ANNEX I: APPROACH TAKEN TO AMENDING LEGISLATION AND GUIDANCE

I. Approach taken to EU directives

The UK already transposes EU directives into EU law, therefore the UK legislative vehicles that implement this EU law remain in place and any further legal changes arising from our EU exit will be via changes to the following principal statutory instruments: The Human Medicines Regulations 2012 (HMR), The Medicines for Human Use (Clinical Trials) Regulations 2004, Medical Devices Regulations 2002, and The Medicines (Products for Human Use) (Fees) Regulations 2016. The changes will be primarily be made under powers in the EU (Withdrawal) Act 2018, in particular section 8 (dealing with deficiencies arising from withdrawal).

II. Approach taken to directly applicable EU regulations

Those EU Regulations which need to remain in place post-exit (Paediatric, Orphan, ATMP, Variations, Conditional Marketing authorisation) will be transposed into the HMRs with appropriate modifications, in order to have a single piece of legislation governing the regulation of medicinal products and to ensure a coherent and clear structure. The EU Regulations themselves will therefore be revoked.

III. Approach taken to tertiary legislative functions the EU currently has, such as issuing GMP guidance, GDP guidance and GPvP guidance

It is proposed that UK and NI Ministers, acting through the MHRA, would take over any tertiary legislative functions the EU currently has, including in respect of Implementing Regulations and the issuing of guidance. For example, the terms of the Pharmacovigilance Implementing Regulation will be incorporated in to domestic legislation with appropriate modifications, in particular to reflect the fact that the UK is no longer a Member State, with power to amend, revoke or modify by regulations in future. Any extant EU guidance will be preserved until the MHRA issues its own, or modifies or amends the EU guidance. Examples are: issuing the guidelines on good manufacturing practice as set out in the Good Manufacturing Directive.

IV. Legal definitions

Various definitions will be amended to reflect the fact that the UK is no longer a Member State. New definitions will be inserted which relate to the EU Regulations which are transposed.

V. Criminal offences

Transitional provision is made to preserve the ability to prosecute offences which occurred before Exit day, even if that offence is amended or revoked from Exit Day.

ANNEX II: NARRATIVE ON CHANGES TO THE HUMAN MEDICINES REGULATIONS 2012

Technical information for industry that is not being consulted on (except as provided in the areas above) but provided for information. This information is provided to enable consultees to understand the wider policy thinking behind the consultation questions. Policies are still being developed and is not intended to be a definitive statement of the changes that will be made, except as it has been outlined in the Technical Notices related to human medicines, clinical trials and medical devices.

Marketing Authorisations and variations

1. It is proposed that the term "UK marketing authorisation" will be used in the revised HMRs as the main way of describing an MA which is valid for the UK. References to EU MAs authorising the MAH to supply the product in the UK would be removed, because EU MAs will not be valid for the UK post exit.

2. The national licensing regime for UK MAs continues as before and will be the only route to an MA which is valid for the UK. Where the centralised procedure route was compulsory for certain products (orphan, ATMP, conditional MAs), the relevant provisions from the corresponding EU Regulations on these areas would be inserted into the HMRs, as would the requirements in relation to paediatric matters.

Data and marketing exclusivity for Marketing Authorisations

3. 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. 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. This is to discourage companies from delaying bringing innovative products to the UK market and is aimed at protecting public health in the UK.

Mutual recognition and DCP

4. Any references which assume the UK is part of the harmonised EU mutual recognition and decentralised procedure routes to national MAs would be removed.

5. It is proposed that transitional provisions will be made for MRP and DCP procedures in progress immediately before Exit day. These are already national MA applications. We will complete the assessments, but they will be approved as purely national MAs and we will not be in the MRP. Applicants will not need to resubmit the application to us and we will not charge further fees.

Suspensions and article 31 referrals

6. It is proposed that transitional provision is made to ensure that suspensions imposed in respect of a UK MA that have effect immediately before Exit Day under Chapter IV of Title III of the 2001

Directive, continue in effect and are treated as if imposed under Part 5 of the HMRs. It is also proposed that transitional provision is made as regards Article 31 2001 Directive referrals that are in progress at Exit Day concerning suspension, variation or revocation of a central or UK MA. The basic premise is that unless the procedure was substantially complete, the licensing authority has to make a determination on the suspension, revocation or variation in accordance with Part 5 HMRs, but it may take account what has gone before in doing so. It may also take into account or adopt decisions at EU level that post-date Exit day. This allows the licensing authority to take a risk-based approach to such referrals that are in progress at Exit Day.

