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Human Medicines

Improving the management of shortages

A new national initiative has been established to better manage medicines shortages and their impact on Irish patients.

Medicine shortages are increasingly prevalent globally, and Ireland, like all European countries, has the potential to be affected. The HPRA has created a new function internally to co-ordinate the management of medicine shortages and it will work closely with various stakeholders who have already fully committed to playing their role as part of a national strategy. The HPRA has also created a dedicated section on its website to provide information on the medicines which are in short supply, and their anticipated return to the market. This will be regularly updated as new information becomes available.

The Medicine Shortages Framework is a collaborative initiative that brings together key players in the health sector with the aim of developing strategies to mitigate the effect of shortages in Ireland so that patient health is protected. This new framework will result in a co-ordinated national response to managing medicine shortages and provides mechanisms that can be swiftly activated if a shortage of a particular medicine does occur. It strengthens and improves procedures which provide enhanced protection for patients through forward planning and shortage identification. It was developed after extensive consultation with a wide range of stakeholders involved in the provision of medicines, including other state health sector bodies, healthcare professionals, patient groups, and industry.

The framework document, information on medicines which are in short supply, notification forms and other information to assist all stakeholders in the management of medicines shortages are available on the HPRA's website on this page. The HPRA's shortages function can be contacted via email at shortages@hpra.ie. Stakeholders are asked to read the framework and to be particularly aware of their roles in the management and prevention of shortages and the notification process for shortages.

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HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Multilingual Packaging

The HPRA views the management of medicines availability as a key priority in the protection of public health. The HPRA is therefore actively working with companies to ensure that the impact of Brexit on medicine availability is minimised.

The use of multilingual packaging can be key to companies retaining medicines on the Irish market. The HPRA is therefore committed to working with companies to develop multilingual labelling while remaining compliant with regulatory requirements to safeguard continued patient access.

To encourage the use of multilingual labelling the HPRA will proactively work with other European regulators to help optimise opportunities for multilingual labelling. Additionally, the HPRA 'Guide to labels and leaflets of Human Medicines' is in the process of being updated to give specific guidance on the development of multilingual labelling and will be available on the HPRA website shortly.

Veterinary Medicines

Challenges to maintaining joint labelling of veterinary medicines with the UK

The HPRA is aware of the benefit of having joint labelling between Ireland and the UK, and has promoted this initiative since 2000. Today, approximately 50% of the products on the market in Ireland benefit from a joint UK/Ireland label, meaning that the products involved can be transported to either market according to market demands. The HPRA continues to work closely with our colleagues in the UK's Veterinary Medicines Directorate to safeguard this system into the future, even if that future is uncertain.

The HPRA is awaiting the judgment in a High Court action by an Irish citizen that was held in Dublin on 24-25 July 2018. That action, which was taken against the Department of Agriculture, Food and the Marine, relates to the availability of Irish language on veterinary medicines supplied to the market here. The outcome of the case could have far-reaching implications and will be eagerly awaited.

Changes processing of New – National applications

The HPRA is changing how new national applications are processed.

In order to ensure predictability in assessment timelines for applicants, to streamline time from submission to decision and to ensure optimal use of assessment resources, it has been decided that new national applications will now follow the timetable (including clock-stops) currently used for the decentralised procedure (210 day timeline with 90 day clock-stop).

Consequently, following commencement of assessment of a new national application and if questions are raised by the HPRA assessors, the applicant will have a period of 3 months (extendible up to 6 months) to respond. Only in exceptional circumstances may the clock-stop period for the applicant to respond to questions be extended beyond 6 months. Failure to provide responses within the timeframe provided will necessitate withdrawal of the application and re-submission at a later date, accompanied by any additional information/data deemed to have been lacking at the time of initial submission

Changes to procedure for withdrawal of applications for veterinary medicines

The HPRA is currently reviewing and updating the form and applicable guidance for the withdrawal of applications for marketing authorisation. The purpose of this review is to be able to analyse the reasons for withdrawal and to gather information regarding alternative products, either in Ireland, or in other markets. We wish to draw attention to our policy initiative to improve availability of veterinary medicines in Ireland, and would urge marketing authorisation holders to discuss the situation in advance with the Director of Veterinary Sciences (contact via aisling.condren@hpra.ie) should they be considering to cease marketing products in Ireland.

