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New EudraVigilance System: Changes to Reporting Requirements - Go-Live Planning

The new EudraVigilance System will go-live at 9:00am on 22 November 2017. From this time, all reporting shall be in line with the final reporting arrangements as described in Directive 2001/83/EC as amended by 2010/84/EU. Therefore all serious ICSRs that occur within or outside the EU will be reportable directly to EudraVigilance and not to individual National Competent Authorities (NCAs)/Marketing Authorisation Holders (MAHs). All non-serious cases occurring in the EU will also be reportable to EudraVigilance by NCAs and MAHs. These final reporting arrangements are further described in Revision 2 of GVP Module VI (Management and reporting of adverse reactions to medicinal products), which comes into effect on 22 November 2017.

To allow the transition from the current EudraVigilance system to the new one, the European Medicines Agency (EMA) have planned for a downtime or 'cutover' period during which EudraVigilance functionalities will be limited. This will run from 00:00 on 8 November 2017 to 09:00 on 22 November 2017. During this time there can be no submissions to EudraVigilance by NCAs/MAHs.

In order to manage our own changeover, the HPRA will close its gateway at 00:00 on 4 November 2017 and MAHs should cease submitting ICSRs to HPRA from this time. Any Irish ICSRs due for submission between 4 and 21 November should be submitted directly to EudraVigilance after the new system go-live on 22 November. There will be a 3-day 'cutover legacy' period from 22 – 24 November when all 'backlog' ICSRs should be submitted to EudraVigilance. Compliance timelines will be adjusted to take account of the downtime during this period.

For investigators and sponsors of clinical trials the same downtime applies. SUSARs may be submitted to EVCTM up until 8th November 2017. Any Irish SUSARs submitted from 4 November 2017 onwards should be sent to the HPRA alongside the other legacy cases after go-live on 22 November 2017. It should be noted that in accordance with the HPRA's national Guide to Clinical Trials Applications, sponsors and investigators are obliged to notify the HPRA within 3 days of any action needed to protect the health and safety of clinical trial subjects.

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A key aspect of the new EudraVigilance system is its compatibility with the E2B(R3) format. Stakeholders may submit and receive ICSRs and SUSARs in the E2B(R3) format from 22 November 2017 onwards, if their internal systems have been updated to meet this requirement. Any reports generated in EVWEB will be in the E2B(R3) format.

The EMA has published a detailed EudraVigilance Go-Live Plan on their website at www.ema.europa.eu. This gives a full overview of the go-live strategy, including arrangements for individual NCAs. MAHs and sponsors should consult this document and consider the impact on internal processes in November 2017. Stakeholders should also consult the dedicated EudraVigilance training resources on the EMA website.

Use of the rabbit pyrogen test

The revised general chapter Monocyte-activation test (2.6.30), which provides for the detection of endotoxin and non-endotoxin pyrogens, was published in the Ph. Eur. Supplement 9.2 and came into effect in July 2017. The monocyte activation test (MAT) is used to detect or quantify substances that activate human monocytes or monocytic cells to release endogenous mediators which have a role in the human fever response. The MAT is suitable, after product-specific validation, as a replacement for the rabbit pyrogen test (RPT). The MAT offers significant advantages over the use of the rabbit pyrogen test (RPT) as based on the human fever response, it provides a more relevant prediction of pyrogenic activity than the RPT, it can detect endotoxin and non-endotoxin pyrogens and it is applicable to a greater variety of products than the RPT. Moreover, it is more accurate and more cost- and time-effective than the RPT.

Article 13 of Directive 2010/63/EU states that a procedure shall not be carried out on an animal if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union. It is incumbent therefore upon MAHs to ensure that if non-animal alternative tests have been validated for their specific products, tests using animals are not conducted in place of these non-animal alternative tests. It is hoped that this revision of the general chapter will lead to a further reduction in the use of laboratory animals. The HPRA will continue to engage with MAHs to replace animal studies for testing medicinal products wherever possible.

