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Human Medicines
Brexit MAH survey and medicine supply

The HPRA and HSE issued a detailed survey to all marketing authorisation holders (MAHs) in late August/early September. Your responses to our questions relating to the supply routes and levels for marketed products are critically important to inform and support the medicines availability in the event of a ‘no-deal Brexit’, in particular for those products with exposure to the land bridge. We appreciate that supply data may be fluid and challenging to predict and is commercially sensitive. We commit to treating your feedback as private and confidential.

To those of you who have responded to date, thank you for your valuable contribution to this multi-stakeholder effort.

To those of you who have yet to complete, we would request that you do so no later than 30 September 2019.

Reminder to MAH’s to monitor CMDh website for relevant updates

MAHs for nationally authorised products, in particular for those authorised the mutual recognition and decentralised procedures are strongly recommended to continually monitor the [CMDh website](https://www.ccmdh.org) for information relating to their product portfolio. CMDh (the Co-ordination Group for Mutual Recognition and Decentralised Procedures-human) is established under Article 27 of Directive 2001/83/EC of the European Parliament and of the Council on the Union code relating to medicinal products for human use, to examine any question relating to a marketing authorisation of a medicinal product in two or more Member States. Such questions cover a variety of issues related to new applications, variations, renewals and pharmacovigilance activities and currently also Brexit related activities.

CMDh hold monthly meetings attended by representatives of the EU/EEA member states in order to discuss and resolve issues arising.

The outcomes of these meetings are conveyed in the monthly press release issued immediately after the meeting on the website, in the minutes published approx. 2 months later, and elaborated in ‘procedural guidances’, and ‘advices to MAH’s’. Therefore, MAHs should routinely review the resources on the CMDh website in relation to their product portfolio, and take the required actions according to the requested timeframe.

For example, applicants should note the recent simplification of work-sharing procedure for variations ([Chapter 7](https://www.ccmdh.org)) which has shortened and simplified the request phase as it is sent directly to the preferred RMS, and avail of this opportunity for coordinated submission of suitable variations.
The HPRA requests that MAH's for liposomal and pegylated liposomal products consult the CMDH press release of July 2019 and take the outlined actions, to ensure that all liposomal and pegylated liposomal medicinal products across the European Union are named in a consistent manner. This is a joint CMDh-CHMP position which will ensure that such products, whether authorised through the centralised procedure or nationally, will include a qualifier in the name - ‘liposomal’ or ‘pegylated liposomal’ - and will use the EDQM standard term ‘dispersion’ in the description of the pharmaceutical form. This will help healthcare professional and patients distinguish between liposomal and non-liposomal products of the same active substance, which if inadvertently substituted can result in serious medication errors. MAHs therefore are requested as a matter of urgency, to submit the required type IB variation (A.2.a or A.2.b) to add the appropriate qualifier to their product name (whether INN or invented name) and the EDQM standard term ‘dispersion’, in the manner and order outlined, as soon as possible and at the latest by end of September 2019. These variations should be submitted to the HPRA for national authorisations (via MR/DCP or purely national route as applicable), or to EMA (via the centralised route) for centralised products.

*Liposomes are small spherical enclosed compartments separating an aqueous medium from another by a phospholipid bilayer. It is a formulation technique used to improve pharmacokinetics and biodistribution of therapeutic agents.

The UK is scheduled to leave the EU and become a third country on 31 October. In the absence of a withdrawal agreement manufacturing sites in the UK will not be legally eligible to act as batch release sites for the EU market after this date and companies have been requested to prepare for this scenario. This means that where a UK manufacturing site is currently the sole batch release site for the EU market, an alternative EU batch release site should be registered by way of a type IA variation by 31 October (variation category B.II.b.2 Change to batch release arrangements and quality control testing of the finished product).

In order to facilitate IE/UK joint labelling post-Brexit the HPRA has no objection to the manufacturer(s) responsible for batch release for the UK market being listed on the leaflet along with the manufacturer(s) responsible for batch release for the EU market.

In order to prevent the need to further update packaging, the HPRA shall accept the presence of all registered batch release sites on the package leaflet (UK and EU) on the basis that batch release can only occur from sites within the EU 27 after 31 October 2019. If Brexit occurs without agreement on 31 October, the onus will be on the Qualified Person to only certify batches from the registered EU site regardless of the release site(s) stated on the leaflet.

Implementation of new leaflet:

Where a new leaflet has been implemented with an amended listing of batch release sites the expectation is that the updated package leaflet would be used in the next scheduled packaging run. However, in order to minimise supply issues which could result from this expectation the HPRA can accept a longer period before which the leaflet is used but would expect that the revised package leaflet be used in packaging runs no later than 6 months after the change to the site of batch release has taken place.