A conditional MA (CMA)

7. A CMA is one which is granted in defined circumstances in advance of all the information being available, in order to get medicines for life threatening and seriously debilitating conditions into the market as soon as possible. They are valid for one year and are renewable. They may only be granted by the EU at present and are governed by the CMA Regulation. Post-exit, it is proposed that the MHRA will be able to grant CMAs. The CMA Regulation would be revoked and the relevant provisions inserted into the HMRs with appropriate amendments.

Article 126a authorisations

8. It is proposed that the HMRs are amended to remove references throughout to this type of authorisation. This article of the Directive permits Member States, for justified public health reasons, to authorise the placing on the market of medicinal products authorised in another EEA state in the absence of a national MA for their territory. The UK has never had, and currently has, no such authorisations in place and in the context of no deal, it is considered it would be inappropriate to retain this type of authorisation (relying on the authorisation of another MS, in the absence of being a part of the framework for medicines). No transitional provision is considered necessary given that we currently have no such authorisations.

Variations

9. All variations to MAs will in future be dealt with under Part 5 of the HMRs. Much of the detail of the variation procedure is currently contained in Regulation 1234/2008 (tertiary Commission regulation) including for purely national variations. As much of this Regulation would become defunct in a no deal scenario, and what needs retaining requires some amendment to reflect that the UK is not a Member State, it is proposed that this Regulation will be revoked. Instead the HMRs will contain provisions that remain relevant to purely national variations that mirror the purely national variation scheme in the revoked Regulation, with an appropriate regulation-making power to vary the scheme for variations in future. Alongside this it is proposed that the current EU classification guidance on variations would continue to be substantially retained, with power for the MHRA to revoke, amend or modify that classification guidance in future.

10. There would be transitional provisions to deal with variations that were being dealt with at EU level (centralised, MRP, DCP) that had not concluded at Exit day. The basic premise that is proposed is that unless the procedure was substantially complete, the licensing authority has to make a determination on the variation in accordance with the new provisions, but it may take account what has gone before in doing so. It may also take into account or adopt decisions at EU-level that post -date Exit day. This allows the licensing authority to take a risk-based approach to variations in progress at Exit day.

11. A type IA variation will be required for a change in QPPV.

Selling or supplying unauthorised medicines

12. It is currently an offence to sell or supply, or to offer to sell or supply, unauthorised medicines to a person within the EEA (regulation 46 HMR). After EU Exit, the offence will be limited to sales and supplies in the United Kingdom.

Pharmacovigilance

13. It is proposed that the MHRA will have responsibility for the oversight of all pharmacovigilance activities in relation to UK MAs, certificates of registration and traditional herbal registrations. The QPPV should be established in the UK by the end of 2020. Companies must tell us how they will provide the UK with access to their company-wide safety data when required, including in those situations that require access at very short notice. Making provision for this will ultimately be the responsibility of the MAH. It is proposed that the PV Implementing Regulation will be revoked, with the appropriately modified text being restated in the HMRs.

14. Currently, the majority of periodic safety update reports (PSURs) and post-authorisation safety studies (PASS) are submitted and assessed at EU-level and, post-Exit, these will need to be submitted to and assessed by the MHRA.

15. It is proposed that there would be transitional provisions to deal with the various types of pharmacovigilance referrals that may be on-going at Exit day at EU-level under Title IX of the 2001 Directive (both Art 107i referrals and Art 31 referrals that are driven by pharmacovigilance data.) The basic premise is that unless the procedure was substantially complete, the licensing authority has to make a determination on the pharmacovigilance issue in accordance with Part 11 of the HMRs, but it may take account what has gone before in doing so. It may also take into account or adopt decisions at EU-level that post-date Exit day. This allows the licensing authority to take a risk-based approach to pharmacovigilance referrals in progress at Exit day. There would be further transitional measures to cater for PSURs and PASS that have been submitted for assessment at EU-level but where that assessment is not complete immediately before Exit day.