Veterinary Medicines

Best Practice Guide on Measures Improving Predictability of Submissions/Responses and Adherence to Communicated Submission/Responses Deadlines.

The HPRA wishes to draw the attention of applicants to the production of a new best practice guide that has been developed by the EMA/HMA to optimise the operation and functioning of the mutual recognition, decentralised and centralised procedures. The guide is intended to provide guidance on initial Marketing Authorisation Applications (MAA) submission dates, receipt of preliminary / draft assessment reports, draft List of Questions (LoQ) and/or draft List of Outstanding Issues (LoOI) and responses to those. The document was elaborated following communications with stakeholders and represents a commitment on the part of those concerned to improve the functioning and predictability of the procedures. The document is available on the EMA and HPRA websites. The HPRA is pleased to have been part of the working group which elaborated the document and hopes that it will be of value to everyone.

Brexit Preparations

Brexit preparations are continuing, at national and EMA levels, as well as at the Heads of Medicines Agency level. It is clear that the UK is a major contributor in the network currently, so Brexit will pose a significant challenge to the capacity of the regulatory systems for veterinary medicines in the EU. However, the HPRA is actively involved in managing the situation.

In relation to the engagement of a Reference Member State to take over new and existing procedures for which the UK currently has this responsibility, the HPRA is available to marketing authorisation holders (MAHs) who would like us to take on this role. As it is important to plan for the additional capacity that will be needed, we would like those MAHs concerned to contact us as soon as possible and in the case of existing procedures to do so before March 2018 (grainne.flanagan@hpra.ie). Procedure transfers advised after this date will be undertaken only if capacity allows. 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).

Outcome of Brexit Survey – Industry Desire to Maintain Joint Labelling

The HPRA would like to thank all those who completed our recent Brexit preparedness survey and those who attended our Brexit Stakeholder Information event. In relation to the survey, we had an excellent response; 75% of respondents indicated that where joint-labelling was already in place between Ireland and the UK, they would expect that it be maintained. Some 50% of respondents indicated that in light of Brexit they were very likely to consider Ireland as a replacement RMS in the MRP/DCP. Some 42% indicated that for new procedures they would be very likely to choose Ireland as the RMS. Moreover, 57% of respondents opined that Brexit would not cause them to withdraw products in Ireland where Ireland and the UK were the only member states involved in the procedure. The HPRA welcomes the industry wish to prioritise medicines availability. Acknowledging that the final shape of Brexit is still not known, it is clear that there is a relatively short period of time left for the industry to ensure that needed preparations are completed in order to ensure that there is no interruption of supply of veterinary medicines into the EU market. The HPRA is available to discuss the implications of Brexit for individual companies. Queries on this matter should be sent to mary.ogrady@hpra.ie.

Obligations Regarding the Withdrawal of Marketing Authorisations in Ireland

In accordance with the requirements of national legislation (Article 11 [7][b] of SI No. 786 of 2007, as amended), where a MAH wishes to withdraw a marketing authorisation and cease to market the product in Ireland, the MAH is required to inform the HPRA (vetinfo@hpra.ie) **at least two months in advance** of the proposed withdrawal date and give the reasons for this action. In the interest of availability of an adequate range of veterinary medicines on the market in this country, it is important that MAHs comply with the legislation in this regard.

Number 1 in Europe

The HPRA is delighted to have moved to the position of number 1 authority for the number of outgoing procedures for MRP and DCP for the first six months of 2017, as reported by the Chair of the CMDv to a recent meeting of the Heads of Medicines Agency. We appreciate that the Animal Health industry can choose the Reference Member State from any of the Member States of the EU. We are investing further in our resources over the coming period and look forward to improving our service in the years ahead.