The HPRA would like to remind sponsors that EU clinical trials legislation requires that the sponsor or legal representative of the sponsor is established in the EU/ EEA, and also that an EU site of batch release and an EU site of importation are registered with the HPRA. Arising from Brexit, you are requested to comply with these legal requirements before 31 May 2019, the next date when the UK may become a third country. Sponsors are now requested to submit any outstanding substantial amendments. The HPRA understands that there may be a problem with EudraCT. However, the substantial amendment form should still be submitted to the HPRA. The XML can be submitted when EudraCT issues have been resolved. If the clinical trial has ended, please submit an end of trial declaration. If the clinical trial did not commence please notify us at clinicaltrials@hpra.ie. Please also notify the HPRA of any change in contact details as soon as possible at clinicaltrials@hpra.ie.
Based on certain responses to the regulatory questions in the HPRA survey on the supply medicines to the Irish market post-Brexit, it is anticipated that there may be regulatory compliance issues with a cohort of non-marketed product(s) if the UK leaves the EU on 31 October 2019. Companies who have stated that their product(s) are not currently marketed in Ireland will be asked to confirm that they commit to addressing these issues prior to marketing their product(s) in Ireland.

The mutual recognition supplement fee codes 205 (Type II standard), 213 (Type IB) and 219 (Type II complex) will not be charged when Ireland is the Reference Member State (RMS) and there are no Concerned Member States (CMS). This scenario is most likely to occur as a result of Brexit where IE and the UK have been the only member states involved in a procedure.

The Task Force that was established by the HPRA’s Advisory Committee for Veterinary Medicines (ACVM) to review the method of supply of antiparasitic veterinary medicinal products that are intended for food-producing animals against the criteria set out in Directive 2006/130/EC and Regulation 2019/6 held a consultation with marketing authorisation holders and interested parties between 20 May and 21 June 2019. A summary of the results of that consultation is available here. The Task Force expects to finalise the Report during October 2019. The Report will then be considered by the ACVM and, in December 2019, by the Authority of the HPRA. It is expected that the final report will be uploaded to the HPRA web site, once the Authority has had time to consider it.

Should any change to the current method of supply of the products concerned be deemed necessary as a result of the Report, the HPRA will consult with stakeholders regarding the timelines for transition.

Type 1A variations should require minimal review without the need to request supplementary documentation from the applicant. However, experience shows that errors in submissions frequently necessitate requests to provide missing/amended documents with consequential delays in processing of the applications. The following are the most frequent errors identified with type 1A variations:

- The relevant page from the classification guideline not completed. The variation classification guideline page is required to be submitted in every variation application. When submitting this page, the applicant should clearly indicate that each relevant condition is met. This is usually done by ticking the condition or stating that the condition is fulfilled. This is the only document that confirms that the conditions have been fulfilled and therefore it must be completed correctly.
- All documentation listed as being required as per the variation classification guideline must be submitted in the application.
- The dossier should be updated in accordance with the variation, preferably a track change copy should be provided to facilitate review.
• The present and proposed sections of the application form should be clear and should detail the precise change applied for. Reference to a separate document or an appendix for this information should be avoided.

• QP declarations, when applicable, should be filled out correctly:
  – The manufacturers function should be stated as per the registered details for the product
  – The on-site audits which form the basis of the declaration should be conducted within 3 years
  – The declaration must be signed by the QP

• The SPC and product literature should be submitted as clean and track changed versions. If revised text are required to be provided during the procedure, all changes being made throughout the procedure should remain tracked.

• When submitting notifications or changes that do not require a variation, along with the variation application, the notification change should be detailed in the cover letter and in the application form in the section ‘PRECISE SCOPE AND BACKGROUND FOR CHANGE, AND JUSTIFICATION FOR GROUPING, WORKSHARING AND CLASSIFICATION OF UNFORESEEN CHANGES’. The application should also include supporting documentation for the notification e.g. email correspondence from the RMS agreeing to accept the change as a notification.

The above points are highlighted to reduce the occurrence of minor errors with type 1A variation applications and increase the speed and efficiency of their processing.

In order to facilitate timely assessment of applications for national marketing authorisations in Ireland only, the HPRA now requires applicants to complete a pre-submission request form before a New National Application for a Veterinary Medicinal Product is submitted. The purpose of this change is to improve and streamline the New National application process and avoid potential delays at validation.

