU) for the UK adds complexity and is undesirable.

It would be preferable to implement a simple administrative procedure to register the UK QPPV for all concerned products.

## **Change M2: New Marketing Authorisation assessment routes**

### **Summary of proposal**

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.

**Q7:** *Do you agree with the proposed new targeted assessment process?*

**YES**

*Please explain your answer*

The ABPI and BIA welcome the proposed introduction of new assessment procedures that aim to facilitate approval of new medicines in the UK, while minimising the burden for businesses.

We agree in principle with the concept of the new targeted assessment process; it appears to be a pragmatic proposal that is in the spirit of models of regulatory collaboration that are being considered in other regions. There are, however, several points that the ABPI and BIA would like to be addressed in the SI and/or in supporting guidance with respect to the targeted assessment:

- The final guidance needs to be clear that the choice of application route is at the applicant's discretion, as applicants need clarity and predictability on the procedure and anticipated timelines prior to submission. Whilst the draft legal text (page 4) gives the licensing authority discretion over the mechanisms that allow for the use of targeted assessment, it should be clarified that the choice of application route remains with the applicant.
- The consultation indicates that MHRA would not be seeking to repeat questions or work, and that UK decisions would only differ from EU in certain circumstances. Such a commitment is welcomed, but we note that the draft legal text in this respect is less clear ("the licensing authority may, if it considers it appropriate, have regard to"). There should be a firm commitment to follow the EU unless there is strong reason to differ. The UK decision should only differ from the EU where there is a "significant public health concern", as stated in the Impact Assessment (the word "significant" is missing from the consultation). There also needs to be clarity on

what “significant public health concern” means and that any concern raised will be justified by MHRA; as a basis for UK guidance, reference could be made to the [Commission guideline on definition of potential serious risk to public health in context of Art.29\(1\) and \(2\) of Dir.2001/83/EC, Mar 2006](#), which applies in the EU Mutual Recognition and Decentralised Procedures.

- We support the proposed 67-day timeline for granting a UK marketing authorisation, although we note that this timeline is not mentioned in the Impact Assessment or draft legal text. This timeline should be confirmed, as should the timelines and procedure to be followed in the (exceptional) cases where the UK decision differs from the EU. A lengthy appeal procedure should be avoided.
- The proposed 67-day timeline implies that the application is expected immediately following the CHMP Opinion, so that the UK authorisation can be granted no later than the Commission Decision. Companies may not have the capacity to submit in the period around the CHMP Opinion. There needs to be flexibility allowed for the timing of the UK submission (before or following the CHMP Opinion), as preferred by the applicant, recognising that relevant updates to the scientific dossier may need to be provided.
- Use of the same dossier submitted to the EMA is welcomed, but clarity is needed on how this integrates with MHRA’s proposals for PIPs and orphan designations in the UK (Changes M5 and M6). Where targeted assessment is used, the UK should align with EU decisions on the PIP and orphan designation for the product concerned, otherwise applicants will face an additional burden with addressing different scientific dossier content. Specifically, in cases where the UK has adopted the EU PIP decision (as proposed in Change M5), there should be no need for a UK PIP compliance check, as this must already have been completed for the EU.
- The consultation document lists specific assessment reports that the applicant should provide. Flexibility needs to be allowed in case one of these reports has not been prepared (e.g. if accelerated assessment was used). There also needs to be clarity on the content of the scientific dossier to be submitted (e.g. inclusion of applicant’s responses to questions).
- The consultation document suggests that the scope of targeted assessment is limited to new active substances and biosimilars assessed through the Centralised Procedure. The extension of the scope to other major submissions, including new indications and line extensions and other lifecycle activities such as safety updates, would potentially also be of benefit and should be considered to avoid delaying access to new medicines. Such an extension of scope could be considered where the original new active substance or biosimilar license has been awarded through a targeted assessment process. It should also be clarified that the targeted assessment route would be open to products going through a Decentralised or Mutual Recognition Procedure, as seems to be implied by paragraph (4A)(c) of the draft SI legal text.

- It should be confirmed that the opinions and decisions upon which MHRA may base targeted assessment, as listed in the draft legal text (4A) (a-c), would also be applicable to pandemic and emergency preparedness situations.
- The provision in the draft SI legal text “The licensing authority may under paragraph (4A)– determine and publish a list of the countries other than the United Kingdom whose decisions to grant a marketing authorisation should be relevant for the purposes of paragraph (4A)(c)” is welcomed and supported. Further clarity is required on this list.

