EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH
AND FOOD SAFETY

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Brussels, 13 March 2020
REV3 - replaces the notice (REV2) dated 1 February 2019 and the Q&A document (REV4) dated 1 February 2019

NOTICE TO STAKEHOLDERS

WITHDRAWAL OF THE UNITED KINGDOM AND EU RULES FOR MEDICINAL PRODUCTS FOR HUMAN USE AND VETERINARY MEDICINAL PRODUCTS

Contents

INTRODUCTION

Since 1 February 2020, the United Kingdom has withdrawn from the European Union and has become a 'third country'.[1] The Withdrawal Agreement[2] provides for a transition period ending on 31 December 2020.[3] Until that date, EU law in its entirety applies to and in the United Kingdom.[4]

During the transition period, the EU and the United Kingdom will negotiate an agreement on a new partnership, providing notably for a free trade area. However, it is not certain whether such an agreement will be concluded and will enter into force at the end of the transition period. In any event, such an agreement would create a relationship which in terms of market access conditions will be very different from the United Kingdom's participation in the internal market,[5] in the EU Customs Union, and in the VAT and excise duty area.

Therefore, all interested parties, and especially economic operators, are reminded of the legal situation as of the end of the transition period (Part A below). This notice also explains certain relevant separation provisions of the Withdrawal Agreement (Part B below), as well as the rules applicable to Northern Ireland as of the end of the transition period (Part C below).

Advice to stakeholders:

To address the consequences set out in this notice, marketing authorisation holders and manufacturing authorisation holders, as well as wholesalers are in particular advised to:

- take all steps to take account of the United Kingdom being outside the EU's regulatory system for medicinal products in all respects (marketing authorisation procedures, importation requirements, (co-)labelling, sourcing of medicines, etc.) as of the end of the transition period;

- consider, in all business decisions, that all goods, including medicinal products, shipped from the United Kingdom to the EU will be subject to procedures/controls in respect of fiscal (customs duties, origin, VAT) and non-fiscal (batch release) requirements as of the end of the transition period.

---

1 A third country is a country not member of the EU.

2 Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, OJ L 29, 31.1.2020, p. 7 ("Withdrawal Agreement").

3 The transition period may, before 1 July 2020, be extended once for up to 1 or 2 years (Article 132(1) of the Withdrawal Agreement). The UK government has so far ruled out such an extension.

4 Subject to certain exceptions provided for in Article 127 of the Withdrawal Agreement, none of which is relevant in the context of this notice.

5 In particular, a free trade agreement does not provide for internal market concepts (in the area of goods and services) such as mutual recognition, the 'country of origin principle', and harmonisation. Nor does a free trade agreement remove customs formalities and controls, including those concerning the origin of goods and their input, as well as prohibitions and restrictions for imports and exports.

A. LEGAL SITUATION AS OF THE END OF THE TRANSITION PERIOD

As of the end of the transition period, the EU rules in the field of medicinal products, in particular Regulation (EC) No 726/2004,[6] Directive 2001/83/EC,[7] and Directive 2001/82/EC,[8] no longer apply to the United Kingdom.[9] This has in particular the following consequences:

1. ISSUES RELATED TO MARKETING AUTHORISATION, MARKETING AUTHORISATION PROCEDURES

1.1. Marketing authorisation holder, applicant

According to Article 2 of Regulation (EC) No 726/2004, the marketing authorisation holder must be established in the Union.

Thus, as of the end of the transition period, a marketing authorisation holder currently established in the United Kingdom has to have transferred its marketing authorisation to a holder established in the EU.[10] This means that the addressee of the marketing authorisation decision changes to the new addressee. The transfer of the marketing authorisation must be fully completed and implemented by the marketing authorisation holder before the end of the transition period.

Any application for marketing authorisations must be made by applicants established in the Union. Therefore, applications made by applicants established in the United Kingdom will need to change to an applicant established in the EU. It is strongly recommended that applicants established in the United Kingdom consider such change in advance of the submission of the marketing authorisation application.

1.2. Reference medicinal product (generic or hybrid application)

A generic or hybrid application in accordance with Article 10 of Directive 2001/83/EC or Article 13 of Directive 2001/82/EC refers to information that is

---

6 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p. 1.

7 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67.

8 Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products, OJ L 311, 28.11.2001, p. 1.

9 Regarding the applicability of the EU law on medicinal products to Northern Ireland, see Part C of this notice.

10 For centrally authorised medicinal products, cf. Commission Regulation (EC) No 2141/96 of 7 November 1996 concerning the examination of an application for the transfer of a marketing authorization for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93, OJ L 286, 8.11.1996, p. 6. See also EMA Q&A on transfer.

contained in the dossier of a reference medicinal product (RefMP) that is or has been authorised in the Union.[11]

Generic/hybrid marketing authorisations granted before the end of the transition period referring to a RefMP authorised by the UK (UK RefMP) remain valid in the EU.

