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Questions and answers to Stakeholders on the implications of Regulation (EU) 2023/1182 for centrally authorised medicinal products for human use

Practical guidance on the applicable rules to centrally authorised medicinal products for human use intended to be placed on the market in Northern Ireland before and after the application of Regulation (EU) 2023/1182

¹ Revision 1 adds section 8 on the changes required in the Article 57 database and section 9 on the safety reporting into EudraVigilance and access to EudraVigilance data



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Introduction

The United Kingdom of Great Britain and Northern Ireland (UK) left the European Union (EU) and the European Atomic Energy Community as of 31 January 2020. The agreement regarding terms and conditions for the withdrawal of the UK from the EU and the European Atomic Energy Community (the 'Withdrawal agreement') was concluded on behalf of the Union by Council Decision (EU) 2020/135 and entered into force on 1 February 2020, with a transition period up to and including 31 December 2020. During the transition period, the Union law continued to apply to and in the UK.

Special rules were negotiated between the UK and the EU to address the unique circumstances on the island of Ireland. This agreement was formalised in the 'Protocol on Ireland/Northern Ireland' (the 'Protocol')/Windsor Framework² which forms part of the Withdrawal agreement and started to apply after the end of the transition period. Based on the Windsor Framework, EU pharmaceutical law applies to and in the UK in respect of Northern Ireland only, as of 1 January 2021 and to the extent provided for in the Windsor Framework.

The operation of the Protocol presented some challenges that led the European Commission and the Government of the United Kingdom to reach, on 27 February 2023, a political agreement on a comprehensive set of joint solutions aimed at addressing, in a definitive way, the practical challenges faced by citizens and businesses in Northern Ireland, thereby providing them with lasting certainty and predictability.

With regard to medicinal products, joint solutions have been implemented in the EU through [Regulation \(EU\) 2023/1182](#) which has introduced relevant changes as regards medicinal products for human use intended to be placed on the market in Northern Ireland³.

This practical guidance document includes information related to the impact of Regulation (EU) 2023/1182 on medicinal products for human use authorised pursuant to Regulation (EC) No 726/2004 [centrally authorised medicinal products (CAPs)]. When not specifically mentioned, the guidance below applies as of the date on which Regulation (EU) 2023/1182 becomes applicable (for further information please see Section 11 below). For the impact of Regulation (EU) 2023/1182 on medicinal products authorised by EU/EEA Member States [nationally authorised products (NAPs)], including medicinal products authorised through mutual recognition procedures (MRPs) and decentralised procedures (DCPs) for human use, applicants/marketing authorisation holders are advised to contact the relevant national regulatory authorities. With regard to the impact of the Windsor Framework on medicinal products for human use placed on the market in the UK (including Northern Ireland), applicants/MAHs are invited to liaise with the UK authorities.

The information provided in this document complements and, where applicable, updates guidance provided on the [Notice to the Stakeholders - Withdrawal of the United Kingdom and EU rules for medicinal products for human use and veterinary medicinal products](#), the [Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure](#) and the [Questions and answers to Stakeholders on the implementation of the Protocol on Ireland/Northern Ireland](#).

² Pursuant to Joint Declaration No 1/2023 of the Union and the United Kingdom in the Joint Committee established by the Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community of 24 March 2023 (OJ L 102, 17.4.2023, p. 87, reflecting the arrangements laid down in Decision No 1/2023 of the Joint Committee, the Protocol, as amended by that Joint Committee Decision, should now be known as the 'Windsor Framework'.

³ [Regulation \(EU\) 2023/1182](#) of the European Parliament and of the Council of 14 June 2023 on specific rules relating to medicinal products for human use intended to be placed on the market in Northern Ireland and amending Directive 2001/83/EC, OJ L157, 20.6.2023

1. What is the scope of Regulation (EU) 2023/1182 regarding medicinal products?

Regulation (EU) 2023/1182 applies to medicinal products for human use to be placed on the market in Northern Ireland in accordance with Article 6 of Directive 2001/83/EC, i.e.: all medicinal products for human use that can be placed on the market of EU/EEA Member States if a marketing authorisation is granted. Medicinal products for veterinary use do not fall within the scope of Regulation (EU) 2023/1182.

