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HPRA MEDICINAL PRODUCTS NEWSLETTER

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Human Medicines

Preparing for simplified reporting and introduction of the ICH E2B (R3) standard

EudraVigilance stakeholders will be aware that preparations have been underway for some time to facilitate the move to simplified reporting and the ICH E2B(R3) standard in 2017. The system has now undergone an independent audit, the outcome of which is expected shortly, with the new functionalities due to be operational for all stakeholders in November 2017.

Marketing authorisation holders (MAHs) should have change management plans in place to address the updated requirements including, (but not limited to):

Process

- Existing processes updated to allow for:

- Discontinuation of sending ICSRs to national competent authorities in the EEA – transmit only to EudraVigilance in compliance with the pharmacovigilance legislation.
- Downloading ICSRs submitted by national competent authorities in the EEA from EudraVigilance using the EudraVigilance ICSR download functionalities.
- Reporting of non-serious ICSRs to EudraVigilance within 90 days of receipt.
- Complying with the provisions set out in revision 2 of GVP Module VI (when published).
- Performing signal detection and validation in line with GVP Module IX and the new EVDAS reports, and supporting the submission of validated signals to the EMA and national competent authorities in the EEA.

People

- Ensuring users are registered and trained (see also the e-learning modules available on the Eudra Vigilance website).
- Considering resource implications associated with the implementation of ICH E2B(R3) (or an interim backwards/forwards conversion tool), the new signal management requirements, the legal requirement to report non-serious cases, the mechanism for searching and downloading ICSRs using the ICSR download functionality etc.

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Technology

- Configuration of the local Gateway (where applicable) to support ICH E2B(R3) messages (or install a backwards/forwards conversion tool ad interim).
- Upgrading and move to an ICH E2B(R3) compliant system.
- Planning for testing – the new external testing system (XCOMP) is scheduled to 'go-live' in June 2017.

Information

- Considering communications needed to affiliates, contractual partners and other stakeholder regarding process changes.

The HPRA is also working to implement changes to the above areas to address the updated requirements and will no longer directly submit ICSRs reported by HCPs/MOPs to relevant MAHs, with these cases also routed via EudraVigilance. It is important to note that in accordance with guidance, HPRA and MAH interaction on ICSR follow up and case report reconciliation will continue as necessary and appropriate.

Stakeholders are advised to review the European Medicines Agency's website on a regular basis to access the most up to date details in addition to the numerous information and training resources provided.

Veterinary Medicines

Brexit and implications for veterinary medicines availability

Now that the UK has formally triggered Article 50, the HPRA is giving some thought to the implications for both the availability of medicines in Ireland as well as operational matters relating to the responsibilities for maintenance of marketing authorisations where the UK is the Reference Member State and Ireland is a Concerned Member State. In relation to the former, the HPRA's aim is to maintain availability of the current range of products for as long as the UK maintains equivalency of regulatory standards, thereby supporting the maintenance of products with joint UK/Irish labelling. In relation to the selection of a new Reference Member State to take over those procedures for which the UK currently has this responsibility, the HPRA is available to marketing authorisation holders who would like us to assume this role. For those concerned, please contact the Planning & Authorisation Manager, Ms. Grainne Flanagan (grainne.flanagan@hpra.ie) in the first instance. The HPRA has enjoyed a close working relationship with the Veterinary Medicines Directorate for many years and we would hope to continue to work closely with UK colleagues for as long as possible, knowing that the final shape of the ongoing governmental discussions on Brexit will not be known for some time. Within the HPRA, Ms. Mary O'Grady, Pharmaceutical Assessment Manager, has responsibility for helping prepare the organisation with respect to the veterinary implications of Brexit. For those with concerns in this area, you may contact Mary by email (mary.ogrady@hpra.ie).

New template for a 'combined label-leaflet' now available on the European Medicines Agency's website

The HPRA wishes to highlight the fact that the European Medicines Agency's Quality Review of Documents (QRD) Group has recently published a new template for a 'combined label-leaflet' on the European Medicines Agency's website.

The template has been created following an identified need by both industry and competent authorities. The template has been published for an 18 month consultation period (ending in October 2018) to enable applicants and competent authorities to gain experience in using the template. The aim after the pilot phase is to incorporate the combined label-leaflet template within the main set of QRD veterinary templates.