Introduction of 'Value' or Promotional Packs of Veterinary Medicines

MAHs wishing to use a 'value' or promotional pack size containing multiple pack sizes that are currently authorised should note that if they are being packaged in a new outer carton this is considered to be a new presentation and must be registered and authorised by the HPRA and detailed on the SPC. This can be done by means of a variation application (B.II.e.5 Change in pack size of the finished product). The new outer packaging must contain the approved QRD text and comply with national requirements with respect to legibility etc. These aspects will be assessed and approved during the variation procedure. In the situation where two or more currently approved pack sizes are being sold together and are physically connected, for example, by transparent adhesive / plastic covering etc, but each pack remains in the currently approved outer carton, a variation is not required, provided all of the currently approved QRD text is present and visible. Note that the HPRA will not generally approve the use of promotional packs in respect of antibiotics, as this is against responsible use principles. In situations where a dosing device is provided with the product, the dosing device must be registered through a B.IV.1.2 variation, and listed on the SPC. Unauthorised packs may be seized by officers of the Department of Agriculture, Food and the Marine, as they are not in compliance with their marketing authorisation.

Veterinary Sciences

Veterinary Medicinal Products Containing Zinc oxide to be Administered Orally to Food-Producing Species

On 16 March 2017 the EMA concluded its assessment of the benefit-risk balance of veterinary medicines containing zinc oxide that are administered orally to pigs. The assessment, which was conducted by the Committee for Medicinal Products for Veterinary Use (CVMP), concluded that overall the benefit-risk balance for the products concerned is negative, as the benefits of zinc oxide for the prevention of diarrhoea in pigs do not outweigh the risks for the environment. A decision in respect of the CVMP recommendation was taken on 19 June 2017, following a meeting between the European Commission and Member State governments in Brussels. That decision was to withdraw the products concerned throughout the European Union, over a maximum of 5 years, i.e. before 26 June 2022.

In accordance with the Commission Implementing Decision of 26 June 2017, the HPRA (as well as competent authorities in other Member States), is directed to withdraw existing national marketing authorisations for the products concerned within 5 years. It follows that no new marketing authorisations for zinc oxide to be administered orally to food-producing species may be granted, given the decision taken and that the marketing authorisations for concerned products already authorised in Ireland will cease to be valid on 26 June 2022. Please refer to the relevant safety notice published on the HPRA website (link here) for further information.

Compliance

HPRA Regional Information Evenings - Cosmetic Products

The Health Products Regulatory Authority (HPRA) is hosting a number of information evenings in locations across Ireland to explain the cosmetic regulations to small and medium-sized manufacturers, distributors and 'responsible persons' for cosmetic products. The evening will consist of presentations outlining the cosmetic regulation, and you will also have the opportunity to meet with HPRA representatives, one to one, to ask any questions you may have.

The information evenings will be held on the following dates:

11 October 2017 at 6pm – *Landmark Hotel in Carrick on Shannon.*

12 October 2017 at 6pm – *HPRA offices in Dublin.*

19 October 2017 at 6pm – *Maldron Hotel in Limerick.*

To register for a cosmetics information evening, visit the HPRA website (hpra.ie). For further information on these events, please email us at cosmetics@hpra.ie.

The HPRA has also recently launched a Cosmetic Products Information Pack to assist entrepreneurs and existing cosmetic product business owners to understand what they need to do to provide safe cosmetic products for consumers. The information pack offers useful and important information on the steps necessary to meet legal and regulatory requirements before placing a cosmetic product on the market in Ireland and the EU.

Responding to a Data Integrity Failure

Data integrity breaches can occur at any time, by any employee. Failures may involve omissions, alterations, deletions, non-contemporaneous record completion or completion of records for which the data has not been obtained or the action has not been performed. Failures in data integrity are not limited to fraud or falsification, they can be unintentional and still pose risk.

Investigation

In the event that a data integrity breach is found or suspected, management need to understand the reasons behind the failure to enable sufficient investigation of the issue and implementation of effective corrective and preventative actions. The investigation should be performed within the company quality management system and according to a defined process. The scope, extent and timeframe of the issue should be determined with justification for the boundaries applied. In determining the scope, a company should investigate what data, processes and product batches are implicated.