The pre-submission request form is available here. Once completed, it should be submitted to vetinfo@hpra.ie for the attention of the Planning and Authorisations Manager.

The HPRA will correspond by email regarding acceptance or refusal of the proposed national application, to the contact person mentioned on the request form as soon as possible.

Where a New National Application is received without a pre-submission request form having been provided, the application will not be progressed and assessment will not commence until a valid pre-submission request form has been received and reviewed.

From 02 September 2019, where a variation results in an update to an SPC (Summary of Product Characteristics), the SPC will no longer be emailed to the applicant. Instead the applicant will receive an automatic notice, advising that their variation has been issued. Where the variation has resulted in an update to the SPC, it will be available for viewing via the HPRA website www.hpra.ie within 24 hours.

Applicants are requested to review the SPC to ensure accuracy of the information. In the event that amendment is required, notice should be made to the HPRA within 14 days.

In respect of proceedings relating to the provision of bilingual packaging of veterinary medicines in Irish and English languages brought against the Department of Agriculture Food and the Marine (DAFM) by a citizen in July 2018, on 26 July 2019 Judge Ní Raifeartaigh indicated that she accepts that Directive 2001/82/EC was not properly transposed into Irish law. The applicant had argued that as both Irish and English are official languages of the State, packaging should be in both languages. The DAFM had argued that this would cause practical consequences for the Animal Health industry and would adversely affect medicines availability in this country.

The High Court judge advised that she had difficulty in finalising the order however, because Regulation 2019/6 has been adopted in the meantime. This regulation comes into effect on 28 January 2022 and will have the effect of allowing the State to choose the language of the text used in the package leaflet and labelling. The judge invited further legal submissions on whether or not a domestic court has discretion not to grant relief when it has found a failure to transpose an EU directive. A further hearing of the matter is planned during October. The HPRA will continue to monitor developments in this case.

Update to process for submitting New National Applications

Update on Irish language case

Update to process where SPCs are updated during a variation
Requirements for Ensuring Traceability and Transparency within the Wholesale Distribution Supply Chain

The regulations governing wholesaling of medicinal products for human use have been amended by the Medicinal Products (Control of Wholesale Distribution) (Amendment) Regulations 2019 (S.I No. 217 of 2019) which was signed into law on 15 May 2019. The consolidated regulations are known as the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 to 2019.

On foot of this recent amendment, a holder of a wholesale distribution authorisation is now obliged to provide greater traceability and transparency in the wholesale distribution supply chain. These changes may affect retail pharmacy businesses that also hold a wholesale distribution authorisation.

Companies/persons which operate both an authorised wholesaling business and a retail pharmacy business (RPB) from the same premises are entitled to procure medicinal products by virtue of either being an authorised wholesaler or an RPB. However, according to Schedule 2, Paragraph 4, the authorisation holder shall only order and obtain his or her supplies of medicinal products which are intended for onward supply through his or her wholesaler’s authorisation via an account or equivalent supply arrangement established with his or her supplier exclusively for the purpose of obtaining medicinal products for wholesale distribution.

In other words, the procurement and onward supply of medicines from wholesaler to wholesaler shall be via an account that is entirely separate from an account for the sale and supply of medicines from wholesaler to RPB.

In order to comply with the amended Regulations, a wholesale distributor, that is also a RPB, is required to establish a separate account, or an equivalent supply arrangement, with its supplier(s) of medicines, which is distinct from its RPB account(s).

Regarding wholesalers and their entitlement to supply, Schedule 2, Paragraph 4 lists the persons to whom the holder of a wholesaler’s authorisation shall sell medicinal products by wholesale. These include persons –

4(a) who are themselves the holders of a wholesaler’s authorisation relating to those products,

4(b) who are authorised or entitled to supply the said medicinal products to the public, and

4A In the case of paragraph 4(d), the authorisation holder shall only supply medicinal products via an account or equivalent supply arrangement established with the recipient exclusively for the purpose of supply to the public and no further wholesale distribution of the products shall take place.

In other words, the sale and supply of medicines from wholesaler to wholesaler shall be via an account that is entirely separate from an account for the sale and supply of medicines from wholesaler to RPB.

In order to comply with the amended Regulations, a wholesale distributor is required to establish an account, or an equivalent supply arrangement, with a wholesaler (that is also an RPB) that is separate from the account via which medicines are sold or supplied to that RPB.