For generic/hybrid applications for which marketing authorisations will be granted after the end of the transition period the following applies:

- Where the RefMP has been authorised before the end of the transition period, it is advised that applicant refers to a RefMP that has been authorised in an EU-27 Member State. This will facilitate management of generic/hybrid product's life cycle in the post-authorisation phase, considering for example the need to implement changes to the product information of the EU RefMP also for the generic/hybrid products.[12]

- Where the RefMP has been authorised after the end of the transition period, it has to be authorised in an EU Member States.

1.3. Bioequivalence studies

According to Article 10(1) of Directive 2001/83/EC or Article 13(1) of Directive 2001/82/EC the applicant can submit an abridged application if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised in the EU for not less than eight years. According to Article 10(2)(b) of Directive 2001/83/EC and Article 13(2)(b) of Directive 2001/82/EC, generic medicinal product means a medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

The comparator used in a bioavailability study should be sourced, i.e. manufactured in the EU.[13]

Generic/hybrid applications for which marketing authorisations will be granted after the end of the transition period should refer to pivotal studies (bioequivalence, in vitro dissolution tests or therapeutic equivalence studies, as appropriate) that have been conducted with a medicinal product sourced in the EU. In cases where bioequivalence studies have been conducted with a reference product sourced in the

---

[11] See also the electronic application form for marketing authorisation applications, section 1.4.2.2. or 1.4.3.2.

[12] For the (exceptional) situation where a RefMP is or has been authorised in the United Kingdom, and access to the dossier is necessary for a marketing authorisation in the EU, see Article 45(1) of the Withdrawal Agreement.

[13] In exceptional cases where bioequivalence studies are intended for use in new applications which will be submitted before the end of the transition period and if these bioequivalence studies have been already completed the applicants may consider contacting the competent authority to discuss the particular circumstances of their application in order to avoid unnecessary repetition of studies in humans or animals.

United Kingdom before the end of the transition period and when this product is the same as an EU reference product, authorised either via the centralised procedure or mutual recognition or decentralised procedure based on the same dossier, the applicant may consider contacting the competent authority to discuss the particular circumstances of the application also in cases when the application cannot be submitted before the end of the transition period, in order to avoid unnecessary repetition of studies in humans or animals.

1.4. Marketing authorisation (applications) for biosimilars (medicinal products for human use)

The considerations described under section 1.2. and 1.3. regarding the choice of RefMP and the source of the comparator are also applicable to biosimilars.[14]

1.5. Well-established use

According to Article 10a of Directive 2001/83/EC and Article 13a of Directive 2001/82/EC it is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature if it can be demonstrated that the active substances of a medicinal product in the claimed therapeutic indication and (for veterinary products) target species have been in well-established use within the EU for at least ten years, with recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I of Directive 2001/83/EC or Annex I of Directive 2001/82/EC are to apply.

Data sourced from the United Kingdom before the end of the transition period can be taken into account to demonstrate that the active substances of a medicinal product in the claimed therapeutic indication and (for veterinary products) target species have been in well-established use within the EU for at least ten years, with recognised efficacy and an acceptable level of safety.

1.6. Global marketing authorisation (GMA)

The concept of 'global marketing authorisation' within the meaning of Article 6(1) of Directive 2001/83/EC and Article 5(1) of Directive 2001/82/EC covers the initial marketing authorisation and all subsequent developments of the original medicinal product, irrespective of their authorisation procedures, namely variation or grant of a separate marketing authorisation to the same marketing authorisation holder. The global marketing authorisation is accompanied only by a single regulatory data protection period which applies both to data relating to the original medicinal product and to data presented for any subsequent developments. That regulatory data protection period begins with the grant of the initial marketing authorisation in the EU.

Marketing authorisations granted before the end of the transition period by the United Kingdom are considered as the initial marketing authorisation in the EU.

[14] The Guideline on similar biological medicinal products are however to be consulted for the available scientific guidance when considering using a non-EU authorised comparator (i.e. a non-EU authorised version of the reference medicinal product) in the development of a biosimilar.

1.7. Minor Use Minor Species/limited market (veterinary medicinal products)

According to Article 79 of Regulation (EC) No 726/2004, in the case of veterinary products which have limited markets, or in the case of veterinary medicinal products intended for diseases with a regional distribution, the Management Board of the European Medicines Agency is to adopt the necessary measures to provide assistance to companies at the time of submission of their applications. This activity supports applicants for marketing authorisations, which in accordance with the general rules have to be established in the EU.

If the sponsor/applicant is established in the United Kingdom, the Minor Use Minor Species/limited market (hereafter 'MUMS/limited market') incentives provided on the basis of Article 79 of Regulation (EC) No 726/2004 would no longer be applicable after the end of the transition period, as a sponsor/applicant established within a third country cannot seek and receive MUMS/limited market classification in the EU. However, MUMS/limited market classification is connected to the product/indication and therefore transferable together with the product.

To formally acknowledge the transfer, the EMA requires a letter from the original sponsor/applicant officially informing the EMA of the transfer of the classification product and the MUMS/limited market classification from the original sponsor/applicant to a sponsor/ applicant established in the EU. This letter should state the document reference number of the MUMS outcome letter confirming the MUMS classification.