**Q8:** *Do you agree with the proposed new fees for targeted assessment?*

**YES**

*Please explain your answer*

As the proposed targeted assessment appears analogous to an EU Mutual Recognition Procedure in which the UK is a Concerned Member State, the initial setting of fees is at the same level as an incoming MRP.

The MHRA should commit to undertake a detailed and transparent analysis of fees once experience has been gained with the proposed new procedures, to ensure that the fees charged for each activity properly reflect the cost of that activity.

### **Change M3: Converting centrally authorised products (CAPs) to UK MAs – referred to as ‘grandfathering’ of licences**

#### **Summary of proposal**

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.

**Q9:** *Do you agree with the requirements for data provision for grandfathered CAPs?*

**NO**

*Please explain your answer*

The ABPI and BIA do **not** agree with the proposed requirements for data provision for grandfathered CAPs as currently set out. Industry's strong preference is that submission of a baseline sequence should not be needed. The MHRA should explore again the possibility to directly obtain baseline data from EMA.

If baseline data must be provided by MAH, industry has significant concerns with the proposed timing and content of the baseline submission:

- Regarding timing, the grace period of 1 year is welcomed. However, this period will in practice have little relevance if the proposed approach is implemented: the majority of CAPs will have submission activity (variations) at the time of or soon after Exit day, necessitating prior or simultaneous submission of a baseline sequence. The compiling of baselines is a time-consuming and labour-intensive process which impacts MAHs' staff administrative costs, and will be challenging, if not impossible, for companies to complete for all concerned products in the time available. The high volume of baseline submissions required around Exit day will also likely place a strain on MHRA systems and resources. Instead of the limited exceptions (e.g. urgent safety variations) to prior or simultaneous submission of baseline data, there needs to be greater flexibility: the timing of the baseline submission should not be linked to other submissions. If necessary for a specific variation, the MAH could provide the relevant current dossier content with that variation, so that MHRA assessors have the appropriate background information. Other baseline data could be provided within the 1 year grace period.
- Regarding content, the proposal is unclear, but appears to suggest that a single baseline sequence must be submitted. Internal processes and systems differ between companies, which will affect their ability and the resource needed to create the required format and content. To provide all modules in a single sequence in the current eCTD format with a list of all submissions and sequence numbers would be a huge undertaking for many companies. Other approaches (e.g. the submission of existing eCTD sequences) may be preferable. The details and technical requirements for the baseline content should be subject to further consultation as a matter of urgency with industry, to ensure that they are feasible for all MAH, and to facilitate MAH's planning.

The following aspects of the proposed approach should also be addressed:

- It should be clarified that "held in an electronic format" means that only those data currently included in the EU eCTD need to be provided.
- When companies are requested to indicate which CAPs they wish to grandfather, the company should have the possibility at the same time to inform MHRA of the UK MAH

and relevant contact persons (QPPV, MAH contact, etc.), to avoid unnecessary subsequent administrative procedures.

- It would be helpful if UK PL numbers could be allocated prior to “Exit day” for CAPs that will be grandfathered.

**Q10:** *Do you agree with the proposed approach to handling variations for CAP grandfathered products?*

**NO**

*Please explain your answer*

Although the general principles relating to handling variations appear pragmatic, there are a number of concerns to be addressed (see also response to Q9 above):

- If a baseline submission is required, we welcome the possibility to include the ongoing variations with the baseline. It is stated that the criteria to determine which variations can be included in the baseline are to be confirmed. We strongly suggest that all variations should be permitted – differentiating will give rise to unnecessary complexity.
- It should be confirmed that if variations are included in the baseline submission, no separate UK variation submission should be needed. MHRA should use the information on the variation in the baseline dossier for assessment.
- Instead of the possibility of limited exceptions (e.g. urgent safety and CMC variations) to submission of baseline data prior to or with variations, there needs to be greater flexibility; the timing of the baseline submission should be delinked from other submissions. This would facilitate MAHs’ submission of baseline data, and – given the large volume of submissions anticipated around Exit day – would remove a potentially large work burden from MHRA associated with evaluating and responding to requests for exceptions.
- To avoid duplication, MHRA should apply a targeted assessment approach for all initial and post-authorisation assessments ongoing at Exit day and in the future, and not just those “late in the assessment process”. It is important to emphasise that targeted assessment should be offered to future variations to grandfathered CAPs, based on the EMA variation and line extension submissions and CHMP assessment reports.