The investigation should ensure that all related data and evidence are secured in a timely manner to ensure the integrity of the investigation e.g. ensure any camera footage is secured and not overwritten. It may be appropriate to perform interviews with employees to understand the nature of the failure, how it occurred and what might have been done to prevent and detect the issue sooner. This should include discussions with supervisory / management personnel and quality assurance. Underlying root cause(s) of the issue need to be considered, including potential management pressures and incentives, for example, a lack of adequate resources.

Impact of the data failure should be based on risk assessment. Impact to product quality, risk to patient health (including a medical assessment as appropriate), risk to ongoing operations, risk to previous product manufactured and supplied to the market, and any impact on data submitted to regulatory agencies should be considered. The investigation should not be limited to the specific issue identified but should also consider potential impact on previous decisions based upon the data and systems that may now be found to be unreliable. There should be consideration for wider implications and corrective actions, particularly if the system in place or working culture is similar in other operations or affiliate companies.

Corrective and Preventative Action

When all root causes have been identified a corrective action / preventive action plan commensurate with the investigation findings and risk assessment should be documented and implemented. The plan should describe what evidence is available and what additional actions will be taken to ensure reliability and completeness of all data generated. If applicable, the plan should indicate whether the individuals responsible for the data failure remain able to influence GxP related data, and if so, justification for their continued role should be documented. In certain circumstances, the services of a qualified third-party consultant with specific expertise in the areas where potential breaches were identified may be deemed necessary.

Interim corrective actions may include HPRA notification, customer notification, quarantine or recall of product, additional testing, placing batches on stability, enhanced complaint monitoring or drug application actions. Longer term actions include review and change of the process, methods, control measures, management oversight and training. Actions may require realignment of management expectations and allocation of additional resources to prevent recurrence in the future.

Notification to Regulatory Authorities

Health authorities should be notified if the investigation identifies potential significant impact on patients, products, reported information or on application dossiers. Notify the HPRA of a data integrity issue using the email contact compliance@hpra.ie or by calling HPRA offices at 01 6764971. It is also reccommended to contact the inspector who last performed an inspection at the site in question.

It is recognised that some data integrity breaches may result in disciplinary action and / or lead to legal action. The company may need to ensure the confidentiality of information linked to any ongoing proceedings. All information reviewed by the HPRA is treated as confidential. Investigation records shown to the HPRA should accurately reflect the extent of the issue, root cause and corrective action taken. It is unacceptable that company personnel disciplinary procedures should result in the minimising of investigation details revealed to competent authorities such that the true root cause or extent of the data breaches are not adequately communicated.

Recommended Reading

Further guidance on addressing data reliability issues can be found in the links below.

PIC/S PI 041-1 Draft 2 (August 2016)

https://picscheme.org/layout/document.php?id=715

WHO Technical Report Series 996, Annex 5 (2016) Guidance on good data and record management practices

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf?ua=1

European Commission Delegated Regulation for Safety Features on Medicinal Products for Human Use

The Commission Delegated Regulation (EU) 2016/161 that supplements Directive 2001/83/EC, with detailed rules for the safety features appearing on the packaging of medicinal products for human use was published in the Official Journal of the European Union on the 9 February 2016. The Delegated Regulation will apply in Ireland from the 9 February 2019 (3 years after its publication). The Delegated Regulation can be accessed at the following link:- https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2016_161/reg_2016_161_en.pdf

The publication of the Delegated Regulation was accompanied by the publication of the following documents which can be accessed through the links provided below:-

1. Q&A document on the European Commission website https://ec.europa.eu/health/human-use/falsified_medicines_en
2. The Implementation Plan for Centrally Authorised Products (CAPs) on the European Medicines Agency on the EMA website
3. The Implementation Plan for Nationally Authorised Products (NAPs) on the Head of Medicines Agencies (HMA: CMDh) website