Veterinary Medicines

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 (also known as the 'out of scope' list), on the basis of concerns relating to carcinogenicity and genotoxicity. Subsequently, 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 consequence of this development is currently being considered by the HPRA and a review of the authorisations of the products concerned has commenced. However, it will not be possible to authorise new veterinary medicinal products containing DEA that are indicated for food-producing animals pending the elaboration of appropriate MRLs by the CVMP, on foot of an application to the European Medicines Agency.

Implementation of European Commission decisions

In accordance with Article 38(3) of Directive 2001/82/EC, following the publication of a European Commission decision (for example, following a referral to the CVMP), the HPRA as a national competent authority is required to implement the outcome of that decision within 30 days of its notification.

In order to ensure compliance with the above legal requirement and to ensure a harmonised approach to the implementation of Commission decisions, the HPRA will in future write to the marketing authorisation holders of all products concerned by a Commission decision that are nationally authorised in Ireland or where IE is the Reference Member State for a product, requesting that the appropriate variation application under C.I.1 of the Commission's Guidelines on the various categories of variations, be submitted to the HPRA by a given date.

In that way, the marketing authorisations of products concerned by the Commission decision will be changed (varied) in accordance with the Commission decision at the same point in time.

In addition, once the required changes to the marketing authorisations have been implemented, a decision will be taken by the HPRA in accordance with the HPRA's 'Guide to implementation of packaging changes to authorised veterinary medicinal products' concerning the deadline by which any necessary changes to the product labelling and/or leaflet should be implemented. The HPRA will write to the marketing authorisation holders of the products concerned by the Commission decision advising them of that deadline, so that the marketing authorisation holders may make the necessary arrangements to ensure that all product released to the Irish market complies with any required changes to the product labelling and/or leaflet by that date.

The above process is intended to ensure that the timing of implementation of Commission decisions is consistent for all concerned products.

Updates to product labelling as a result of efforts to address antimicrobial resistance (AMR)

Stakeholders will be aware of the draft European Regulation on the authorisation and monitoring of veterinary medicinal products and of the suite of regulatory measures that will be available to address AMR in the future. Ahead of the adoption and implementation of the applicable European legislation, the relevant Community bodies (e.g. EU Commission, the Committee for Medicinal Products for Veterinary Use [CVMP]) are continuing efforts to improve the labelling of veterinary antibiotics, in an effort to address AMR, to promote responsible use and to ensure that the products concerned perform optimally in the field.

As a result of these efforts the labelling of various classes of veterinary antibiotics have been updated over recent years. The latest change is to the labelling of veterinary medicinal products containing enrofloxacin that are administered via the drinking water to chickens and/or turkeys. For those products, the CVMP has determined that the existing dosage regimen was not optimised to limit the emergence of resistant sub-populations and that the indication for E. coli should be withdrawn. Consequently, the Marketing Authorisation Holders (MAHs) concerned have been required to submit variation applications (Type IA variation) to update the labelling of the products concerned.

Veterinary Medicines

MAHs are encouraged to closely follow developments of the CVMP in relation to AMR, to submit variation applications according to the outcome of the CVMP referral procedures and to advise customers of the changes to the authorised conditions of use. In accordance with the HPRA policy on packaging and labelling changes, the updated labelling and leaflet should be implemented within 6 months of the date of the approval of the variation.

Feedback on veterinary medicines information day

The HPRA held a Veterinary Medicines Information Day on 13 June 2018. Some 91 external delegates attended the meeting. The focus of the day was on the new EU Regulation on veterinary medicinal products as well as the effects of Brexit on the animal health industry in Ireland. Other topic sessions included HPRA performance and KPIs, as well as Pharmacovigilance, revision of the GMP Annex I and the conduct of clinical trials in Ireland. A novel feature of the day was a poster session on miscellaneous items not covered in the formal programme. Feedback on the meeting itself and on the venue and hospitality arrangements was hugely positive. We are grateful to everyone who supported the event. For anyone who was unable to attend the event, the presentations for the meeting are now available on request, from Ms. Aisling Condren (aisling.condren@hpra.ie).