2. How does Regulation (EU) 2023/1182 impact centrally authorised medicinal products (CAPs) for human use?

Pursuant to Article 4 of Regulation (EU) 2023/1182, medicinal products for human use eligible to the mandatory and optional scope of the centralised procedure pursuant to Article 3(1) and (2) of Regulation (EC) No 726/2004 can be placed on the market in Northern Ireland only if authorised by the UK authorities in accordance with the law of the United Kingdom and under the terms of the authorisation granted by them.

As a consequence, all medicinal products eligible to the centralised procedure that were or can be assessed by the European Medicines Agency and approved by the Commission will be available in Northern Ireland only if approved by the UK authorities in accordance with UK authorisation procedures and rules. UK procedures and rules will also apply with regards to the supervision of these medicinal products as of the date on which Regulation (EU) 2023/1182 becomes applicable. For further information on the impact of the Windsor Framework on the regulatory framework for medicinal products for human use in the UK (including Northern Ireland), applicants/MAHs are invited to liaise with the UK authorities.

2.1. What is the consequence for the temporary authorisation process under Article 5a of Directive 2001/83/EC?

Under Article 5a of Directive 2001/83/EC⁴ a specific mechanism was introduced for the authorisation of medicinal products in Northern Ireland that are not covered yet by an EU centralised marketing authorisation. More specifically, the competent authority of the UK in respect of Northern Ireland may grant a temporary marketing authorisation in accordance with the law of the UK for a medicinal product falling under the scope of the centralised procedure and supply it to Northern Ireland for maximum six months or until a marketing authorisation is granted or refused in the EU. Pursuant to Article 13 of Regulation (EU) 2023/1182, Article 5a of Directive 2001/83/EC is deleted with effect from the date on which the Regulation becomes applicable. For further information on the approval of medicinal products for human use to be placed on the market in Northern Ireland that would fall under the scope of the centralised procedure as of the date above mentioned, applicants/MAHs are invited to liaise with the UK authorities.

⁴ 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. 0067

3. What happens to CAPs for human use lawfully placed on the market in Northern Ireland before the date of application of Regulation (EU) 2023/1182?

As an exception to the general rule provided for in Article 4 of Regulation (EU) 2023/1182, batches of medicinal products for human use authorised through the centralised procedure (including stocks) which have been lawfully placed on the market in Northern Ireland before the date of application of the Regulation and not repackaged or relabelled after that date may remain on the market in Northern Ireland until their expiry date without being required to comply with the specific rules laid down under Articles 3, 4 and 55 of Regulation (EU) 2023/1182 (e.g. the removal of safety features or having an individual label with the words 'UK only'). However, these medicinal products cannot be moved from Northern Ireland to an EU/EEA Member State or be placed on the market in an EU/EEA Member State. No new batches of authorised CAPs can be released on the market in Northern Ireland after Regulation (EU) 2023/1182 becomes applicable, therefore the release of those CAPs by a Qualified Person (QP) has to be planned accordingly and cannot be performed after this date. For further information on placing medicinal products on the Northern Ireland market after the application of Regulation (EU) 2023/1182 applicants/MAHs are invited to liaise with the UK authorities.

4. How are multi-country packs for CAPs between Northern Ireland/UK and an EU/EEA member state affected?

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

For CAPs, multi-country packs between Northern Ireland and an EU/EEA Member State will no longer be possible. Marketing authorisation holders who make use of these multi-country packs should consider taking the appropriate measure ahead of the date on which Regulation (EU) 2023/1182 becomes applicable to adapt the labelling of their medicinal products.

Multi-country packs of CAPs lawfully placed on the market in an EU/EEA Member State before Regulation (EU) 2023/1182 becomes applicable and not repackaged or relabelled after that date may remain on the market of the EU/EEA Member State until the expiry date.

