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HPRA MEDICINAL PRODUCTS NEWSLETTER

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Human Medicines

Brexit – The HPRA's position on the importation of finished products

Directives 2001/82/EC and 2001/83/EC stipulate a requirement for all batches intended for EU markets to undergo control testing in a Member State. The control tests which define the quality of the batch are those in the finished product specification. If the batch has already undergone these finished product tests in a member state then the results from these tests together with knowledge of the storage conditions of the batch since testing, may be taken into account by the QP when certifying the batch on importation into Ireland.

Post Brexit, if the batch is tested and certified in the UK before Brexit and is stored in the UK, or subject to a 'Testing Exemption' then the following would apply:

1) Each batch of product imported from the UK post Brexit must be received at a manufacturing site which is authorised as a site of physical importation – i.e. cannot be supplied direct to a wholesaler
2) Each batch must undergo certification by a QP at the manufacturing site appointed for the purpose of batch release within the MA. This may or may not be the same site to which the product is physically imported.
3) The QP may take into account, the results of finished product testing conducted at a laboratory (EU or UK Exempt), together with knowledge of the storage of the batch since testing was conducted, when dispositioning each imported batch.
4) The certifying QP should be in a position to confirm all necessary steps in the manufacture and QC of the product have been carried out in accordance with GMP and the MA and be responsible for all steps in the process carried out in a third country.
5) The certifying QP can rely on the quality management system within a third country providing that this reliance is well founded.
6) The site of batch release should be named in the MA and the QP should have access to the MA.

The certifying QP must be listed on the Manufacturer's Licence of the batch release site and complete batch certification at the named site of batch release.

Registering your site of importation if different from your site of batch release

Variation category B.II.b.2 of Commission Regulation (EC) No. 1234/2008 (variations) states that replacement or addition of a manufacturer responsible for importation and/or batch release is a IAIN. Therefore, changes to the site of importation require submission of a IA variation. Sites of physical importation are listed in the application form.

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Clinical Trials – Impact of Brexit

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.

Update on HPRA national scientific advice procedure

The HPRA national scientific advice procedure which commenced in 2017 has been expanded to include additional therapeutic areas for stakeholders seeking scientific advice. These areas which include: anti-infective products, vaccines, disorders of haemostasis and thrombosis, cardiovascular diseases, common allergic conditions, advanced therapies in certain clinical indications and biostatistics.

Further information and guidance is available on the HPRA website. Please send any queries to the HPRA mailbox scientificadvice@hpra.ie

Update on fire hazard associated with paraffin-containing topical medicines

The HPRA are undertaking regulatory action to update the product information of paraffin containing topical medicinal products to include updated warnings related to the risk of fire due to reports of fatalities associated with this risk in the UK. Bandages, dressings, clothes and bedding which come in contact with paraffin-based topical products are easily ignited when exposed to a naked flame. The HPRA will be in contact with the market authorisation holders of affected products in due course.

New human medicines electronic workflow system

The human medicines department have transitioned into a new electronic workflow system which underpins the process for assessing and issuing the marketing authorisations for medicinal products for human use.

The new solution has introduced additional features which will continue to support our functions and enhance our interaction with stakeholders.

The system was implemented by the end of August 2018 and is currently undergoing a stabilisation focus on three key areas, performance, searching/reporting and SPC editor.

Below is a list of known changes on the system since Go Live:

- **Case Reference Number (CRN)**

Previously CRNs were displayed as seven digits. These will now be alpha numerical for any new cases e.g. CRN00011X. The HPRA will still be able to identify any closed or ongoing cases using the old CRN.

- **Product Specific Details (PSD)**

The product specific information will no longer form part of the product licence document. Previously the product licence document consisted of the licence cover page, PSD and Summary of Product Characteristics (SPC). In future, the product licence document will consist of the licence cover page and the SPC only. The information previously detailed in the PSD will be logged on the HPRA database and remain a registered part of the product marketing authorisation.

- **Summary of Product Characteristics (SmPC)**

Updated SmPCs and Package Leafelts will publish on the website 24 hours after case closure.

Font and format of SmPCs will now display Segoe 10 in body, 11 in headings, font style Regular IU 10.

We acknowledge some known formatting issues with SPCs on the website and in due course, we will publish a "HPRA SmPC standard document" to identify best practice SmPC word submissions which will help eliminate some of these known formatting issues.

- **PA numbers**

Newly allocated PA numbers for new holders will now contain 5 digit prefix.

- **Digital communications**

All cases on the new system will be assigned a dedicated e-mail address e.g. [CaseNumber]@case.hpra.ie. This will enable you to send the HPRA case-specific communications directly to the case and the allocated team. E-mail correspondence sent to you from the HPRA that is relevant to the case will come from this dedicated e-mail address. The European e-mail boxes will still be used where applicable.