For already authorised MUMS/limited market veterinary medicinal products it is important to note that a transfer of marketing authorisation does not include a transfer of a MUMS/limited designation as this is subject to a different procedure. Therefore, for those authorised MUMS/limited market veterinary medicinal products the marketing authorisation holder needs to transfer the marketing authorisation (see section 1.1 above)) and separately the MUMS/ limited market classification (see above). The five year period of validity for MUMS/limited market classification is not affected by the transfer of classification.

1.8. Financial and administrative assistance in accordance with Commission Regulation (EC) No 2049/2005 (the 'SME Regulation')

According to Article 2 of Commission Regulation (EC) No 2049/2005 of 15 December 2005,[15] in order to be eligible for financial and administrative assistance, companies must be established in the EU and meet the definition of an SME.

As of the end of the transition period, the guidance for non-EU based companies applies also to UK based companies. Further information is available on the EMA website (link) and in the SME User Guide (link).

[15] Commission Regulation (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises, OJ L 329, 16.12.2005, p. 4.

1.9. 'Sunset clause'

According to Article 24(4) to (6) of Directive 2001/83/EC, Article 28(4) to (6) of Directive 2001/82/EC and Articles 14(4) to (6) and 39(4) to (6) of Regulation (EC) No 726/2004, any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State or on the Union market will cease to be valid. When an authorised product previously placed on the market in the authorising Member State or in the Union is no longer actually present on the market for a period of three consecutive years, the authorisation for that product will cease to be valid.

In case a medicinal product has been marketed in the United Kingdom, the placing on the UK market before the end of the transition period will be taken into account to determine the applicability of the sunset clause for the medicinal product concerned. In this respect, if after the end of the transition period, the medicinal product is not placed on any other market of the remaining Member States, the three year period for the sunset clause will start running from the last date the medicinal product was placed on the UK market before the end of the transition period.

1.10. CHMP scientific opinion for ancillary medicinal substances in medical devices assessed by UK notified bodies (medicinal products for human use)

According to Article 1(4) of Directive 93/42/EEC where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, that device shall be assessed and authorised in accordance with Directive 93/42/EEC. In accordance with Annex I of Directive 93/42/EEC for a new medical device, the notified body acts as the applicant in an initial consultation procedure with EMA concerning the scientific opinion on the ancillary medicinal substances incorporated in the medical devices.

Union product legislation requires Notified Bodies to be established in a Member State and be designated by a Member State notifying authority.

As of the end of the transition period, UK notified bodies will lose their status as EU notified bodies. They will no longer be able to be an applicant in an initial consultation procedure with EMA and EMA will not be able to issue a scientific opinion to them as notified bodies of a third country.[it is advised to insert here reference to the Brexit notice on medical devices/notified bodies]

1.11. Referral procedures ongoing at the end of the transition period

Referral procedures[16] ongoing at the end of the transition period will continue, irrespective of the Member State that triggered the referral, with the exception of referral procedures on applications with the United Kingdom as the reference member state.[17]

---

16 Cf. Article 29 et sequ of Directive 2001/83/EC and Article 33 et sequ of Directive 2001/82/EC.

17 It is recalled that that during the transition period, the United Kingdom cannot act as reference Member State (Article 128(6) of the Withdrawal Agreement).

The fees for referrals are determined at the start date of procedure. For medicinal products for human use the fees for Pharmacovigilance referrals are calculated based on products authorised in the EU (as recorded in 'Article 57 database') at that time. Until the end of the transition period this includes UK nationally approved products.

2. MANUFACTURING AND IMPORTATION OF FINISHED PRODUCTS AND ACTIVE PHARMACEUTICAL INGREDIENTS

2.1. Import authorisation

According to Article 40(3) of Directive 2001/83/EC and Article 44(3) of Directive 2001/82/EC, the competent authorities of the Union are to ensure that the import of medicinal products into their territory is subject to an authorisation. The authorisation is granted when a number of conditions, as defined in Articles 41 and 42 of Directive 2001/83/EC and Articles 45 and 46 of Directive 2001/82/EC, are fulfilled (e.g. availability of a qualified person within the EU, GMP[18] inspection).

As of the end of the transition period, medicinal products shipped from the United Kingdom to the EU will be imported medicinal products, and the requirements for importers apply.[19]

2.2. Supervision of manufacturing sites of medicinal products in third countries

According to Articles 18 and 43 of Regulation (EC) No 726/2004, in case of medicinal products imported from third countries the supervisory authorities are to be the competent authorities of the Member State or Member States that granted the authorisation provided for in Article 40(3) of Directive 2001/83/EC or Article 44(3) of Directive 2001/82/EC respectively to the importer of the concerned medicinal product.

As of the end of the transition period, UK authorities will no longer undertake the role of a supervisory authority.