MAHs are invited to liaise with the relevant EU/EEA Member State for the particular situation of remaining multi-country packaging with Northern Ireland or UK that was approved before Regulation (EU) 2023/1182 becomes applicable.

⁵ For further information on the general applicability of Article 3 and 5 to NAPs (including MRPs and DCPs), applicants/MAHs are advised to contact the relevant national regulatory authority. For the impact on these articles on products that would be eligible for the centralised procedure applicants/MAHs are invited to liaise with the UK authorities.

5. How to update the product information of CAPs regarding the local representative for Northern Ireland?

With the applicability of Regulation (EU) 2023/1182 the mentioning of the local representative for Northern Ireland in the product information of CAPs will become obsolete.

As of this date and at the earliest opportunity the marketing authorisation holders should update the product information during any upcoming regulatory procedure that affects the Annexes of the marketing authorisation (e.g.: variation, renewal) as a change to align with the revised Quality Review of Documents (QRD) Product Information template ([updated template \(version 10.4\) available since 29 February 2024](#)). For medicinal products that will have no regulatory procedure affecting the marketing authorisation Annexes within 36 months, the marketing authorisation holder should submit a dedicated notification under Article 61(3) of Directive 2001/83/EC.

Additionally, it is also acceptable to request the deletion of the local representative for Northern Ireland in any regulatory procedure affecting the Annexes of the marketing authorisation submitted after 1 July 2024, provided that this change is only implemented after the date that Regulation (EU) 2023/1182 becomes applicable.

6. What is the impact on the marketing status report for CAPs in Northern Ireland and EU/EEA member states?

Until the day before Regulation (EU) 2023/1182 becomes applicable, the marketing status of CAPs in Northern Ireland should continue to be reported to the EMA as per the current process (see reference below). As of the date on which Regulation (EU) 2023/1182 becomes applicable, the reporting of the marketing status of those products in Northern Ireland to the EMA is no longer applicable.

As a result, for CAPs for human use placed on the market only in Northern Ireland and not placed on the market in any EU/EEA Member State the sunset clause timer will start on the date on which Regulation (EU) 2023/1182 becomes applicable. Therefore, the marketing authorisation will cease to be valid if the CAP is not marketed in any EU/EEA Member State for three consecutive years following the date on which Regulation (EU) 2023/1182 becomes applicable.

MAHs are reminded to notify a change of marketing status of a CAP for human use per presentation and per Member State in accordance with Q. 4 to Q. 6 of the EMA post-authorisation procedural advice "[Notifying a change of marketing status](#)" available at EMA website.

7. How does parallel distribution work in relation to medicinal products?

7.1. Are there any parallel distribution notices with the UK (Northern Ireland) as the destination country?

From the EU pharmaceutical Law perspective and irrespective of any consideration regarding intellectual property laws, parallel distribution notices for centrally authorised human medicinal products with the UK as the only destination country with respect to the territory of Northern Ireland will no longer be valid. Parallel distribution notices for centrally authorised human medicinal products with more than one destination country and including the UK with respect to the territory of Northern

Ireland will be amended to remove the UK. Parallel distribution notices for centrally authorised veterinary medicinal products are not affected.

7.2. Are there any parallel distribution notices with the UK (Northern Ireland) as the sourcing country?

From the perspective of the EU pharmaceutical law, the notices with UK for centrally authorised human medicinal products with respect to the territory of Northern Ireland as the only sourcing country will no longer be valid. Parallel distribution notices for centrally authorised human medicinal products with more than one sourcing country and including UK with respect to the territory of Northern Ireland will be amended to remove UK. Parallel distribution notices for centrally authorised veterinary medicinal products are not affected.

8. Changes required in the Article 57 database

Until the date on which Regulation (EU) 2023/1182 becomes applicable, there is no change in the current Article 57 submission rules for medicinal products approved **via the centralised procedure and with a marketing authorisation valid in the territory of Northern Ireland**. I.e.: marketing authorisation holders continue to report product information on medicinal products authorised via the centralised procedure with a marketing authorisation valid in Northern Ireland:

- by referencing the country code 'EU', corresponding to 'European Union', as the country of authorisation in the product entry and
- by referencing 'EU authorisation procedures - Centralised Procedure' as the authorisation procedure in the product entry.