Reporting suspected Adverse Drug Reactions

16. The MHRA already holds its own database of Pharmacovigilance information. Reporting of suspected Adverse Drug Reactions will need to be made directly to the MHRA for the UK rather than to the current EU database known as the Eudravigilance database. References to the EU Eudravigilance database in the HMRs will need be replaced with references to the purely national pharmacovigilance data base.

Good Pharmacovigilance Practice guidance

17. It is proposed that the MHRA would have the power to publish its own guidance on good pharmacovigilance practice, with the current EU guidance remaining in place unless and until the MHRA does so.

PAES studies

18. It is proposed that an amendment would be incorporated into the HMRs to create a power for Ministers to supplement the provisions of regulations 59 and 61 in order to specify the circumstances in which a post-authorisation efficacy study may be required to replace the power being lost under Article 22b of the 2001 Directive at EU level.

Additional monitoring

19. It is proposed that a new power would be conferred on the licensing authority to establish a list of products subject to additional monitoring to replace the current list under Article 23 of regulation 726/2004 maintained at EU level. On exit day the list would remain the same as in the EU and any proposed changes would be made public. Such products have to denote their status with a symbol (a Black Triangle) that we would retain.

Sale and supply to the public

20. No major changes are needed here, as sale and supply to the public is not governed by EU law. There are consequential changes only.

Online sellers

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

Packaging and leaflets

22. It is envisaged that there would be no substantive amendments other than a consequence of other changes to MAs described above. The bulk of the amendments would relate to ATMPs and the proposal to draw in to the HMRs the requirements from the ATMP Regulation.

Advertising

23. It is envisaged that there would be no substantive amendments.

Manufacturing and wholesale dealing

24. This covers manufacturing licences, wholesale dealing licences, registration as a broker and registration as an importer, manufacturer or distributor of active substances.

GxP Guidelines

25. It is envisaged that the current GMP Directive would be preserved with appropriate modifications to reflect that the UK is no longer a Member State, but with a regulation-making power conferred on ministers to amend, modify or revoke the Directive in future. It is proposed that a power would be conferred on the MHRA to publish guidelines on good manufacturing practice and good distribution practice: this may be by way of modifying or amending those that already exist at EU level, or replacing them in their entirety. Until they do so, it is proposed that the EU Directive and guidelines issued under Article 47 and 84 of the 2001 Directive remain in place.

Brokering

26. In order to broker a medicinal product, brokers must be registered with the MHRA. A medicinal product may not be brokered unless it is authorised by the MHRA [or in future, it is proposed, with an equivalent regulatory body in a designated country].

API registration

27. In relation to registration requirements for importing, manufacturing or distributing active substances, there are no major amendments except to insert references to the designated country list rather than the equivalent list currently maintained by the EU under Article 11b of the 2001 Directive and to remove some inappropriate references to EEA States (so that all imports are treated equally).

Orphans Exclusivity Period

28. It is envisaged that the period of exclusivity for an orphan product would be treated as starting on the date on which the product is authorised in the UK or EU, whichever is earlier. This is for the same reasons as outlined above in relation to exclusivity for non-orphan products.

Homeopathic medicines

29. The basic premise is that as to matters such as place of establishment, variations, transitionals for matters on-going at EU level at Exit Day, the policy follows that for MAs. So a person will not be able to hold a certificate of registration in the UK unless they are established in the UK, with appropriate transitional provision.

Herbal medicines

30. The basic premise is that as to matters such as place of establishment, variations, matters on-going at EU level at Exit Day, the policy follows that for MA. Therefore, a person will not be able to hold a traditional herbal registration in the UK unless they are established in the UK.

31. However, it is proposed that the MHRA will have the option of expanding the list of countries from where it will accept well established use from for herbals: at the moment a product has to have been used for 30 years, and in the EU for 15 years. In future the 15 year part of the requirement will be linked to use in a designated country rather than the EU. The no deal amendments also provide for the licensing authority to have the power to have its own herbal monographs rather than rely on the EU established monographs though the EU list would be preserved pending the publication by the MHRA of its own. The no deal amendments also create a domestic procedure for consideration of a product that has been used for less than 15 years to replace a similar procedure lost at EU level.

ATMP

32. Advanced therapy medicinal products (ATMPs) are currently all authorised centrally by the EU. The ATMP Regulation governs the applications, and it is proposed it will be revoked and the relevant provisions inserted into the HMRs with appropriate amendments.