**Q11:** *Do you envisage any problems with the proposed approach to packaging for CAP grandfathered products?*

**YES**

*Please explain your answer*

The approach outlined provides enough time until end of 2021 for updates to packaging for CAP grandfathered products. However, there are two practical challenges that are likely to generate problems:

1. It is stated in paragraph 44 of the Impact Assessment that “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”. This means not all products will be able to benefit from the transition period proposed. Further consideration needs to be given to what sort of regulatory intervention should instigate an immediate packaging change.
2. The EMA encourages the use of combined SmPCs for different strengths of the same pharmaceutical form when the SmPCs are completely identical, except for the few strength-specific details. We would welcome the possibility to take the same approach during “grandfathering”, to avoid the administrative burden of creating separate SmPCs in the UK.

## **Change M4: Packaging**

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

#### **Summary of proposal**

MAHs would have additional time to amend packaging and leaflets for medicinal products on the UK market with UK administrative information that changes as a result of EU Exit.

The UK would continue to accept shared packs for medicinal products.

**Q12:** *Do you agree with the proposed approach on packaging, including the period of time proposed to allow for changes?*

**YES**

*Please explain your answer*

The ABPI and BIA welcome the proposed approach on packaging and support the proposal by the UK to continue to approve shared packs. However, we would like to raise the following points for clarification and further consideration:

- Regarding timing, we welcome the proposed approach to give industry until end of 2021 to amend packaging and leaflets for products on the UK market. However, further guidance is required on what sort of regulatory intervention would instigate an immediate packaging change (see our response to Q11 above).

- Regarding the Falsified Medicines Directive, we recognise the risk that the UK may not have access to the EU central data hub underpinning the FMD safety measures. However, other options should be pursued as a measure of security for all European citizens, in line with the cooperation terms for Interpol and other security systems. The proposals are practical insofar as the UK will accept packs containing the FMD safety features. However, this will need to be considered in more detail (see our response to Q13 below).

## **B) Safety Features under the Falsified Medicines Directive (FMD)**

### **Summary of proposal**

In a no-deal, we expect the UK would not have access to the EU central data hub, and therefore stakeholders would be unable to upload, verify and decommission the unique identifier on packs of medicines in the UK. 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, we will evaluate the options around a future national falsified medicines framework, which would inform the detail of any short or longer-term modifications.

**Q13:** *Do you agree with the proposed approach regarding Safety Features under the Falsified Medicines Directive?*

**NO**

*Please explain your answer*

The reassurance given in paragraph 48 of the Impact Assessment that “Packs containing the FMD features would still be accepted in the UK, provided that they are in line with other UK packaging requirements” is welcomed.

The Impact Assessment disappointingly fails to recognise further serious consequences of revocation.

1. The approach proposed may significantly compromise the security of the remaining European Medicines Verification System (EMVS) e.g. specifically, if the legislation is pro-actively and unilaterally revoked in the UK, packs of medicines already on the UK market before 29 March 2019 will not subsequently be decommissioned and will therefore introduce a security risk to all other national systems (especially those sharing multi-market packs).

2. The gap in patient safety provision which would arise if the legislation was unilaterally revoked by the UK, and the future threat of being a country target for counterfeiters and other fraudsters has also seemingly been ignored.
3. Significant time and investment have already been made by marketing authorisation holders to the development of the UK's SecurMed 'safety features' verification system – which may be entirely redundant on revocation of the legislation.

We look forward to working with MHRA and Government on consequential commitments and plans to:

1. ensure security is not compromised in the remaining EMVS and the medicines supply chain for EU patients;
2. continue to support UK patient safety to the level enjoyed by patients across the rest of Europe, and challenges any targeting of the UK by criminal gangs and other counterfeiters; and
3. provide financial compensation to manufacturers, MAHs and other stakeholders for investments already made which will be redundant on revocation by the UK of the FMD 'safety features' legislation.