After the date on which Regulation (EU) 2023/1182 become applicable, the information recorded in the Article 57 database and any new submission for a medicinal product approved via the centralised procedure and referencing 'EU' as the country of authorisation will automatically no longer include the territory of Northern Ireland.

If, after this date a medicinal product authorised by the European Commission via the centralised procedure with a marketing authorisation valid in the EU/EEA is also granted an equivalent marketing authorisation by the UK authorities in accordance with UK authorisation procedures and rules valid in the territory of Northern Ireland, then the MAH may additionally report the product information in the Article 57 database on voluntary basis for that equivalent authorisation. In case of voluntary submission, the product entry in the Article 57 database must reference:

- the country code 'GB', corresponding to 'United Kingdom', as the country of authorisation and
- the authorisation procedure 'Non EU authorisation procedure'.

There is no change in the current Article 57 submission rules for medicinal products approved **nationally** (i.e. via a national procedure, mutual recognition procedure and/or decentralised procedure) **by the MHRA and with marketing authorisation valid in the territory of Northern Ireland**. I.e.: Marketing authorisation holders continue to report product information on medicinal products authorised nationally with a marketing authorisation valid in Northern Ireland:

- by referencing the country code 'XI', corresponding to 'United Kingdom (Northern Ireland)', as the country of authorisation in the product entry and
- by referencing the relevant EU procedure as the authorisation procedure in the product entry.

9. Safety reporting into EudraVigilance and access to EudraVigilance data

9.1. Safety information reporting into EudraVigilance

With the applicability of Regulation (EU) 2023/1182 there will be medicinal products in the territory of Northern Ireland approved under Article 6 of Directive 2001/83/EC (i.e. with a marketing authorisation issued by the United Kingdom (UK) authorities in accordance with Directive 2001/83/EC) and medicinal products approved by the UK authorities under the UK law and procedures following Article 4 of Regulation (EU) 2023/1182 (i.e. products that would be eligible to the centralised procedure and approved by the European Commission in accordance with Regulation (EC) No 726/2004).

To limit the risk of errors regarding ICSRs management, and to facilitate the identification of potential duplicate ICSRs, the reporting requirements applicable since 1 January 2021 will continue to apply once Regulation (EU) 2023/1182 becomes applicable. Information on new and previously submitted ICSRs from the Northern Ireland territory that are received from 1 January 2025 onwards should be submitted to EudraVigilance in accordance with the 15-day (for serious cases) and the 90-day (for non-serious cases) compliance timeframes while applying the guidance provided in GVP Module VI. Serious ICSRs from the rest of the UK (or when the occurrence is unknown between Northern Ireland and the rest of the country) should be submitted to EudraVigilance in accordance with the 15-day compliance timeframes, while applying the guidance provided in GVP Module VI.

- The UK authorities will continue to have partial access to the EudraVigilance database (write access via the Gateway); this will allow the submission to EudraVigilance by the UK Authorities of all serious and non-serious ICSRs from the Northern Ireland territory received directly from patients or healthcare professionals, irrespective of the authorisation legal framework for the suspected medicinal products.
- Marketing Authorisation Holders (MAHs) should continue to submit to EudraVigilance all serious and non-serious ICSRs from the Northern Ireland territory received directly from patients and health care professionals for:
 - o Medicinal products authorised in the Northern Ireland territory by the UK Authorities in accordance with Article 6 of Directive 2001/83/EC.
 - o Medicinal products authorised in the Northern Ireland territory in accordance with UK authorisation procedures and rules, provided that an equivalent marketing authorisation was granted in EU/EEA in accordance with Article 6 of Directive 2001/83/EC.