ANNEX III: NARRATIVE ON CHANGES TO CLINICAL TRIALS LEGISLATION AND PROCESS

Technical information for industry that is not being consulted on but provided for information

As at present, sponsors will apply to the MHRA for a national authorisation under the Medicines for Human Use (Clinical Trials) Regulations 2004. The new EU Clinical Trials Regulation No. 536/2014 will not be in force in the UK on exit day and is therefore excluded from the scope of this consultation. The main familiarisation changes will be around the supporting information systems that enable the current UK system to continue on exit day, in no deal.

EU IT systems that UK will need to replicate

1. **The existing EU systems supporting clinical trials regulation are:**

    - the EudraCT database and register, and
    - the Common European Submission Portal (CESP) which provides a secure mechanism for exchange of information between applicants and EU regulatory agencies.

2. **Current UK systems are:**

    - IRAS for ethics applications submissions (run by the Health Research Authority (HRA))

Changes for sponsors

- **Reference number generation.** The EudraCT application system can still be used to generate a number in no deal as this is available for use by applicants in any country. This number is free to obtain, anyone based anywhere in the world can apply for this number (and not necessarily use it) and will be being obtained now for applicants intending to submit post-Exit. This is a well-known number which applicants and competent authorities refer to for tracking purposes and will continue to be important for querying historic data.

- **Application preparation.** The application forms for UK trials will be developed in UK IRAS. This process is currently used by most non-commercial sponsors. Use of all the application systems is free for the applicant.

- **Application submission (portal).** Use CESP or if not available, UK would need to establish an immediate alternative to CESP.

- **Registration.** There is an HRA condition of ethics approval of registration of the trial and results. This could include the USA or EU registers in no deal. For national trials there would be a gap and this needs to be considered, and is covered in the transparency question CT2 of the consultation document. Additionally, upon the UK exiting the EU, EU/EEA countries would become third countries. As a result, an IMP manufacturer's

licence for import would be required to import IMPs into the UK from the EU/EEA. It is proposed that a transitional provision will be put in place for those who need a different type of licence as a result of the changes.

ANNEX IV: NARRATIVE ON CHANGES TO MEDICAL DEVICES LEGISLATION

Technical information for industry that is not being consulted on but provided for information

1. **A new 'UK mark' to replace or run alongside the CE mark could be developed in future, but not for Exit day.** A new 'UK mark' and/or other agreed international 'marks' could replace or supplement CE marks as indication of conformity with UK requirements.

2. **New EU Devices Regulations**

   Elements of the new EU Devices Regulations have been applied directly in UK law since May 2017, meaning devices, including IVDs, can now be legally placed on the UK market if they are in conformity with the new Regulations, invoking all relevant requirements. In addition, during the implementation period agreed with the EU, the EU Medical Devices Regulation will be fully applied from May 2020. This would not automatically follow for the new EU Regulation for *in vitro* Diagnostic Medical Devices, which does not apply until May 2022.

   Under the EU (Withdrawal) Act, Section 4(1) preserves "rights, powers, liabilities, obligations, restrictions, remedies and procedures, so far as they are recognised, available and followed immediately before exit day" as domestic law. Therefore, upon exit under a no-deal scenario, the UK would retain this dual regulatory framework, and medical devices could be placed on our market (and put into service) either in conformity with the current requirements (based on EU Directives) or in conformity with the requirements derived from the new EU Regulations.

   The UK would comply, and align UK law with, with all key elements of the Medical Devices Regulation (MDR) and the in vitro diagnostic Regulations (IVDR) - which will apply in the EU from May 2020 and 2022 respectively – subject to the usual parliamentary approvals.

3. **Notified Bodies**

   The MHRA will be unable to designate UK conformity assessment bodies as EU notified bodies. Existing UK notified bodies for medical devices would need to transfer functions to EU27.

ANNEX V: FURTHER BACKGROUND ON NEW/AMENDED MHRA FEES FOR SIX PROCESSES/SERVICES PREVIOUSLY PROVIDED CENTRALLY BY EC/EMA

1. Plasma Master File (PMF) certification and certified annual updates

Proposed new fees – £8,309 for the initial certification of a PMF; £277 for a certified annual update of a PMF involving epidemiology updates only; and £734 for a certified annual update of a PMF where there are significant changes to safety-related information.