The template may be used with immediate effect and may be used in applications submitted using the National, Decentralised, Mutual Recognition or Centralised application routes.

The format of the template follows that of the package leaflet template with additional sections from the immediate/outer packaging template included.

This template is intended for use where applicants do not wish to provide a separate package leaflet and instead propose to include all required labelling and package leaflet information on the immediate packaging (as foreseen by Art. 61(1) of Directive 2001/82/EC). The template is only intended for use where all the printed information is directly visible on the immediate container and cannot therefore be used if a fold-out or concertina-style format is proposed.

Recent updates to Chapters 1 & 3 of EudraLex Volume 6A of the Notice to Applicants

The HPRA wishes to highlight the fact that the European Commission has recently published updated versions of Chapter 1 and Chapter 3 of EudraLex Volume 6A concerning Notice to Applicants (NtA) and regulatory guidelines for medicinal products for veterinary use. A link to the relevant webpage of the European Commission can be found here.

The 'Notice to Applicants' (NtA) has been prepared by the European Commission in consultation with the competent authorities of the Member States and the European Medicines Agency and was first published in 1986 and is regularly updated.

Volume 6 of the publication 'The rules governing medicinal products in the European Union' includes information on procedures for marketing authorisations (Volume 6A), information and advice on the presentation and content of the dossier (Volume 6B) and a list of regulatory guidelines related to various aspects of marketing authorisation applications (e.g. preparation of the Summary of Product Characteristics, processing renewals, packaging requirements).

Concerning the updates to Volume 6A, Chapter 1 addresses the various types of marketing authorisations and procedures.

Chapter 3 addresses Union referral procedures under:

- Article 33 of Directive 20021/82/EC (Mutual Recognition and Decentralised referral),
- Article 34 of Directive 20021/82/EC (Harmonisation referral),
- Article 35 of Directive 20021/82/EC (Union interest referral),
- Article 78 of Directive 20021/82/EC (Urgent Union procedure),
- Article 45 of Regulation (EC) No 726/2004 (Procedure for centrally authorised products),
- Article 13 of Commission Regulation (EC) No 1234/2008 (Referral when there is disagreement between Member States on a type II variation procedure).

The HPRA recommends that companies planning to submit applications should review the updated Chapters (in particular Chapter 1) beforehand, to ensure that their applications are compliant and that any planned references to the NtA are current.

Updated versions of the QRD templates (version 8.1) recently published by the European Medicines Agency

The European Medicines Agency's Quality Review of Documents (QRD) Group and the Co-ordination Group for Mutual Recognition and Decentralised procedures - veterinary (CMDv) have revised the veterinary product information templates that relate to the summary of product characteristics, packaging texts and package leaflet texts. This revision comes after gaining four years of experience with the previous version. The template for each European language, as well as an annotated template in English (clean and tracked changes versions) are available on the CMDv pages of the Heads of Medicines Agencies website.

An implementation plan for using the updated version of the product information template is also provided on the CMDv pages of the website. A separate implementation plan is published on the European Medicines Agency's website for the centralised procedure.

The implementation plan for applications submitted using either the National, Mutual Recognition (MR) or Decentralised (DC) routes may be summarised as follows.

For applications that are still pending:
Applicants should comply with the updated version of the template at time of submission of the application.

For ongoing applications for new marketing authorisations (MA) via MR/DC procedures:
For applications already submitted at the time of publication of the updated version (15th February 2017), applicants should switch to it during the course of the procedure by day 65 at the latest for MR procedures and by day 170 at the latest for DC procedures.

However, for applications that have already passed day 54 of the MR procedure or day 145 of the DC procedure at the time of publication of the updated version, the applicant will not be required to use the updated version of the template unless they choose to do so.

For ongoing post-authorisation applications:
For post-authorisation applications ongoing at the time of publication of the updated version, applicants should discuss switching to the updated version of the template with the Reference Member State for MR/DC procedures or with the National Competent Authority for purely national applications, as appropriate.

For existing Marketing Authorisations (MA) already granted:
Marketing Authorisation Holders should align the Product Information (PI) of their products with the updated version at the next post-authorisation procedure affecting the PI (e.g. variation) and at the latest, by the time of renewal of the MA (if applicable).