### **Change M5: Paediatrics investigation plans (PIPs) and studies**

#### **Summary of proposal**

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.

**Q14:** *Do you agree with the proposal for UK paediatric investigation plans (PIPs) and newly completed paediatric studies?*

**NO**

*Please explain your answer*

The intent for the UK to adopt EU PIP opinions is welcomed, but the draft SI legal text appears to suggest that this would only apply as a transitional measure to PIPs, deferrals, waivers or requests for modification submitted to EMA before Exit day. It should be clear that PDCO opinions relating to paediatric submissions made after Exit day may also be adopted in the UK. It should also be clear that the UK adoption of PDCO opinions will apply to requests for modification, and not only to the initial PIP request.

However, it is exceptionally unlikely that a paediatric need that is considered an unmet medical need is unique to the UK. For the types of products intended to be developed for rare paediatric conditions the requirement for a dedicated and unique UK PIP would be an extraordinary additional burden for biotech SMEs developing such therapies. A UK PIP should only be required where a product may have a unique paediatric purpose in the UK. In this case there should be clear guidance on when it is acceptable for the EU PIP to be modified in the context of clinical use in the UK. We believe that this should be limited to serious public health concerns (including lack of efficacy).

The need to publish information about PIPs and paediatric MAs is acknowledged and should be in line with the current EMA publication of PIP decisions and PUMAs.

We understand that there would be new provisions to mirror the rewards currently available in the EU legislation, including the 6-month extension of supplementary protection certificates (SPCs), additional 2-year market exclusivity for orphan products, as well as the possibility of obtaining a PUMA, which is welcome. However, the 2-year market exclusivity for orphan medicines would be less predictable than in the EU system, since orphan status itself would only be conferred at the time of MA approval and assessment of orphan status (see our response to Q15 below).

## **Change M6: Orphan designation**

### **Summary of proposal**

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.

**Q15:** *Do you agree with the proposal to explore incentivising submission of MA applications for products intended to treat rare diseases in UK?*

**NO**

*Please explain your answer*

The ABPI and BIA agree with the MHRA proposal to explore incentivising submission of MA applications for orphan products and retention of the 10-year market exclusivity incentive.

However, we strongly disagree with the presumption in paragraph 69 of the Impact Assessment, that “a separate UK only designation is unlikely to further incentivise industry”, and the need to have UK specific criteria.

We have outlined below our key concerns:

- Lack of incentives linked to research and development in rare diseases (e.g. fee waivers for scientific advice/protocol assistance), which are critically important for SMEs and all our members to adequately plan evidence generation and demonstrate significant benefit. These incentives should be introduced in the UK framework.
- The proposed separation of the UK framework from the EU legal system and removal of any incentives linked to research and development of orphan medicines dramatically reduces predictability for the UK market.

- An earlier EU approval should not be used as the starting date for UK orphan exclusivity, as it could reduce the potential value of the incentive. MHRA acknowledges in the Impact Assessment that there is a risk, in a no-deal scenario, that new medicines might be authorised in the UK after they are authorised in the EU. There are several possible reasons for this, e.g. even in cases where the applicant does not apply later in the UK, delays may be encountered in the MHRA's assessment and approval. The starting date for orphan exclusivity in the UK should be the date of UK marketing authorisation, so that the exclusivity it affords will run from the time UK marketing is possible.
- We require clarity and practical and technical guidance on the assessment process and the new UK framework to consider the feasibility of the proposed UK framework. We would welcome further discussion with the MHRA on the proposal for orphan designations in the UK.

### **Change M7: Abridged applications**

#### **Summary of proposal**

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 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.

**Q16:** *Do you agree with the proposal for abridged applications?*

**YES**

*Please explain your answer*

In general, the ABPI and BIA support the proposal for abridged applications. However, the inability to rely on a European reference product post-Exit could have a significant impact on development costs and possibly deter companies from launching their products in the UK, and even from submitting an MA application after Exit day.

### **Change M8: Increased requirements for needing a manufacturer's licence for import or a wholesaler dealer's licence**

#### **Summary of proposal**

An existing manufacturer's licence for import (MIA) or wholesale dealer's licence would remain valid. However, it is proposed that human medicines with a UK MA, which are imported into the UK from the EU/EEA, should require a MIA post-Exit.