Changes to the requirements for the sourcing of exempt medicinal products

These amending Regulations also enable the sourcing of exempt medicinal products from non-European Economic Area countries by holders of wholesale distribution authorisations whose authorisations permit this activity. Should wholesalers wish to commence this activity, they should ensure that their wholesale distribution authorisations include the correct medicinal product categories. Related amendments have also been made to the Medicinal Products (Control of Placing on the Market) Regulations 2007 to 2019, via S.I. No. 218 of 2019; and to the Medicinal Products (Control of Manufacture) Regulations 2007 to 2019, via S.I No. 219 of 2019.

During the course of our inspections of wholesalers, we will check for compliance with these Regulations.
Update on US – EU mutual recognition agreement on GMP inspection

The mutual recognition agreement (MRA) between the United States (US) and the European Union (EU) contains a sectoral annex for pharmaceutical good manufacturing practices (GMPs). The European Commission and US Food and Drug Administration (FDA) signed the MRA and it entered into force on 1 November 2017 with a transition phase for recognition of GMP inspection systems of EU Member States until July 2019. Please refer to the [HPRA website](https://www.hpra.ie) and HPRA Newsletter, issue 56 for further details.

**What's new?** The waiver on batch import testing came into force on 11 July 2019 when the MRA became fully operational. The Article 9 waiver was conditional on all EU Member States authorities responsible for human medicines being recognised by the US FDA.

**What does this mean?** For batches of human medicines imported into the EU on or after 11 July 2019, qualified persons (QPs) in the EU Member States will be relieved of their responsibility for carrying out the controls on human medicines, that are within scope of the MRA, provided that they have verified that the product was manufactured, and the controls have been carried out, in the US, (i.e. retesting on importation, from the US, of a batch of medicinal product for human use is no longer required).

Each batch/lot should be accompanied by a batch certificate (in alignment with the WHO certification scheme on the quality of medicinal products) issued by the manufacturer certifying that the product complies with requirements of the marketing authorisation and signed by the person responsible for releasing the batch/lot at the US site of manufacture. It is essential to note that the requirement for the QP at the EU site of importation to certify each imported batch remains. Please refer to the [EMA’s published Q&A](https://www.ema.europa.eu/en/news/ema-q-a-questions-answers) if you would like further details.

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Extension of Safety Features ‘Use and Learn’ Period in Ireland beyond September 2019

**Introduction**

New Falsified Medicines Directive (FMD) safety feature requirements came into effect on 9 February 2019. Since then the system in Ireland has been in a ‘use and learn’ phase to ensure the continuity of safe supply of medicines to patients while all parties gained a better understanding of the new system.

Significant progress has been made on several fronts since 9 February 2019:

- The vast majority of pharmacies, hospitals and wholesalers have registered with the Irish Medicines Verification Organisation (IMVO) and are connected to the national system.
- Almost 11.3 million scans of packs of medicines have taken place in Irish pharmacies, hospitals and wholesalers since February and the number of scans is growing weekly.
- Barcode data for over 180 million packs has been uploaded to the national system by manufacturers.
- Extensive analysis of alerts is taking place across Europe, resulting in greater understanding of their root causes and the rollout of initiatives to reduce the number of alerts being generated. These initiatives are taking effect and the rate of alerts vs scans continues to fall and now stands at 3.5% (down from a high of 20%).

**Decision to extend use and learn period**

The National Safety Features Oversight Group comprising the IMVO, the Department of Health, the Health Products Regulatory Authority (HPRA), the Pharmaceutical Society of Ireland (PSI), the Health Service Executive (HSE) and the Private Hospitals Association (PHA) has been closely monitoring progress since go live on 9 February 2019. Taking all factors into account, the group has decided that the use and learn period will be further extended to allow additional time for the system to stabilise and to ensure that everyone is ready when it becomes mandatory to investigate and close out all alerts before supplying the packs. The use and learn period will end on a phased basis, and a detailed plan as to how this will be done, including dates, will be published at the end of September.

In the meantime, pharmacies, hospitals, wholesalers and manufacturers/MAHs are asked to continue following the instructions given to them when the use and learn period was last extended in May, please refer to [HPRA’s website](https://www.hpra.ie) for details. In particular, pharmacies, hospitals and wholesalers must scan packs where obliged to do so. The data generated from these scans is critical for identifying root causes of alerts and other issues that need to be resolved in order to ensure an orderly ending of the use and learn period with minimal disruption to end-user workflow and patient supply. FMD is an important patient safety initiative and end-users’ support at this stage by way of scanning is vital for its successful implementation.
On 1 February 2019, the EU Commission published Questions and Answers Related to the United Kingdom’s withdrawal from the European Union with regard to industrial products in order to provide further information on the impact of a ‘no-deal’ Brexit on cosmetic products (and other products covered under the New Approach legislation).