EIRCODE and product PIL and labelling

Ireland's postcode system, EIRCODE, was launched in July 2015. Although not mandatory, the HPRA will allow manufacturing authorisation holders to update the product packaging and/or patient information leaflet (PIL) of veterinary products with EIRCODE details without needing to submit a variation application.

Compliance

Concept paper on Good Manufacturing Practice in relation to Marketing Authorisation Holders

Concept Paper EMA/582064/2016 on Good Manufacturing Practice (GMP) in relation to marketing authorisation holders (MAHs) and their ability to meet their GMP related regulatory responsibilities, was published on 1 September 2016 following agreement by the GMP/GDP Inspectors Working Group in May 2016. This concept paper arose from concerns expressed by inspectors, from across the European regulatory agencies, that there was a lack of clarity and awareness amongst MAHs as to their various responsibilities. The lack of clarity appeared to stem, at least in part, from the fact that MAH responsibilities relating to compliance with GMP are spread across the current EU Guide to GMP and related legislation, and, as such, those MAH responsibilities are not available in a concise format within one document.

It had been found that the responsibilities of MAHs, in companies where the supply chain was diverse and complex, were not always correctly understood and that the communication of MA variations and regulatory commitments to the various manufacturing sites, if not completed correctly, had a significant impact on MA compliance.

The purpose of this concept paper was to enable the creation of a reflection paper that will capture all of the GMP related responsibilities that apply to MAHs and to enable them to understand and fulfil those responsibilities more effectively and comprehensively.

The public consultation on the concept paper ended in December 2016. Work on the development of the reflection paper is to commence in June 2017, at which time the comments received during the public consultation on the concept paper will be considered.

US – EU mutual recognition agreement on GMP inspection

Earlier this year, the European Commission and the United States Food and Drug Administration (FDA) put in place a mutual recognition agreement (MRA) on good manufacturing practice (GMP) inspections. The agreement is an annex to the EU-US MRA which was signed originally in 1998 but was not implemented subsequently. Within the 2017 provisions, pharmaceutical inspections and official GMP documents issued by one territory may be recognised by the inspectorates of the other. Thus, in general, the FDA will recognise inspections of manufacturers of medicines carried out by EU authorities, and vice versa, without the need for each authority to perform their own inspection.

Each authority will retain the right to inspect a manufacturing facility in the territory of the other party and there may be specific circumstances where this is required. However, such inspections would be considered the exception to the agreed approach.

The provisions of the agreement apply to finished medicines for human use, intermediates and in-process materials, certain biological products and active pharmaceutical ingredients. Veterinary medicines will be considered for inclusion by July 2019, while vaccines and plasma derived products may be considered in later years. Human blood, plasma, tissues and organs, and veterinary immunologicals are excluded from the scope of the agreement.

The MRA will become progressively operational from 1 November 2017.

Testing of imported batches

As per MRAs between the EU and other third countries, the recognition of quality controls, as provided in Article 51, paragraph 2, of Directive 2001/83/EC and in Article 55, paragraph 2, of Directive 2001/82/EC has been included in the US-EU MRA. This effectively means that quality control testing of batches imported into the EU will not be required provided the following criteria are met:

- quality control testing was carried out in the United States;
- the product was manufactured in the United States; and
- each batch or lot is accompanied by a batch certificate issued by the manufacturer certifying that the product complies with the requirements of the marketing authorisation and is signed by the person responsible for releasing the batch or lot.

This particular provision of the MRA will not apply until all EU Member State GMP inspectorates have been successfully assessed by the FDA, which is anticipated to be in July 2019. Importation by an authorised manufacturer and certification of each batch by a qualified person will remain in place.

Mechanism for Assessment

Criteria for assessment and a related procedure are specified within the agreement. The EU assessment of the FDA is scheduled to be completed by July 2017. The FDA assessment of the EU authorities is in progress and assessment of at least eight EU Member States will be completed by 1 November 2017. The remaining FDA assessments will be completed in transitional phases by 15 July 2019.

To facilitate its assessment of EU inspectorates, the FDA is observing evaluations of national authority GMP inspectorates that are carried out under the Joint Audit Programme (JAP). The JAP is overseen by the EEA Heads of Medicines Agencies (HMA) and is focused on legislation, GMP inspection, licensing, defects and recalls, and sampling and analysis of medicines. The audit of the HPRA under the programme is scheduled for mid- May 2017.

The full text of the agreement can be found on European Commission website.

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