HPRA personnel changes as a result of work-planning for Brexit

We are pleased to announce a number of further staff changes that have arisen as a result of our plans to improve our capacity to meet the assessment needs due to Brexit. Ms. Gloria McAndrew has been appointed as Pharmaceutical Assessor on 1 June 2018 and her replacement Ms. Aoife Lordan was appointed Scientific Officer and will take up her post in September 2018. Dr. Aideen Brownen was appointed Veterinary Assessor and took up her role on 13 August 2018. The HPRA has further plans to strengthen the team over the coming period, depending on forecasted demands for our services and financial trends.

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

Compliance

New expedited variation process available for IMP manufacturer's authorisations

In relation to the manufacturer's / importer's authorisation (MIA) for investigational medicinal products (IMPs), the HPRA, in June 2018, introduced an expedited assessment of variations related to contract manufacturers (listed in Annex 3 of the MIA) and contract laboratories (listed in Annex 4 of the MIA). The reason for the introduction of the expedited assessment is to assist in the effective regulation of the dynamic and fast paced IMP manufacturing environment in Ireland. The expedited process offers a seven working day turnaround for completion of the assessment, provided that the required information is supplied. For more information relating to the expedited variation assessment and the specific requirements please visit www.hpra.ie.

Safety Features – Key Messages

Manufacturers and Marketing Authorisation Holders (MAHs)

Safety features will become obligatory in Ireland and in all other EEA countries (with the exception of Italy and Greece) from the 9 February 2019. In effect this means that a Qualified Person (QP) certifying batches of medicinal products within the scope of the Commission Delegated Regulation (EU) 2016/16, for these markets, on or after the 9 February 2019, must ensure that the packs bear the 2D unique identifier and anti-tampering device.

For manufacturers and MAHs there are important tasks to complete:

- Regulatory procedures for packaging changes – see HPRA FAQs on www.hpra.ie/homepage/medicines/special-topics/falsified-medicines-legislation/safety-features-for-medicinal-products-for-human-use
- 'On board' with the European Medicines Verification Organisation (EMVO). Refer to https://emvo-medicines.eu/ for details.
- Register with the National Medicines Verification Organisation in each EEA market where relevant medicinal products will be distributed. For the Irish Medicines Verification Organisation, refer to www.imvo.ie
- Inform primary wholesalers in advance of supplying serialised packs to them.
- In circumstances where manufacturers have already released batches that bear the safety features to EEA markets, or intend to do so before the 9 February 2019 deadline, they, or the MAH, must ensure that the required data are uploaded to the repositories system before the 9 February to avoid interruptions in the supply of medicines to patients. If the data have not been uploaded for the relevant packs this will lead to a significant number of alerts being generated by the system when the packs are scanned at wholesaler and/or pharmacy level. These system alerts will require investigation by the relevant stakeholders including the MAH, manufacturer and, in some cases, the competent authority and could potentially impact on the supply of essential medicines to patients.

Wholesalers

Wholesalers must be prepared to verify and decommission unique identifiers present on prescription only medicine packs for human use from 9th February 2019. From that date, wholesalers who physically handle medicinal products bearing the safety features must be connected to the central repository managed by the Irish Medicines Verification Organisation (IMVO). They must have the necessary software, scanners and procedures in place to perform these tasks.

The requirements apply almost exclusively to prescription only medicines but there are a small number of exceptions. Further details on products impacted are included under Annexes 1 and 2 (the 'white' and 'black' list) of Regulation EU/2016/161.

The IMVO will contact wholesalers by email with details of how to onboard and connect to the repository. Further information is available on the IMVO website, including details of introductory webinars for wholesalers.

GDP requirements for procurement and supply of active substances for human use

The purpose of this article is to remind holders of active substance registrations, specifically those importers and distributors performing procurement, supply and export activities only, of the requirements detailed in the Guidelines of 19 March 2015 on the Principles of Good Distribution Practice of active substances for medicinal products for human use (2015/C 95/01).