The new EU supervisory authority responsible for supervision of manufacturing sites located in the United Kingdom and third country sites previously inspected by the United Kingdom will decide, using a risk-based approach, when an inspection of the site(s) concerned will be required, in order to confirm or re-confirm GMP compliance.

2.3. Batch release

In accordance with Article 51(1) of Directive 2001/83/EC and Article 55(1) of Directive 2001/82/EC, the qualified person of the manufacturing and importation authorisation holder is responsible to certify that each batch of medicinal product

[18] Good manufacturing practices.

[19] In case of a new authorised importer established in the EU, the corresponding variation has to be submitted (see Variation Guideline (2013/ C 223/01), classification B.II.b.2).

intended to be placed on the EU market was manufactured in accordance with EU GMP requirements and the marketing authorisation.

Each batch imported into the EU has to undergo upon importation a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation.[20]

As of the end of the transition period, these requirements apply to medicinal products imported from the United Kingdom to the EU.

2.4. Official Control Authority batch release

According to Article 114 of Directive 2001/83/EC and Article 82 of Directive 2001/82/EC, Member States may require the marketing authorisation holder of a human immunological medicinal product or a medicinal product derived from human blood or plasma or immunological veterinary medicinal product to submit samples from each batch of the bulk and/or the medicinal product for examination by an Official Medicines Control Laboratory (OMCL) or a laboratory that a Member State has designated for that purpose before the release on the market. This is referred to as Official Control Authority Batch Release (OCABR).

According to the EU Administrative Procedure for Official Control Authority Batch Release[21], prior to marketing in the EU, batches of medicinal products subject to independent testing are to obtain an Official Control Authority Batch Release Certificate common to all Member States. Such certificate demonstrates that the batch of medicinal product has been examined and tested by an OMCL within the EU in accordance with this procedure and with Official Control Authority Batch Release guidelines pertaining to the medicinal product and that it is in compliance with the approved specifications laid down in the relevant monographs of the European Pharmacopoeia (Ph. Eur.) and in the relevant marketing authorisation.

For products placed on the market as of the end of the transition period, OCABR cannot be carried out by an OMCL located in the United Kingdom. OCABR has to be carried out by an OMCL located within the EU. The marketing authorisation holder will therefore need to identify an OMCL located in the EU for official batch release or an officially recognised partner (as stated above) for official batch release. A list of the OMCLs that may be in a position to provide EU OCABR certificates for different products is available to manufacturers from the European Directorate for the Quality of Medicines & Healthcare (EDQM) of the Council of Europe on request at batchrelease@edqm.eu.

Where the UK OCML had issued a OCABR before the end of the transition period, the OMCL of an EU Member State may take account of the certificate issued by the UK OMCL when issuing a OCABR for products placed on the EU market after the end of the transition period.

---

[20] Where a batch release site is transferred to the EU, the corresponding variation has to be submitted (see Variation Guideline (2013/ C 223/01), classification B.II.b.2).

[21] Guideline for the administrative procedure to be followed by the competent OMCL authorities for the implementation of Directive 2001/83/EC Article 114 as amended by Directive 2004/27/EC, available at https://www.edqm.eu/en/batch-release-human-biologicals-vaccines-blood-and-plasma-derivatives

The Official Control Authority Batch Release (OCABR) of the OMCL of an EU Member State remains valid even if the marketing authorisation holder changes.

2.5. Official Batch Protocol Review (veterinary medicinal products)

According to Article 81 of Directive 2001/82/EC, Member States may require the marketing authorisation holder for immunological veterinary medicinal products to submit to the competent authorities copies of all the control reports signed by the qualified person in accordance with Article 55 of Directive 2001/82/EC in order to verify that control tests were carried out in accordance with the methods laid down for the purposes of marketing authorisation. This is referred to as an 'Official Batch Protocol Review' (OBPR).

For products placed on the market after the end of the transition period, OBPR cannot be carried out by a UK Competent Authority. The marketing authorisation holder will therefore need to identify another Competent Authority located in the EU or an officially recognised partner (as stated above) for official batch protocol review.

2.6. Imports of active substances (medicinal products for human use)

According to Article 46b(2) of Directive 2001/83/EC, active substances for medicinal products for human use are to only be imported in the EU if, inter alia, the active substances are accompanied by a written confirmation from the competent authority of the exporting third country which, as regards the plant manufacturing that exported active substance, confirms that the standards of good manufacturing practice and control of the plant are equivalent to those in the EU.

As of the end of the transition period, active substances manufactured in the United Kingdom and imported into the EU are subject to this requirement.

3. PARALLEL TRADE

3.1. Sourcing medicinal products in the United Kingdom

Parallel trade of medicinal products in the internal market is possible in particular because of (i) the rules in the internal market for the exhaustion of trade mark rights; and (ii) the fact that the summary of product characteristics and the labelling of medicinal products are – apart from issues of language used – identical.

As of the transition period, the rules for exhaustion of trade mark rights in the EU no longer apply in respect of products placed on the UK market. Moreover, the terms of the marketing authorisation will over time differ.[22]

Hence, parallel trade of medicines sourced in the United Kingdom is in practice no longer possible as of the end of the transition period.