The EU authorities will remain responsible for the monitoring of suspected adverse reactions reported in the above cases to the extent the suspected product is authorised following Article 6 of Directive 2001/83/EC.

To avoid duplicate ICSRs, MAHs should not submit to EudraVigilance ICSRs from the Northern Ireland territory they receive or access from the UK authorities since these cases will be directly submitted to EudraVigilance by these Authorities. However, MAHs should continue to submit to EudraVigilance all serious cases from the rest of the UK received directly from patients or healthcare professionals, or received or accessed from the UK authorities since these ICSRs are not submitted to EudraVigilance by these authorities.

Non-serious cases from the rest of the UK submitted before 1 January 2021 should not be changed to invalid and nullified unless new information provides justification for a nullification in line with GVP

module VI. MAHs may also send follow-up reports on non-serious ICSRs from the rest of the UK in addition to serious ICSRs if they were sent before 1 January 2021 and new information is received.

With regard to the information on the case country code, the guidance applicable since 1 January 2021 will continue to apply:

- For ICSRs from the Northern Ireland territory:
 - The country code "XI" should be used in the 'Reporter's Country Code' data element (ICH E2B(R3) C.2.r.3) when designated as 'Primary Source for Regulatory Purposes' (i.e., ICH E2B(R3) C.2.r.5 reported with value 1).
 - The country code "XI" or "GB" can be used in the 'Worldwide Unique Case Identification Number' data element (ICH E2B(R3) C.1.8.1) and in the 'Sender's (case) Safety Report Unique Identifier' data element (ICH E2B(R3) C.1.1).
 - For follow-up cases initially submitted before 1 January 2021, the country code "GB" should be kept in the 'Worldwide Unique Case Identification Number' data element (ICH E2B(R3) C.1.8.1); if needed, the country code can be changed to "XI" in the 'Sender's (case) Safety Report Unique Identifier' data element (ICH E2B(R3) C.1.1).
- For ICSRs from the rest of the United Kingdom, or when the occurrence is unknown between Northern Ireland and the rest of the country:
 - The country code "GB" should be used in all relevant ICH E2B(R3) data elements.

9.2. Access to EudraVigilance data

The EudraVigilance access policy⁶ grants Level 2 access to MAHs for the ICSRs held in EudraVigilance concerning their medicinal products that are authorised in the EU. This access is calculated based on the data on valid EU/EEA marketing authorisations which are held in the XEVMPD system of the Article 57 database for the respective organisation. Since 1 January 2021 products in the XEVMPD that have the authorisation country United Kingdom (assigned country code "GB") are excluded from this calculation and products with the authorisation country Northern Ireland (assigned country code "XI") are included in the calculation for granting Level 2 access to ICSRs.

10. What is the significance of pivotal studies conducted with a centrally authorised reference product sourced in Northern Ireland?

Generic/hybrid applications 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. For the acceptability of using a centrally authorised reference medicinal product sourced in Northern Ireland until the date that Regulation (EU) 2023/1182 becomes applicable for studies to be used in a centralised marketing authorisation application, the applicant is invited to contact the Agency to discuss the particular circumstances of their application.

⁶ [European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use \(europa.eu\)](https://european-council.europa.eu/media/en/press-room/image/asset-detail/2023-11-16-EMA-policy-on-access-to-eudravigilance-data-for-medicinal-products-for-human-use)

11. When does Regulation (EU) 2023/1182 become applicable?

Regulation (EU) 2023/1182 has entered into force on 21 June 2023 (i.e.: the day following that of its publication in the Official Journal of the European Union), and it should apply from 1 January 2025 provided that the UK has provided the written guarantees referred to in Article 8 of that Regulation and the Commission has published in the Official Journal of the European Union prior to that date a notice indicating the date of application. .

This date could be anticipated or postponed depending on when the UK will provide written guarantees to the Commission. In that case the Regulation will become applicable the first day of the month following the month during which the UK provides the above-mentioned written guarantees.

The Commission will publish a notice in the Official Journal of the European Union indicating the date from which this Regulation applies.