The UK MIA used for importation into the UK would allow the naming of Qualified Persons (QPs) in countries that are on the relevant MHRA designated country list.

It is proposed that a transitional provision would be put in place for those who need a different type of licence as a result of the changes.

**Q17:** *The transitional provision for this area is still be considered. Have you views on the length of time that should be allowed for organisations to obtain MIAs, and what arrangements should be put in place during that period?*

We welcome that a manufacturer's licence for import (MIA) used for importation into the UK would allow reliance on Qualified Persons (QPs) in countries that are on the relevant MHRA designated country lists. However, names of individual QPs should not be included in the MIAs, as this will give rise to a significant number of ongoing MIA licence variations, particularly for companies with many sites and, therefore, likely an even larger number of QPs. We propose that only the sites at which the QPs are located should be included in the MIA. It is important to note the practical implications of recruiting and training QPs.

In the interest of continuity of supply to UK patients, under a no-deal Brexit scenario, it is reasonable for transitional provisions to be in place for those that currently hold an EU or UK wholesale dealer's licence to supply a UK 'end user', e.g. NHS Trust hospitals. However, these transitional provisions should be for a limited and defined period of time only, to allow time for these organisations to obtain MIAs.

However, we note that a high number of new MIAs would need to be issued. Manufacturers and wholesalers would potentially need several MIAs – consideration should be given to having just one MIA covering all their UK activities. These proposals would introduce significant additional costs in terms of licensing, plus the additional cost of maintaining a

GMP quality management system (QMS) rather than a GDP QMS. Arrangements in place could include nomination of a UK contact person on behalf of the nominated QP or use of the existing Responsible Person named on the wholesale distribution authorisation.

### **Change M9: Recognition of prescriptions**

#### **Summary of proposal**

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.

**Q18:** *Do you agree with the proposal to enable continued recognition of prescriptions issued in an EU / EEA country?*

**YES**

*Please explain your answer*

The ABPI and BIA agree with the proposal.

### **Impact Assessment – Medicines**

#### **Summary of impact assessment**

The following costs have been identified for the medicines impact assessment that will need additional information from industry to quantify.

- 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 - this includes the cost of labour for these representatives, the cost of establishing premises for these representatives, familiarisation and administration costs to ensure these representatives are able to do these jobs.
- The labour (staff time) and administration cost for spent dealing with the MHRA additional application procedure for those who used the EMA centralised procedure previously.
- Cost of maintaining the additional UK Marketing Authorisation for those who used the EMA centralised procedure previously
- Labour costs in terms of staff time spent providing baseline data for CAPs
- Costs to businesses of maintaining their UK MA for grandfathered CAPs, including legal and administrative costs

- The administrative and manufacturing cost to industry of amending packaging to include their UK information
- Labour costs in terms of staff time, and administration costs associated with the MIA requirement for those companies that do not currently have an MIA for importing medicines with a UK MA into the UK

**Q19:** *If you have evidence to help quantify the costs to business of these proposed changes, please respond below*

Although the contingency legislation is intended to help organisations in their preparations for a no-deal scenario, the consultation impact assessment recognises that there will be resources, additional administrative costs and other ongoing costs incurred by the life sciences industry for maintaining already authorised products and placing new medicines on the UK market. It should be noted that the membership of the ABPI and BIA is wide-ranging from large pharmaceutical companies to emerging and more established bioscience companies, and operating at a national, regional or global level. Therefore, we are not able to quantify the costs of the proposed legislative and regulatory changes given the various and different operational models of our member companies.

## **Section 2 Clinical Trials – Changes CT1-CT3**

### **Change CT1: Legal presence – clinical trials**

#### **Summary of proposal**

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.

**Q23:** *Do you agree with the approach proposed, for a sponsor or legal representative to be established in the UK or a designated country?*

**YES**

*Please explain your answer*

We welcome the proposed flexibility offered by allowing the Legal Representative to be based in the UK or alternatively in another country on the designated list. This approach

seems both pragmatic and proportionate. The draft SI legal text seems to imply that following a review of the countries on the list at the end of the transition period that this could continue beyond that date. We would welcome such an approach.