PMFs are dossiers that contain data on the operation of plasma collection sites, their procedures, virus safety tests, epidemiological data, etc. These are updated each year. One PMF can be linked to several MAs, and one MA can be linked to several PMFs. A PMF gets certified annually (Step 1), and then gets linked to the relevant MA in an administrative step (called Step 2).

PMF certification work is currently undertaken through the centralised procedures CP), with EMA charging fees direct to industry. In a no deal no implementation period (IP) scenario, the MHRA proposes to undertake PMF certification work and PMF annual updated work, and have associated fees, replacing the centralized process.

2. Vaccine Antigen Master File (VAMF) certification

Proposed new fee - £8,309 for the certification of a VAMF.

The VAMF is a stand-alone part of the marketing authorisation approval (MAA) for a vaccine and contains all relevant information of biological, pharmaceutical and chemical nature for one given vaccine antigen. A MA or MAA may contain one or more VAMF certificates and respective VAMF data.

VAMF certification work is currently undertaken through the centralised procedures (CP), with the EMA charging fees direct to industry. In a no deal no IP scenario, the MHRA proposes to undertake VAMF certification work and have an associated fee, replacing the centralized process

3. Pharmacovigilance Post-Authorisation Safety Study (PASS)

Proposed new fees - £8,309 for assessment of a PASS protocol and £8,309 for assessment of PASS results.

A PASS is carried out after a medicine has been authorised in order to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures. The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is currently responsible for assessing the protocols of imposed PASSs and for assessing their results

In a no deal no IP scenario, the MHRA proposes to undertake PASS work and have associated fees, replacing a centralized process. The work is in two stages and involves (1) assessing PASS study protocols and (2) assessing the subsequent PASS results. A licensed medicine that may be subject to

a PASS by the MHRA will include new active substances at the time of authorisation, and currently authorised products that are subject to a major safety review (see 4 below).

4. **Pharmacovigilance Major Safety Review**

Proposed new fee - £51,286

A Major Safety Review (currently known as a Safety Referral) is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines.

At present in a safety referral the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the EU. The medicine, or the class or medicines, is 'referred' to the EMA so that it can make a recommendation for a harmonised position across the EU. There are a number of reasons why a safety referral may be started, ranging from concerns over the safety of a class of medicine to disagreements among Member States on the use of the medicine. Referrals can be started by the European Commission, any Member State or by the company that markets the medicine.

In a no deal scenario, the Agency proposes to undertake Major Safety Reviews work and have an associated fee, replacing the centralized process described above.

5. Pharmacovigilance Periodic Safety Update Reports (PSURs) single assessment

Proposed new fee - £890 for a single assessment of PSURs.

Periodic Safety Update Reports (PSURs) provide an evaluation of the benefit-risk balance of a medicine. Under the existing centralized EMA process, MAHs must submit PSURs to the EMA at defined time points following a medicine's authorisation. PSURs summarise data on the benefits and risks of a medicine and include the results of all studies carried out with this medicine, both in its authorised uses and in unauthorised uses. The EMA uses the information in PSURs to determine if there are new risks identified for a medicine or whether the balance of benefits and risks of a medicine has changed. The EMA can then decide if further investigations need to be carried out or can take action to protect the public from the risks identified, such as updating the information provided for healthcare professionals and patients.

In a no deal no IP scenario, the MHRA proposes to undertake PSUR single assessment and have an associated fee, replacing the centralized process described above. The MHRA proposes that a MAH will be expected to submit a PSUR for a licensed medicine to the MHRA at least every 6-months during the first two years following the initial placing on the market following the grant of the MA, once a year for the following two years and every three years after that unless the MA states otherwise. The MHRA will judge based on the PSUR received whether to undertake a single assessment. If so, the PSUR single assessment fee will be charged to the MAH.

6. Renewals

Proposed amended fee – Amend Renewals fees in a no deal scenario 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 Exit day, are subject to a renewal fee of £9,682 five years after the licence was first granted.

Current MHRA fee for a first renewal of a major application under the outgoing mutual recognition procedure is £9,682. If a number of such applications are made at the same time and in relation to products with the same active ingredient, dosage form, indications, Periodic Safety Update Report (PSUR) and renewal date, the full fee of £9,682 is charged for the first application, but a fee of £747 is payable in respect of each of the other applications.