Please consult with your IT departments to ensure that e-mails of this nature are not blocked in your organisation.

While the HPRA will endeavour to ensure that we adhere to all timelines and that service levels are maintained during stabilisation period, we appreciate your understanding and patience during this time.

Reminder:
Following up on an application:
When contacting the HPRA in relation to an application, we would appreciate if you could provide the Case Reference Number (CRN) and/or PA number, Procedure Number & CESP if available.

Veterinary Medicines

Brexit and potential effect on availability of veterinary medicines

The Veterinary Sciences Department (VSD) is continuing its preparations for Brexit, including various planning scenarios. The VSD remains concerned that the availability of veterinary medicines for minor use and minor species indications in particular could become a casualty in the event of a no-deal Brexit. The VSD is working with marketing authorisation holders and with the Department of Agriculture, Food and the Marine to manage the risk, in the interest of animal health and welfare. If marketing authorisation holders wish to discuss the challenges facing them in order to explore possible solutions, please contact vetinfo@hpra.ie in the first instance, citing Brexit in the title.

Staff changes in the Veterinary Medicines Team

Further to the preparations that the HPRA is making in response to the expected departure of the UK from the network of EU medicine agencies, the Veterinary Sciences Department (VSD) has significantly strengthened its personnel to meet future challenges. In welcoming new colleagues to the team we are conscious of the need to continue to be efficient and effective in our work and to deliver value for our agency. We look forward to the continuing support of marketing authorisation holders in the years ahead.

The up-to-date organogram of personnel in the VSD is available on the HPRA website.

Task Force on method of supply of antiparasitic veterinary medicines for food-producing species

On 13 February 2019, the HPRA's Advisory Committee for Veterinary Medicines (ACVM) established a Task Force 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. This includes products containing all classes of antiparasitic agents and including medicines containing coccidostats.

The membership of the Task Force is as follows:

J. Gabriel Beechinor, Theo DeWaal, Caroline Garvan, Orla Keane, Joe O'Flaherty, James O'Shaughnessy and Aidan Moody.

The Task Force is expected to have a consultation with interested parties before finalising the report. The report is expected to be finalised before October 2019 and will then be considered by the ACVM and the Authority of the HPRA.

Diethanolamine

Diethanolamine (DEA) has been used as an excipient in certain veterinary medicinal products for many years. In January 2018, the Committee for Medicinal Products for Veterinary Use (CVMP) removed DEA from the list of substances considered as not falling within the scope of Regulation (EC) No. 470/2009, with regard to residues of veterinary medicinal products in foodstuffs of animal origin. On 19 July 2018, the CVMP issued an opinion on the consumer safety of veterinary medicinal products containing DEA and advised that if DEA is to be further used in veterinary medicinal products that are intended for use in food-producing animals, an application for a maximum residue limit (MRL) would be needed.

The matter was reviewed by the Advisory Committee for Veterinary Medicines (ACVM) which reviewed the marketing authorisations of the products involved during 2018. The advice of the ACVM was then considered by the Authority of the HPRA, at their meetings on 6 December 2018, and again on 14 March 2019.

The Authority confirmed their decision to suspend the marketing authorisation of the products involved on the basis that DEA does not have a MRL and is not permitted to be administered to food-producing animals. The Authority agreed with the concerns expressed by ACVM that some products containing DEA might still be marketed for food-producing animals and upheld the recommendation of the Management Committee and ACVM that the suspension should take effect 6 months from the date of the Authority decision, on 14 September 2019, save where an application to vary the marketing authorisations concerned to remove DEA has been assessed and approved in the meantime. The Authority considered that the additional period of time was acceptable on the basis that no further product is being placed on the market, and therefore there is no additional risk to the consumer.

Notification of GDP inspections

In our Medicinal Products Newsletter No. 59, published in May 2018, the HPRA communicated to stakeholders that the period of notification prior to most routine GDP inspections would be extended so that authorisation holders would receive notification by email at least 8 weeks in advance of inspection. The expectation was that this notice period would further facilitate authorisation holders in planning and managing their resources, so that there would be little or no requirement to reschedule inspections. Despite this extended period of advance notification, we are continuing to experience a high level of requests for rescheduling or cancellation of GDP inspections which has resulted in the scheduling of these inspections becoming steadily more difficult. The constant rescheduling of routine inspections means that our resources are not used optimally. This, in turn, reduces the capacity of the inspection team to perform inspections, for example those relating to a new licence or variation, within the timeline requested by the applicant or authorisation holder, respectively.