The Guidelines set out the Good Distribution Practice (GDP) requirements for active substances under eight chapter headings. Paragraphs of particular significance to importers and distributors performing procure and supply activities include:

- Distributors of active substances should develop and maintain a quality system setting out responsibilities, processes and risk management principles.
- The distributor should designate a person at each location where distribution activities are performed with defined authority and responsibility for ensuring that a quality system is implemented and maintained.
- Personnel should be trained on the requirements of GDP for active substances.
- Where active substances are procured from a manufacturer, importer or distributor established in the EU, that manufacturer, importer or distributor should be registered with its national competent authority according to Article 52a of Directive 2001/83/EC.
- Supplies within the EU should be made only by distributors of active substances registered according to Article 52a of Directive 2001/83/EC to other distributors, manufacturers or to dispensing pharmacies.

- Records should be kept of each purchase and sale, showing the date of purchase or supply, name of the active substance, batch number, quantity received or supplied, and name and address of the supplier and of the original manufacturer, if not the same, and of the shipping agent and/or the consignee.
- Where storage or transportation of active substances is contracted out, the distributor should ensure that the contract acceptor knows and follows the appropriate storage and transport conditions. There must be a written contract between the contract giver and contract acceptor, which clearly establishes the duties of each party.
- Distributors should transfer all product quality or regulatory information received from an active substance manufacturer to the customer and from the customer to the active substance manufacturer.
- Where the distributor suspects that an active substance procured or imported by him is falsified, he should segregate it either physically or using an equivalent electronic system and inform the national competent authority of the country in which he is registered.
- Records of returned active substances should be maintained.
- Records of complaints should be retained in order to evaluate trends, product related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action. These records should be made available during inspections by competent authorities.
- The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.
- Regular self-inspections should be performed in accordance with an approved schedule.

In addition to the above, note the following documents and records that may be requested during an inspection:

- Procedures regarding routine operations and management of change in the supply chain.
- Records documenting the assessments of proposed suppliers and customers demonstrating that they are registered according to Article 52a of Directive 2001/83/EC within the EU to manufacture, import or distribute active substances. This may be performed through recording assessment of the active substance registration of the supplier / customer and the associated GMP / GDP certificate if this is issued by the national competent authority. Note that the active substance registration and / or certificate issued to the supplier or customer may include restrictions that are not visible through the public view on EudraGMDP.

Additional requirements apply to the importation of active substances, as laid down in Article 46b of Directive 2001/83/EC.

Further guidance can be found in the HPRA 'Guide to Registration Requirements for Active Substance Manufacturers, Importers and Distributors in Ireland' available on our website www.hpra.ie

European Commission public consultation on precursor chemicals legislation

Precursor chemicals are chemicals that are primarily used in the legitimate production of a wide range of products, such as medicines, perfumes, plastics and cosmetics. However, they can also be misused in the illicit production of controlled substances. European legislation is in place to ensure that diversion of precursor chemicals is prevented. The legislation concerned is

- Regulation (EC) No 273/2004 on trade in drug precursors within the EU
- Council Regulation (EC) No 111/2005 on trade in drug precursors between EU and third countries

A questionnaire has been created by the European Commission in order to consult with stakeholders on the effectiveness of this legislation. The purpose of the consultation is to determine if the legislation is effectively striking a balance between the necessary controls to prevent diversion of drug precursors and allowing these to be legitimately traded without creating unnecessary administrative burdens.

The European Commission has specifically requested the views of those affected by the legislation and, accordingly, all precursor chemical operators (natural or legal persons engaged in the production or trade in precursor chemicals) are invited to complete the questionnaire. The questionnaire will take approximately 10 minutes to complete and requests that respondents identify the sections of the Regulations that are most successful at preventing the diversion of drug precursors and the provisions that are considered to be most burdensome. As stakeholders directly affected by the legislation, the HPRA strongly encourages all precursor chemical operators to respond.

The questionnaire can be found at the following link: https://ec.europa.eu/info/consultations/public-consultation-evaluation-eu-drug-precursors-regulations_en

Responses should be provided before 2 November 2018.