EUROPEAN COMMISSION
Directorate-General for Health and Food Safety

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NOTICE TO STAKEHOLDERS

WITHDRAWAL OF THE UNITED KINGDOM AND EU RULES IN THE FIELD OF CLINICAL TRIALS

Since 1 February 2020, the United Kingdom has withdrawn from the European Union and has become a "third country".[1] The Withdrawal Agreement[2] provides for a transition period ending on 31 December 2020.[3] Until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 applicable after 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 after the end of the transition period (Part C below).

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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.

Advice to stakeholders:

To address the consequences set out in this notice, sponsors of clinical trials are in particular advised to:

- ensure establishment of the sponsor or the legal representative in the EU; and
- adapt distribution channels, to take importation requirements into account.

Please note:

This notice does not address

- EU rules on medicinal products other than investigational medicinal products;
- EU rules on personal data protection.

For these aspects, other notices are in preparation or have been published.[6]

A. LEGAL SITUATION AFTER THE END OF THE TRANSITION PERIOD

After the end of the transition period, the EU rules in the field of clinical trials, and in particular Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use,[7] no longer apply to the United Kingdom.[8] This has in particular the following consequences:[9]

1. SUPPLY OF INVESTIGATIONAL MEDICINAL PRODUCTS

According to Article 13(1) of Directive 2001/20/EC, the import of investigational medicinal products into the EU is subject to the holding of an authorisation. This authorisation is also required if only part of the manufacturing (e.g. packaging or repacking, for example as part of blinding activities) is performed in the third country. Article 13(2) of Directive 2001/20/EC requires the holder of this authorisation to have permanently and continuously at his disposal the services of at least one qualified person located in the EU. The qualified person is responsible for ensuring that each production batch of an investigational medicinal product intended

6 https://ec.europa.eu/info/european-union-and-united-kingdom-forging-new-partnership/future-partnership/preparing-end-transition-period_en

7 OJ L 121, 1.5.2001, p. 34.

8 Regarding the applicability of parts of Directive 2001/20/EC in Northern Ireland, see Part C of this notice.

9 Directive 2001/20/EC is going to be repealed by Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use (OJ L 158, 27.5.2014, p. 1). However, in view of the timelines set in its Article 99, this Regulation is not going to apply before the end of the transition period.

to be used in a clinical trial has been manufactured and checked in accordance with the standards of good manufacturing practices at least equivalent to those laid down in the EU and that each production batch has been checked in accordance the clinical trial authorisation (Article 13(3)(b) of Directive 2001/20/EC). Regarding comparator investigational medicinal products which are authorised in a third country, the qualified person is responsible for ensuring, subject to exceptions, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality (Article 13(3)(c) of Directive 2001/20/EC). Retesting (analytical control) in the EU is not mandatory if already carried out in the third country (Article 11(2) second subparagraph of Commission Directive 2003/94/EC[10]).

After the end of the transition period, these rules will apply to investigational medicinal products imported from the United Kingdom into the EU.

2. ESTABLISHMENT REQUIREMENTS

2.1. Sponsor or legal representative

According to Article 19 of Directive 2001/20/EC, the sponsor of a clinical trial or a legal representative must be established in the EU. After the end of the transition period, a sponsor established in the United Kingdom and conducting a clinical trial in the EU has to ensure that a sponsor or a legal representative is established in the EU. The change of the sponsor or of the sponsor's legal representative is typically a substantial amendment,[11] which requires notification to the competent authority/information of the Ethics Committee in accordance with the procedure set out in Article 10(a) of Directive 2001/20/EC.

2.2. Qualified person

According to Article 13(2) of Directive 2001/20/EC, the qualified person (cf. section 1 of this notice) has to be established in the EU.

3. SUBMISSION OF CLINICAL TRIAL INFORMATION

Provisions of EU law relating to clinical trials[12] provide for the submission of certain clinical trial information to the EU clinical trials database EudraCT.

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[10] Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, OJ L 262, 14.10.2003, p. 22.

[11] See point 123(a) of the Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) (OJ, 30.3.2010, p. 1).

[12] Cf. Articles 41 and 46 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use (OJ L 378, 27.12.2006, p. 1), Article 57 of 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,

Regarding protocol-related information, after the end of the transition period, UK-specific trial information will no longer have to be submitted to EudraCT, except when the trial is part of an agreed Paediatric Investigation Plan and the United Kingdom is the only country in which the protocol has been submitted.

Regarding result-related information, results of clinical trials conducted in the United Kingdom and completed before the end of the transition period must be submitted to EudraCT if the reporting of these results is due before the end of the transition period. Results of clinical trials conducted only in the United Kingdom and results of multi-country trials where the United Kingdom was the only EU Member state where the clinical trial was conducted have to be submitted to EudraCT, also after the end of the transition period, if this is required for non-EU studies (i.e. if the trial is part of an agreed Paediatric Investigation Plan or falls in the scope of Article 46 of Regulation (EC) No 1901/2006).

B. RELEVANT SEPARATION PROVISIONS OF THE WITHDRAWAL AGREEMENT

Article 41(1) 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.[13]

For the purposes of that provision, "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 for payment or free of charge.[14] "Supply of a good for distribution, consumption or use" 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."[15]

Example: Investigational medicinal products have to be labelled with name, address and telephone number of the sponsor.[16] An individual investigational medicinal product supplied by the UK-based producer to a UK-based wholesaler before the end of the transition period and labelled with a UK-based sponsor can still be supplied further into the EU without the need to re-label with new sponsor details.

30.4.2004, p. 1), and the implementation guidelines published in EudraLex, Volume 10 (https://ec.europa.eu/health/documents/eudralex/vol-10_en).

13 Article 42 of the Withdrawal Agreement.

14 Article 40(a) and (b) of the Withdrawal Agreement.

15 Article 40(c) of the Withdrawal Agreement.

16 https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf

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

After the end of the transition period, the Protocol on Ireland/Northern Ireland ("IE/NI Protocol") applies.[17] The IE/NI Protocol is subject to periodic consent of the Northern Ireland Legislative Assembly, the initial period of application extending to 4 years after the end of the transition period.[18]

The IE/NI Protocol makes certain provisions of EU law applicable also to and in the United Kingdom in respect of Northern Ireland. In the IE/NI Protocol, the EU and the United Kingdom have furthermore agreed that insofar as EU rules apply to and in the United Kingdom in respect of Northern Ireland, Northern Ireland is treated as if it were a Member State.[19]

The IE/NI Protocol provides that Article 13 of Directive 2001/20/EC applies to and in the United Kingdom in respect of Northern Ireland.[20]

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

- EU rules for good manufacturing practice of investigational medicinal products apply in Northern Ireland;
- an investigational medicinal product manufactured in Northern Ireland and shipped to the EU is not an imported investigational medicinal product;
- an investigational medicinal product shipped from Great Britain to Northern Ireland is an imported investigational medicinal product (see section A of this notice);
- the qualified person may be established in Northern Ireland (see section A.2.2. of this notice).

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;[21]
- invoke the country of origin principle or mutual recognition.[22]

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

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17 Article 185 of the Withdrawal Agreement.

18 Article 18 of the IE/NI Protocol.

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

20 Article 5(4) of the IE/NI Protocol and section 20 of annex 2 to that Protocol.

21 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.

22 First subparagraph of Article 7(3) of the IE/NI Protocol.

- An official batch release by the United Kingdom in respect of Northern Ireland is not recognised in the EU.[23]

The websites of the Commission on clinical trials (https://ec.europa.eu/health/human-use/clinical-trials_en) provide general information. These pages will be updated with further information, where necessary.

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[23] 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).