[22] To this may add national rules on parallel trade of medicinal products with third countries.

3.2. Parallel distribution notifications

Article 76(4) of Directive 2001/83/EC addresses the distribution of a centrally authorised medicinal product from one Member State to another by a pharmaceutical company independent of the marketing-authorisation holder ("parallel distribution"; in the context of this legislation, this notion is to be distinguished from "parallel imports" of nationally authorised products). It does not cover export or import of the product from third countries. Moreover, after the transition period, the scope of central marketing authorisations issued by the Commission no longer includes the United Kingdom. Thus, as of the end of the transition period,

- Article 76(4) of Directive 2001/83/EC no longer applies to medicinal products sourced in the United Kingdom for the purpose of parallel distribution in EU;[23]

- Notices with the United Kingdom as the only destination country will become obsolete, whereas, notices with several destination countries will remain valid with respect to EU destination countries;

- Notices to distributors in the United Kingdom will become obsolete. Please note that the transfer of parallel distribution notices to another entity is not foreseen and a change of address is possible only in case the legal entity remains the same.

- UK sites will have to have been removed, in order for these notices to remain valid.

4. PHARMACOVIGILANCE, INCL. QUALIFIED PERSON FOR PHARMACOVIGILANCE AND POST-MARKETING AUTHORISATION PROCEDURES

4.1. Qualified Person for Pharmacovigilance (QPPV)

According to Article 8 of Directive 2001/83/EC and Article 74 of Directive 2001/82/EC, the qualified person responsible for pharmacovigilance must reside and carry out his/her tasks in a Member State of the EU.

Thus, as of the end of the transition period, QPPVs currently residing/carrying out their tasks in the United Kingdom have to have been transferred to the EU, or a new QPPV residing and carrying out his/her tasks in the EU will need to be appointed.

Changes in the QPPV, including contact details (telephone, and fax numbers, postal address and email address) may, for medicinal products for human use, be updated through the Article 57 database only (without the need for a variation) (see Variation Guideline (2013/C 223/01), classification C.I.8). Regarding medicinal products for veterinary use the changes should be updated through a variation (see Variation Guideline (2013/C 223/01), classification C.I.9).

[23] However, it is recalled that, as set out in section 3.1. above, parallel distribution and parallel imports of medicinal products sourced in the United Kingdom will anyhow in practice no longer be possible after the end of the transition period.

4.2. Pharmacovigilance System Master File (PSMF) (medicinal products for human use)

According to Commission Implementing Regulation (EU) No 520/2012,[24] the PSMF must be located within the EU. The supervisory authority for pharmacovigilance is the competent authority of the Member State in which the pharmacovigilance system master file is located.

Thus, as of the end of the transition period, PSMFs currently located in the United Kingdom have to have been moved to the EU.

Changes to the location of the PSMF (street, city, postcode, country) may be updated through the Article 57 database only (without the need for a variation) (see Variation Guideline (2013/C 223/01), classification C.I.8).

4.3. Back-up arrangements for the Qualified Person's for Pharmacovigilance (QPPV) (medicinal products for human use)

According to Article 2 of Commission Implementing Regulation (EU) No 520/2012 back-up arrangements are to apply in the absence of the QPPV. As the tasks of QPPV need to be carried in a Member State of the EU, the back-up arrangements for cases of absence of the QPPV, which replace such tasks, also need to be performed in the EU.

Where a marketing authorisation holder relies on the services of a deputy QPPV as part of its back-up arrangements in the absence of the QPPV, those arrangements are to ensure that the deputy QPPV is established and performs his/her tasks in the EU as of the end of the transition period.

4.4. Reporting into EudraVigilance of Individual Case Safety Reports (ICSRs) from the United Kingdom (medicinal products for human use)

According to Article 107 of Directive 2001/83/EC **suspected serious adverse reactions** have to be reported no matter if they occurred in the EU or in third countries.

Suspected non-serious adverse reactions occurring in third countries do not have to be reported in the EU. Thus, after the transition period

- non-serious adverse reactions that have occurred in the United Kingdom before the end of the transition period have to be reported;

- it is no longer mandatory to submit to EudraVigilance reports of suspected non-serious adverse reactions that have occurred in the United Kingdom as of the end of the transition period.

Individual cases originating from the United Kingdom and submitted to EudraVigilance before the end of the transition period, when a follow-up information is received by the marketing authorisation holder after the transition

[24] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council, OJ L 159, 20.6.2012, p. 5.

period, are to be submitted to EudraVigilance when third country reporting criteria apply.

As of the end of the transition period, UK authorities will no longer have access to EudraVigilance. Marketing authorisation holders are therefore reminded that they will need to submit into EudraVigilance information that they might receive from UK authorities regarding cases occurring in the United Kingdom, in line with the reporting requirements for non-EU cases.