In light of these challenges, the period of notification prior to most routine GDP inspections will revert to 4-6 weeks. It is important that once notification of an inspection is received the authorisation holder confirms, within the timeline stated on the notification email, that it will host the inspection.

It is noted that the rescheduling of some inspections is requested due to absence of key personnel. Authorisation holders are reminded that measures should be in place for delegation of duties of key personnel during periods of absence. It is expected that a deputy responsible person has adequate knowledge and oversight of the systems in place so that she/he can effectively deputise for the responsible person. This includes hosting of inspections.

The HPRA reserves the right to perform unannounced inspections.

Safety Features – Important Information for Marketing Authorisation Holders (MAHs) in relation to reporting Suspected Quality Defects to the HPRA

The European Commission's Delegated Regulation (EU) 2016/161 on safety features for medicinal products for human use came into operation across Europe on 9 February 2019. This supplemented the Falsified Medicines Directive (FMD), 2011/62/EU, by setting out detailed rules for safety features appearing on the packaging of certain medicinal products for human use.

These new requirements will help enhance patient safety by protecting the pharmaceutical supply chain from infiltration by falsified (including counterfeit) medicines and by introducing new rules to more rigorously regulate the supply chain.

The Irish Medicines Verification Organisation (IMVO) (www.imvo.ie) was established to manage the medicines verification system for Ireland. Since implementation, a 'use and learn' approach has been adopted in relation to the operation of the requirements mandated by the Delegated Regulation (and the associated statutory instrument, S.I. No. 36 of 2019). This 'use and learn' approach has been extended until 9 September 2019, and its purpose is to ensure continuity of the supply of medicines to patients while all parties gain a better understanding of the new system. Please see the FMD webpage for further information.This means that:

- All in scope medicinal products released by MAHs for the Irish market after 9 February 2019 should bear the safety features as required i.e. a tamper proof seal and 2D barcode.
- During the initial 'use and learn' phase, wholesalers, pharmacies and hospitals should scan each pack of a medicine bearing the safety features. If an alert or any other unexpected message is flagged, unless they have overriding concerns that a falsified medicine is involved, they should proceed to supply that pack of a medicine to a pharmacy / patient in accordance with their existing procedures. Where there are such overriding concerns, the pack must be withheld and the matter reported to the HPRA as soon as possible.
- All alerts generated by the medicines verification system upon scanning a pack during this 'use and learn' phase are automatically forwarded to the IMVO, the HPRA and the affected pharmaceutical company so that they can be investigated and monitored.

On receiving details of the alerts generated by the medicines verification system, MAHs will need to ensure that the necessary resources are in place to deal with them as a matter of priority. In certain cases, reports of suspected

quality defects must be submitted by the MAHs (or their manufacturers) to the HPRA. These cases are where there is reason to believe that the safety features on a medicinal product has been tampered with or when the investigation of an alert by the MAH, or its manufacturer, indicates that the pack may not be authentic. Suspected damaged or faulty safety features should also be submitted to the HPRA.

Notwithstanding the above, if a pharmacist or wholesaler has reason to believe that packaging has been interfered with, based on their examination of the anti-tampering device on the pack, they must report their concern to the HPRA (as a suspected quality defect via the usual reporting mechanisms) and must not supply the pack.

Reports of suspected quality defects should be made to the HPRA in the usual manner by completing the Quality Defect Report Form that is available on the HPRA website. The form should be downloaded, completed and emailed to the following email address: qualitydefects@hpra.ie. The subject line of the email should start with the words "Safety Features" followed by the name of the product. Such suspected quality defects should be reported to the HPRA as soon as possible.

The HPRA's guide on 'Reporting and Initial Investigation of Quality Defects in Medicinal Products for Human and Veterinary Use' was revised in February 2019 and reflects the aforementioned reporting requirements for quality defects relating to safety features (Ref. HPRA Document No. SUR-G0023-6, dated 15 February 2019.)

The revised Guide contains a new paragraph entitled 'Safety Features' (paragraph 7.12) in the section entitled Categories of Quality Defects. This new paragraph 7.12 reads as follows:

7.12 Safety features

Suspected quality defects should be reported in the following situations:

- Where there is reason to believe that the packaging of a medicinal product has been tampered with
- When the investigation of an alert by the MAH or its manufacturer results in an indication that the pack may not be authentic

The wording 'Safety Features' should be included in the e-mail subject header when submitting a quality defect form for a safety features issue.

Brexit preparedness - Have you verified if your cosmetic product has a Responsible Person registered within the 'EU-27' Member States?

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.

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 29 November 2018 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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