This Q&A follows on from the publication by the Commission of two ‘Notice to Stakeholders’ documents on 22 January 2018 and on 29 November 2018, and highlights some of the implications for labelling, representation and supply in the event of a ‘no-deal’ Brexit. The ‘Notice to Stakeholders’ of 29 November 2018 was updated and was replaced on 18 July 2019.

This latest Q&A provides examples of when goods are placed onto the market and into the supply chain, and includes clarification on the requirements in relation to the presentation of the Responsible Person (RP) contact details on the labelling.

The Q&A also reinforces the importance of updating the Cosmetic Product Notification Portal (CPNP) for products currently registered with an RP in the UK. In the event of a ‘no-deal’ Brexit, all cosmetic products made available to the EU market as of the date of withdrawal are required to be registered on the CPNP with an RP located in one of the EU-27 Member States. Information is available regarding transfer of an existing notification in CPNP to a future EU-RP in the Commission’s 18 July 2019 Notice to Stakeholders.

In the context of the UK becoming a ‘third country’ post Brexit, the HPRA is taking this opportunity to remind each Irish entity sourcing cosmetic products from the UK for supply to the EU-27 Member States to be aware that it will become an importer and, potentially, the RP for the product if an RP has not already been designated in an EU-27 Member State.

We are continuing to work with the European Commission and other Member States in relation to cosmetic product issues arising from Brexit. We urge Responsible Persons, distributors, manufacturers and retailers to take the appropriate steps in preparation for Brexit in order to ensure supply of compliant cosmetic products to the market. Further information in relation to Brexit and Cosmetic Products is available on our website, which will be updated as required. If there are any specific queries, these can be sent to cosmetics@hpra.ie.

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**Staff changes in the Compliance GMP Team**

Chris Cullen, who worked as a Senior Inspector with the HPRA for over 16 years, retired in June 2019. We wish Chris well in his retirement. Ciara Turley was appointed Senior Inspector in October 2018 and Caitriona McAuley joined the GMP team as an Inspector in January 2019. Ciaran Joyce, Scientific Officer, took up an opportunity as Scientific Officer in Pharmaceutical Assessment in the Human Products Authorisation and Registration (HPAR) department in August 2019.
Brexit Preparedness Checklist

1. Supply Chain
With regard to the supply of medicines and medical devices, companies are requested to:
- Map your supply chain to determine Brexit exposure, including route to market.
- Assess how Brexit may impact your ability to supply the Irish market.
- Take the necessary steps to ensure sufficient stock levels and continuity of supply both in the period leading up to 31 October 2019 and post Brexit.
- Review stocks at wholesale level and ensure arrangements are in place to allow for timely replenishment of such stocks including custom requirements where applicable and allowing for potential delays during transportation.

2. Customs
- Register with Revenue for an EORI number.
- Understand what is needed to fulfil customs declaration requirements.
- Consider a customs agent/broker or in-house management to complete declarations.
- Consider what authorisations or simplifications about customs procedures might be relevant.
- Determine whether you have to comply with UK customs requirements.
- Identify classification codes for devices/products/ingredients.
- For suppliers sourcing devices from the UK, prepare for the additional responsibilities you will have as an importer when sourcing products from the UK post-Brexit.

3. Medicines Regulatory Compliance
Ensure all activities are being undertaken to meet EU regulatory requirements by 31 October. These include the following:
- Transfer of UK MAH to one based in the EU/EEA.
- Relocation of batch release site in the UK to the EU/EEA.
- Relocation of QC testing sites in the UK to the EU/EEA, in the case of a QC testing site extension being granted, by 31 December 2019.
- Transfer of UK RMS to an EU/EEA based RMS.
- The nominated QPPV must be based in an EU/EEA Member State.
- For clinical trials, transfer of any UK based sponsor or legal representative and the site of batch release to the EU/EEA.
- GMP certificates issued by the MHRA and VMD will be considered as part of a risk based approach to confirm the Union GMP compliance in regulatory submissions.

4. Medical Devices
Ensure all activities are being undertaken to meet EU regulatory requirements by 31 October. These include the following:
- For devices certified by UK notified bodies – confirm with the manufacturer that they will transfer to an EU-27 notified body by 31st October and that there is a plan for continued certification of the devices.
- For devices manufactured in the UK or with UK Authorised Representatives – ensure an authorised representative has been designated in an EU-27 Member State.
- For clinical investigations, transfer of any UK based sponsor or legal representative to the EU/EEA.

5. Further Information
www.hpra.ie/brexit  www.revenue.ie