4.5. Periodic Safety Update Reports

According to Article 107b of Directive 2001/83/EC, Article 75(5) of Directive 2001/82/EC, and Article 28 and 49 of Regulation 726/2004 periodic safety update reports (PSURs) are to contain cumulative and interval summaries of global safety data obtained from various sources worldwide. Relevant safety data obtained from UK sources after the transition period are therefore to be included in PSURs as per usual requirements for third country data.

For the calculation of exposure from marketing experience by region, patients exposed in the United Kingdom before the end of the transition period are to be included in the EU estimate. Thereafter, UK patient exposure is to be considered as part of the non-EU regions.

5. ORPHAN MEDICINES, TRADITIONAL HERBAL MEDICINAL PRODUCTS (MEDICINAL PRODUCTS FOR HUMAN USE)

5.1. Orphan designation holder

According to Article 2 of Regulation (EC) No 141/2000 the sponsor of an orphan medicinal product designation must be established in the EU.

Thus, as of the end of the transition period, an orphan designation holder currently located in the United Kingdom has to change the place of establishment to a Member State of the EU and submit the corresponding documentation through a change of name and/or address of the orphan designation holder procedure provided the legal entity remains the same.[25] [26]

5.2. Prevalence for orphan drug designation

For applications for orphan designations or for its maintenance submitted as of the end of the transition period, patients in the United Kingdom should no longer be taken into account in the calculation of the prevalence of the disease in order to meet the requirements for orphan drug designation as set out in Regulation (EC) No 141/2000.

---

[25] See Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another, 27.03.2014.

[26] See Checklist for sponsors applying for the transfer of Orphan Medicinal Product (OMP) designation and the corresponding template.

5.3. Traditional-use registration of traditional herbal medicinal products

The traditional-use registration procedure allows the registration of herbal medicinal products without requiring particulars and documents on tests and trials on safety and efficacy, provided that there is sufficient evidence of the medicinal use of the product throughout a period of at least 30 years, including at least 15 years in the EU.

Data sourced from the United Kingdom before the end of the transition period can be taken into account to demonstrate that the product has been in medicinal use throughout a period of at least 15 years within the EU.

6. PRODUCT INFORMATION AND LABELLING

6.1. Local representative located in the United Kingdom, and nominated for Member States other than the United Kingdom

In view of the specific tasks[27], the local representative mentioned in the product information is to be located in the EU. Therefore, any local representative located in the United Kingdom and nominated for Member States other than the United Kingdom will have to be changed to a local representative located in the EU.

The corresponding amendments to labelling and package leaflet must be fully completed and implemented by the marketing authorisation holder before the end of the transition period, either as part of a regulatory procedure affecting the annexes (e.g. variation, renewal), or through a notification under an Article 61(3) of Directive 2001/83/EC or (for veterinary products) through a Type IAIN variation (see Variation Guideline (2013/ C 223/01), classification C.II.6.a).

6.2. Local representative for UK mentioned in the product information

As of the end of the transition period, the mentioning of the local representative for the United Kingdom in the product information will become obsolete.

The deletion of the local representative for UK in the product information will need to be incorporated as part of a future regulatory procedure affecting the annexes (e.g. variation, renewal) and the earliest opportunity after the transition period should be used.

6.3. 'Multi-country packs' including the United Kingdom

Multi-country packs are medicinal products that are labelled to allow their placing on the market in several Member States with the same packaging. This possibility is subject to the requirements set out in Directive 2001/83/EC in Title V or Directive 2001/82/EC in Title V and requires that the summary of product characteristics is the same in all the markets concerned.

Article 57 and Article 62 of Directive 2001/83/EC and Article 63 of Directive 2001/82/EC allow Member States to require inclusion of certain additional labelling

[27] See Notice to applicants, https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/2015-07_14_3_packaging.pdf.

information in a restricted area (the so-called "blue box") provided that all the strict conditions for application of Article 57 or Article 62 of Directive 2001/83/EC and Article 63 of Directive 2001/82/EC are fulfilled.

In applying these provisions, multi-country packs with the UK market are only possible if

- the product information is exactly the same in the United Kingdom as in the EU; and

- the Member State has allowed additional information labelled in the "blue box". This additional information must be limited to certain administrative information.

In any event the product labelling and package leaflet must be fully in line with the summary of product characteristics as authorised in the EU.

7. SAFETY FEATURES (MEDICINAL PRODUCTS FOR HUMAN USE)

7.1. Information about the unique identifier uploaded to the UK repository until the end of the transition period

Article 33(1) of Commission Delegated Regulation (EU) 2016/161 requires marketing authorisation holders to ensure that unique identifiers and related information are uploaded to the EU repository system before a product is released for sale or distribution. Any information uploaded to the EU hub or a national repository is to be transferred and stored in all national or supranational repositories serving the territory of Member State(s) where the product is intended to be placed on market. Therefore, the information on products released on the market before the end of the transition period will be already present in the national repositories where the product is intended to be placed on the market and there is no need to transfer information from the UK repository.