**Q24:** *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?*

**NO**

*Please explain your answer*

We recognise the need for a UK point of contact to be continuously available to the licensing authority. However, for commercial sponsors, the appropriate point of contact would not be the Chief Investigator (CI) but a nominated point of contact. Commercial sponsors need to have the option to nominate an alternative, UK-based primary point of contact for the licensing authority, from within their own organisation (e.g. the applicant), in the situation where neither the Sponsor nor the Legal Representative, are based in the UK.

To ensure safety and efficiency, the MHRA should have direct contact with the Sponsor or their nominated contact rather than via the UK CI, to ensure that prompt action can be taken by the Sponsor, not only to ensure the protection and well-being of UK trial subjects, but also those in other countries that may also be participating in the same study, e.g. if an issue or potential issue is first identified by the MHRA.

The national point of contact should be established by the clinical trial authorisation applicant/holder. In this manner, non-commercial organisations can identify a chief investigator, if that is appropriate, and commercial organisations can identify their own national point of contact.

### **Change CT2: Transparency**

#### **Summary of proposal**

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.

**Q25:** *Do you agree with this approach?*

**YES**

*Please explain your answer*

We welcome what appears to be a pragmatic approach to ensuring continued transparency. It is important, however, to ensure that the UK remains aligned with the EU transparency requirements, including for example the deferral time periods for publication of information on clinical trials. This is particularly salient for:

- results from Phase I trials; unless the deferral from publication period is aligned with that of the EU, the UK will be at a competitive disadvantage for early stage trials;
- the protocol and IMPD submitted in UK applications for Phase I, II and III clinical trials.

The consultation document suggests that the MHRA will set up a new UK electronic system to enable the publication of this data. We look forward to engaging further with the MHRA on the development and testing this new system and related data disclosure procedures.

### **Change CT3: Use of designated country lists, including for legal presence and importation of investigational medicinal products (IMPs)**

#### **Summary of proposal**

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).

**Q26:** *Do you agree with the proposed designated country lists?*

**YES**

*Please explain your answer*

We agree with the proposed lists and the benefits of this approach. However, we would welcome further clarification in relation to the following points:

1. The designated country list 2, the UK should accept the SmPC as alternative to the Investigators Brochure in both ethics and CTA applications.
2. The criteria that will determine the three country lists. We understand that the designated country list 2 would initially include EU/EEA countries and ICH countries (this is assumed to mean ICH member countries, but this should be clarified).
3. The additional countries, if any, which are being considered for the designated country list 3 (acceptance of IMP QP certification) beyond those in the EU/EEA. The draft SI text indicates that some of these lists (lists 1 and 2) should be reviewed at the end of the transitional period, but it is not clear whether this review would also cover the designated country list 3.
4. QP arrangements: could MHRA confirm our understanding that a QP based in an EU/EEA country on list 3 can release IMPs direct to the UK sites with no additional QP release taking place in the UK. Moreover, we would like to explore whether the acceptance of QP certification from countries on list 3 may potentially be continued beyond the end of the transitional period and hence avoid the need for a UK-based QP for IMPs in the long term.

## **Impact Assessment – Clinical Trials**

### **Summary of impact assessment**

The following costs have been identified for the Clinical Trials section of the impact assessment that will need additional information from industry to quantify.

- The transition (one-off establishing costs) and ongoing cost of having a contactable person (Sponsor or Legal Representative) in the UK for organisations who do not already have one, which would include labour and other administrative costs
- The cost of labour in terms of staff time for businesses in publishing information about clinical trials

**Q27:** *If you have evidence to help quantify the costs to business of these proposed changes, please respond below*

Although the contingency legislation is intended to help organisations in their preparations for a no-deal scenario, the consultation impact assessment recognises that there will be additional resources and administrative costs incurred by the life sciences industry to continue conducting clinical trials in the UK. It should be noted that the membership of the ABPI and BIA is wide-ranging from large pharmaceutical companies to emerging and more established bioscience companies, and operating at a national, regional or global level. Therefore, we are not able to quantify the costs of the proposed legislative and regulatory changes given the various and different operational models of our member companies.

## **Section 3 Medical Devices – Change D1**

### **Change D1: Registration of medical devices**

#### **Summary of proposal**

Registration requirements would be expanded to cover all medical devices and in-vitro diagnostics (IVDs) that are placed on the UK market.

The responsibility for registering the medical device or IVD would fall to the economic operator (e.g. an importer, distributor or manufacturer) that first ‘places the device’ on the UK market.