Repositories System

Article 31 of the Delegated Regulation sets out the provisions related to the establishment of the repositories system. It requires the repositories system, where the information on the safety features shall be contained, to be set up and managed by a non-profit legal entity/entities established in the Union, by manufacturers and marketing authorisation holders of medicinal products bearing the safety features. In setting up the repositories system, the legal entity or entities are required to consult, at a minimum, with wholesalers, persons authorised or entitled to supply medicinal products to the public and relevant national competent authorities. Wholesalers and persons authorised or entitled to supply medicinal products to the public are entitled to participate in the legal entity or entities, on a voluntary basis, at no cost. The costs of the repositories system shall be borne by the manufacturers of medicinal products bearing the safety features, in accordance with Article 54a (2) (e) of Directive 2001/83/EC.

European and national repositories systems

The repositories system is composed of a central information and data router ('European Hub') and national repositories. The national repositories shall be connected to the European Hub.

The European Medicines Verification Organisation (EMVO) is a Belgian non-profit organisation responsible for the set up and management of the European Medicines Verification System (EMVS or 'European Hub').

Further details may be accessed through the following link - https://emvo-medicines.eu/

The Irish Medicines Verification Organisation (IMVO) is a new organisation established as a non-profit company, by a range of stakeholders across the medicines supply chain in Ireland to set up and manage the national repository, i.e., the National Medicines Verification System (NMVS). Further details may be accessed on the IMVO website, www.imvo.ie

Action required by industry

The HPRA has been requested by the EMVO to raise awareness amongst all national stakeholders regarding the 'onboarding' activities required. The EMVO Onboarding Information Package may be found at https://emvo-medicines.eu/eu-hub-on-boarding/on-boarding-process

In accordance with the notification received from the EMVO, **manufacturers** will be required to 'onboard' to the 'European Hub' in 2017/Q1 2018 and to 'conclude a service contract' with the IMVO.

The HPRA has also been requested by the EMVO to raise awareness with other national supply chain partners including **wholesalers** with respect to the connection, access to and use of the NMVS, in order to verify the authenticity of, and to decommission, the unique identifier of medicinal products, in accordance with the provisions in the Delegated Regulation. Wholesalers are requested to make contact with the IMVO in this regard.

Updated Quality Defect Reporting Guidance Note and New Reporting Form

In July 2017, the HPRA's guidance document on 'Reporting and Initial Investigation of Quality Defects in Medicinal Products for Human and Veterinary Use' was extensively updated. This guidance note will be referred to as the 'guidance' for the purpose of this article.

The guidance was introduced in 2010, to assist companies with, and provide clarity on, the requirements of reporting to the HPRA of quality defects in medicinal products for human and veterinary use. The guidance should be used in addition to the direction provided in the relevant regulations and in European legislation. In this, the third revision, the main updates are:

(i) Clarification on the scope of the guidance.

(ii) Further elaboration on what is expected of companies when a suspected quality defect has been discovered.

(iii) The importance of performing a risk assessment.

(iv) The timelines associated with reporting the defect to the HPRA.

(v) Further guidance on the investigation and reporting of certain specific quality defect types.

(vi) A new Quality Defect Reporting form is now available for Marketing Authorisation Holders, Manufacturers and Wholesalers to use when reporting a quality defect. The form should be completed and sent as a Word or PDF document, via email, to the Quality Defect and Recall email address, qualitydefects@hpra.ie. The form should not be altered. The form requires the sender to verify data independently before submission. Any additional information or related documents, such as investigation reports, medical risk assessments and technical reports should be included as attachments in the same email.

The updated guidance and new form are available in the Quality Defects and Recall section of the HPRA website at this link. The HPRA requests that the relevant stakeholders familiarise themselves with the documents and update any related company procedures accordingly. For any questions please contact qualitydefects@hpra.ie.

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