7.2. Safety features for imported medicinal products

The manufacturer placing the safety features, as referred to in Articles 14 and 15 of the Commission Delegated Regulation (EU) No 2016/161, is the manufacturer actually affixing the unique identifier and anti-tampering device on the packaging. There is no requirement that such a manufacturer has to be located in the EU. However, if a manufacturer is not in the EU, then the obligation to ensure that Articles 14 and 15 of the Delegated Regulation (EU) No 2016/161 are complied with lies with the importer.

The Qualified Person at the batch release site in the EU will have to ensure that the safety features have been affixed to the packaging (Article 51(1) of Directive 2001/83/EC). This task may be delegated to appropriately trained personnel or third parties, as set out in Annex 16 to the EU GMP guidelines (section 1.7). For general GMP requirements on outsourced activities, refer to Chapter 7 of the EU GMP guidelines.

The responsibility for ensuring that the information is uploaded in the repositories system lies with the marketing authorisation holder (or the person responsible for placing on the market medicinal products which are parallel distributed/parallel imported). The Delegated Regulation does not prohibit MAHs from subcontracting

or delegating data-upload tasks to on-boarding partners (OBPs) acting on their behalf. However, the infrastructures, hardware and software used for data upload must be physically located in the EU (see question 7.19 in Questions and Answers on Safety Features for Medicinal Products for Human Use).

8. INSPECTION RESULTS

8.1. Outcomes of inspections conducted by the UK competent authority before the end of the transition period

It is expected that findings of inspections, in particular to determine compliance with good manufacturing practice, good clinical practice and pharmacovigilance obligations, conducted by the UK competent authority before the end of the transition period are implemented by the inspected entities in accordance with the applicable legislation, in particular Directive 2003/94/EC, Commission Delegated Regulation (EU) No 1252/2014 and Directive 91/412/EEC with regard to good manufacturing practice, Directive 2001/20/EC and Commission Directive 2005/28/EC with regard to good clinical practice and Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) 520/2012 with regard to pharmacovigilance obligations.

8.2. EU GMP certificate issued by UK authorities before the end of the transition period

All medicinal products for human use and veterinary medicinal products manufactured or imported into the EU, including medicinal products intended for export, are to be manufactured in accordance with the principles and guidelines of good manufacturing practice.[28] A certificate of good manufacturing practice ("GMP certificate") is issued to a manufacturer if the outcome of the inspection shows that the manufacturer complies with the principles and guidelines of good manufacturing practice as provided for by the Union legislation.[29]

While EU legislation does not require an EU GMP certificate issued by an EU Member State for issuing a marketing authorisation[30] or importation of a medicinal product,[31] in practice GMP certificates issued by EU competent authorities are used to confirm EU GMP compliance in regulatory submissions (e.g. marketing authorisation applications) and for imports from third countries. This means that GMP compliance of manufacturing sites in third countries may also be confirmed through other means, based on a risk-based approach (e.g. based on information on GMP compliance from third country regulatory authorities). GMP certificates issued by the UK competent authority before the end of the transition period are to be considered as information on GMP compliance from the third country regulatory authority.

---

28 Commission Directive 2003/94/EC, Recital (1).

29 Directive 2001/83/EC, Article 111(5).

30 Article 8(3)(ha) of Directive 2001/83/EC.

31 Article 51(1)(b) of Directive 2001/83/EC, Article 55(1)(b) of Directive 2001/82/EC.

B. RELEVANT SEPARATION PROVISIONS OF THE WITHDRAWAL AGREEMENT

Article 41 of the Withdrawal Agreement provides that an existing and individually identifiable good lawfully placed on the market in the EU or the United Kingdom before the end of the transition period may be further made available on the market of the EU or of the United Kingdom and circulate between these two markets until it reaches its end-user.

The economic operator relying on that provision bears the burden of proof of demonstrating on the basis of any relevant document that the good was placed on the market in the EU or the United Kingdom before the end of the transition period.[32]

For the purposes of these provisions, "placing on the market" means the first supply of a good for distribution, consumption or use on the market in the course of a commercial activity, whether in return or payment or free of charge.[33] 'Supply' means that 'an existing and individually identifiable good, after the stage of manufacturing has taken place, is the subject matter of a written or verbal agreement between two or more legal or natural persons for the transfer of ownership, any other property right, or possession concerning the good in question, or is the subject matter of an offer to a legal or natural person or persons to conclude such an agreement.'[34]

This means that an individual medicinal product placed on the UK market according to this definition before the end of the transition period can still be made available in the EU after the end of the transition period.

Example: An individual pack of a medicinal product centrally authorised by the Commission and sold by a EU-based manufacturer to a EU-based wholesale distributor before the end of the transition period can still be imported into the UK on the basis of the EU authorisation.

This is without prejudice to non-fiscal controls that may apply to imports as of the end of the transition period.

In addition, concerning the aspect of exhaustion, Article 61 of the Withdrawal Agreement provides that intellectual property rights exhausted both in the EU and the United Kingdom before the end of the transition period remain exhausted.