This economic operator (or UK ‘sponsor’) would need to be established in the UK and provide a registered address. There would be a grace period to allow time for compliance, which would – at least initially – require a small administrative fee broadly in line with the current registration charge for class I devices. See section 4 for other fee changes.

**Q31:** *Do you agree with this approach?*

**YES**

*Please explain your answer and also give any views on the timetable for a transition period*

Given the complexity of the situation we understand that this is the only pragmatic option in the short term regarding device registration in the UK. We support evaluation of a long term solution (i.e. mutual recognition agreement) like the current situation with Turkey and Switzerland. The impact of the new EU Devices Regulations needs to be taken into consideration with respects to the timelines; therefore, we propose a transitional period at least until May 2022 in line with the implementation of the EU Regulation for In vitro Diagnostic Medical Devices. For medical devices with a CE mark, we would propose a transitional period at least until May 2024, in light of Article 120 of the Medical Devices Regulation.

### **Impact Assessment – Devices**

#### **Summary of impact assessment**

The following cost been identified for the devices impact assessment that will need additional information from industry to quantify.

- Costs associated with the device registration, including the labour cost of staff time to understand and complete the registration process.

There will be costs associated with non-UK medical devices manufacturers having to nominate a UK ‘sponsor’ to place their products on the UK market. However, we assume that acting as a ‘sponsor’ for an overseas devices manufacturer would be cost-neutral to the sponsor. This assumes that any regulatory costs incurred by the UK ‘sponsor’ would be passed on to the overseas manufacturer through any commercial agreement between the two parties, allowing the ‘sponsor’ to reclaim the direct costs of regulatory burden. If you have any evidence to challenge this claim, please let us know.

**Q32:** *If you have evidence to help quantify the costs to business of these proposed changes, please respond below*

Although the contingency legislation is intended to help organisations in their preparations for a no-deal scenario, the consultation impact assessment recognises that there will be additional resources and administrative costs with the registration of devices. It should be noted that the membership of the ABPI and BIA is wide-ranging from large pharmaceutical companies to emerging and more established bioscience companies, and operating at a national, regional or global level. Therefore, we are not able to quantify the costs of the proposed legislative and regulatory changes given the various and different operational models of our member companies.

## **Section 4 Fees - Changes F1-F2**

### **Change F1: Fee waivers for orphan products**

#### **Summary of proposal**

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

**Q36:** *Do you agree with the proposal to consider offering new fee waivers for orphan products?*

**YES**

*Please explain your answer*

With reference to our response to question 15 above, the ABPI and BIA strongly support the introduction of research and development incentives like the ones in the EU if the UK framework is to be fully adjusted to the UK life sciences ecosystem (e.g. UK prevalence,

significant benefit). The scientific advice / protocol assistance fee waivers are essential to foster dialogue through development and ensure alignment on these aspects, increasing predictability.

In the current proposal it is unclear whether additional fee incentives would be available such as protocol assistance (paediatric and non-paediatric) or pre-authorisation inspection costs as well as those specifically offered to SMEs e.g. 100% reduction in scientific services or post-authorisation fees in first year of marketing.

As stated in section M6, we urge the MHRA and the UK Government to look beyond EU for inspiration for fee-related incentives, especially in other domestic procedures and possibly any downstream access procedures (e.g. fees on health technology appraisal).

### **Change F2: New/amended MHRA fees for six processes/services previously provided centrally by EC or EMA**

#### **Summary of proposal**

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.

**Q37:** *Do you agree with the proposed new/amended MHRA fees for six processes/services previously provided centrally by EC/EMA?*

**NO**

*Please explain your answer*

With the exception of the targeted assessment fees described in section 1 (M2) the fees described here are reflective of the MHRA being a stand-alone regulator and effectively duplicating the work that is being done at the level of the EU, in addition to introducing opportunity for regulatory divergence. Since all of these fees will be additional to fees already being spent to support CP/MRP/DCP activities, this is undesirable.

We propose instead to introduce **targeted assessment** options for **all** regulatory procedures previously conducted either by EMA for CP or RMS under DCP/MRP, reducing duplication of regulatory assessment/work and limiting any opportunity for regulatory divergence. Fees in that case should be reflective of the level of assessment which would be expected from National/CMS for mutual recognition procedures.

Regarding the targeted assessment fees of £62,421 and £17,330 quoted for full (8.3) and biosimilar (10.4) applications, these fee levels are viewed as appropriate since they correlate with the fee for an Incoming mutual recognition for UK CMS and European reference products for major and abridged complex procedures, respectively. It is unclear however if a targeted assessment would be available for other types of abridged procedures such as 10.1 generic or 10.3 hybrid procedure?

Additional specific comments are as follows:

- With regards to the fees for review of PASS protocols and studies, this fee proposal should include review of imposed PASS studies only (category 1 and 2); it should not include category 3 and 4 studies as this review should not be mandatory but might be requested by the regulators on a case by case basis. Further clarity is needed.
- Similarly to the EU pharmacovigilance fees, the MHRA should propose introducing exemptions for SMEs, and any cost-sharing arrangements for companies with the same active substance, like the EMA's 'chargeable unit' system.

### **Impact Assessment – Fees**

#### **Summary of impact assessment**

The following costs have been identified for the medicines impact assessment that will need additional information from industry to quantify.

- The labour and administration cost in terms of staff time to business of familiarisation with the new MHRA processes and the ongoing labour cost of completing these processes for those who previously used only the EC/EMA processes.

**Q38:** *If you have evidence to help quantify the costs to business of these proposed changes, please respond below*

Although the contingency legislation is intended to help organisations in their preparations for a no-deal scenario, the consultation impact assessment recognises that there will be additional resources and administrative costs associated with the introduction of MHRA regulatory processes/services previously provided at EU level. It should be noted that the membership of the ABPI and BIA is wide-ranging from large pharmaceutical companies to emerging and more established bioscience companies, and operating at a national, regional or global level. Therefore, we are not able to quantify the costs of the proposed legislative and regulatory changes given the various and different operational models of our member companies.

## **Section 5 NIBSC – Change N1**

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

#### **Summary of proposal**

A new power in the 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) requiring batch testing by the National Institute for Biological Standards and Control (NIBSC), and a prohibition on sale or supply until such testing takes place. However, the UK may decide on a risk-based approach to waive the associated laboratory testing for some products/batches and replace it with a paper-based assessment of data.

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.

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.

**Q42:** *Do you agree that, as a standalone national control laboratory, NIBSC certifies batches of biological medicines used in the UK, taking a risk-based approach and accepting evidence of testing by an EU 27 OMCL as discussed above?*

**YES**

*Please explain your answer*

The ABPI and BIA agree to the risk-based approach proposed. It would be helpful to clarify if the Marketing Information Form will still be required to release a batch of a vaccine or blood product to market.

**Q43:** *Do you agree with this proposal for NIBSC OMCL batch testing fees?*

**YES**

*Please explain your answer*

The ABPI and BIA support the proposal. It would be helpful to provide clarification on the scope of products being considered.

## **Impact Assessment – NIBSC**

### **Summary of impact assessment**

The following costs have been identified for the medicines impact assessment that will need additional information from industry to quantify.

- The cost of staff time and administration costs of familiarisation and completion of new NIBSC requirements

**Q44:** *If you have evidence to help quantify the costs to business of these proposed changes, please respond below*

Although the contingency legislation is intended to help organisations in their preparations for a no-deal scenario, the consultation impact assessment recognises that there will be additional resources and administrative costs associated with batch testing of biological medicines. It should be noted that the membership of the ABPI and BIA is wide-ranging from large pharmaceutical companies to emerging and more established bioscience companies, and operating at a national, regional or global level. Therefore, we are not able to quantify the costs of the proposed legislative and regulatory changes given the various and different operational models of our member companies.

## **Section 6 Impact Assessment – Further Comments**

Please give any further comments, including on Impact Assessment areas not already covered, such as

- Small and micro business assessment
- Indirect costs - such as the possible passing the increased costs of regulation to purchasers of medicines
- Public health impacts
- Risks - including the desirability for business of applying to MHRA in a standalone scenario where previously European processes were used, and the ability of business to prepare for a no deal scenario

**Q47:** *If you have any further comments about the content and analysis in the Impact Assessment, please provide them below*

We are concerned that the proposal for data and market exclusivity for marketing authorisations is not being consulted on. Data exclusivity is a critical incentive for innovation and therefore highly important to the life sciences industry.