C. APPLICABLE RULES IN NORTHERN IRELAND AFTER THE END OF THE TRANSITION PERIOD

As from the end of the transition period, the Protocol on Ireland/Northern Ireland ('IE/NI Protocol') applies.[35] The IE/NI Protocol is subject to periodic consent of the Northern

[32] Article 42 of the Withdrawal Agreement.

[33] Article 40(a) and (b) of the Withdrawal Agreement.

[34] Article 40(c) of the Withdrawal Agreement.

[35] Article 185 of the Withdrawal Agreement.

Ireland Legislative Assembly, the initial period of application extending to 4 years after the end of the transition period.[36]

The IE/NI Protocol makes certain provisions of EU law applicable also to and in the United Kingdom in respect of Northern Ireland. It also provides that insofar as EU rules apply to and in the United Kingdom in respect of Northern Ireland, it is assimilated to a Member State.[37]

The IE/NI Protocol provides that the EU pharmaceutical acquis applies to and in the United Kingdom in respect of Northern Ireland.[38]

This means that references to the EU in Parts A and B of this Notice have to be understood as including Northern Ireland, whereas references to the United Kingdom have to be understood as referring only to Great Britain.

More specifically, this means *inter alia* the following:

- A medicinal product placed on the market in Northern Ireland has to comply with the EU *acquis* for medicinal products, i.e. the product has to be covered by a marketing authorisation issued by the Commission or the United Kingdom in applying the EU *acquis* for medicinal products;

- Marketing authorisation applicants who wish to obtain a marketing authorisation for the United Kingdom in respect of Northern Ireland have to include Northern Ireland in the scope of their marketing authorisation application in the decentralised procedure (DCP) or the mutual recognition procedure (MRP);

- UK products will continue be part of Union referral procedures in respect of Northern Ireland; the scientific opinion and Commission Decisions will include UK products in respect of Northern Ireland;

- A medicinal product/active pharmaceutical ingredient shipped from Northern Ireland to the EU is not an imported medicinal product (see above, section A);

- A medicinal product/active pharmaceutical ingredient shipped from Great Britain to Northern Ireland is an imported medicinal product (see above, section A);

- Non-serious adverse events occurring in Northern Ireland have to be reported as if they have occurred in the EU;

- The territory of Norther Ireland is included in the assessment of prevalence, 'well-established use', as well as the 'sunset clause'.

However, the IE/NI Protocol excludes the possibility for the United Kingdom in respect of Northern Ireland to

- participate in the decision-making and decision-shaping of the Union;[39]

---

36 Article 18 of the IE/NI Protocol.

37 Article 7(1) of the Withdrawal Agreement in combination with Article 13(1) of the IE/NI Protocol.

38 Article 5(4) and section 30 of annex 2 to the IE/NI Protocol.

- initiate objections, safeguard or arbitration procedures to the extent that they concern regulations, standards, assessments, registrations, certificates, approvals and authorisations issued or carried out by EU Member States;[40]

- act as leading authority for assessments, examinations and authorisations;[41]

- invoke the country of origin principle or mutual recognition for products placed legally on the market in Northern Ireland.[42]

More specifically, this means *inter alia* the following:

- The United Kingdom, in respect of Northern Ireland, may not act as reference Member State;[43]

- The United Kingdom, in respect of Northern Ireland, may not trigger referrals;[44]

- An official batch release by the United Kingdom in respect of Northern Ireland is not recognised in the EU.[45]

Moreover, with regard to medicinal products it should be stressed that

- a medicinal product authorised in the United Kingdom in respect of Northern Ireland is not to be considered as a reference medicinal product in the Union;[46]

- the marketing authorisation holder of a medicinal product, the registration holder for a traditional herbal medicinal product, and the QPPV may not be established in Northern Ireland, with the exception of authorisations by the United Kingdom in respect of Northern Ireland;[47]

- The principle of exhaustion of intellectual property rights does not apply to the territory of Northern Ireland.

---

39 Where an information exchange or mutual consultation is necessary, this will take place in the joint consultative working group established by Article 15 of the IE/NI Protocol.

40 Fifth subparagraph of Article 7(3) of the IE/NI Protocol.

41 Article 13(6) of the IE/NI Protocol.

42 Article 7(3) of the IE/NI Protocol.

43 Article 13(6) of the IE/NI Protocol.

44 Fifth subparagraph of Article 7(3) of the IE/NI Protocol.

45 However, the batch release by a qualified person of an importer/manufacturer established in Northern Ireland is recognised in the EU (sixth subparagraph of Article 7(3) of the IE/NI Protocol).

46 Section 20 of annex 2 to the IE/NI Protocol.

47 Section 20 of annex 2 to the IE/NI Protocol.

The websites of the Commission (https://ec.europa.eu/health/human-use_en) and of the European Medicines Agency (https://www.ema.europa.eu/en/about-us/united-kingdoms-withdrawal-european-union-brexit) provide additional information. For products authorised in decentralised or mutual recognition procedures, additional information will be provided through the websites of the Coordination Groups. These pages will be updated with further information, where necessary.

European Commission
Directorate-General Health and Food Safety

European Medicines Agency