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HPRA MEDICINAL PRODUCTS NEWSLETTER

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Compliance

Ms Lorraine Nolan has been appointed as the new Chief Executive of the HPRA. Ms Nolan, who takes up office with immediate effect, previously held the position of Director of Human Products Authorisation with the HPRA where she oversaw the evaluation and authorisation of medicines and medical devices for the Irish market. Ms Nolan has extensive experience of the public health sector, the health product sector and the regulatory landscape. She will be responsible for the management of the HPRA whilst leading the organisation nationally and internationally in its ambition to protect and enhance human and animal health.

During her career to date, Ms Nolan has held a number of senior positions within the HPRA spanning the pharmaceutical assessment, products distribution and controlled drugs' departments. Prior to joining the HPRA in 2001, she was Controlled Drugs Manager with the Department of Health and a Forensic Scientist with the Department of Justice, Equality and Law Reform.

Ms Nolan holds a PhD in Chemistry and a Degree in Chemistry from Trinity College, Dublin. Ms Nolan has 20 years of technical and scientific experience attained through working in regulatory (including policy development), technical, senior management, industry and public service areas within the HPRA. She has significant acumen of the public health sector with respect to medicines and health products regulation through managing frontline interaction with manufacturers, distributors, marketing authorisation holders and other stakeholders in this area.

Ms Nolan has an established profile within the national, European and international institutions for medicines, medical devices, cosmetics and controlled drugs regulation. She is a member of the European Medicines Agency (EMA) Management Board; was previously an advisor to the UN's International Narcotic Control Board and represented Ireland at European Committees in the Cosmetics and Drug Precursor areas.

Ms Nolan succeeds Mr Pat O'Mahony who took up the position of Deputy Secretary at the Department of Health in September 2015.

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Emergency Medicines

The Medicinal Products (Prescription and Control of Supply) (Amendment) (No.2) Regulations 2015, SI No 449 of 2015

New legislation for the purpose of saving lives or reducing severe distress in emergency situations was introduced in October 2015 (The Medicinal Products (Prescription and Control of Supply) (Amendment) (No.2) Regulations 2015, SI No 449 of 2015). The Regulations provide for the supply and administration of specified prescription-only medicinal products (Table 1), without a prescription, to a person by a pharmacist or by an individual appointed by a listed organisation (see below for further details). The pharmacist or individual must have completed an approved training course on the emergency administration of such products and the management of any adverse reaction.

An organisation must notify HPRA of its intention to procure a medicinal product, prior to the first procurement. In this way it can become a "listed organisation" as provided for under the legislation. HPRA have designed a portal to facilitate this notification process. HPRA will establish and maintain a list of organisations that have provided a valid notification on the website. This list will include the name and address of each organisation which has made a valid notification, including premises where the medicinal product will be stored; the business name or trading style, if different to the name of the organisation; the medicinal product(s) in respect of which procurement has been notified and the name of the accountable person(s) engaged or employed by the organisation to ensure compliance with the Regulations.

TABLE 1

Medicinal Product	Route of Administration	Conditions of administration
Epinephrine (adrenaline) auto injector presented as a 300mcg pre-filled syringe	Intramuscular injection	Adults: For the emergency treatment of anaphylactic shock
Epinephrine (adrenaline) auto injector presented as a 150mcg pre-filled syringe	Intramuscular injection	Children: For the emergency treatment of anaphylactic shock
Glucagon hydrochloride for injection	Intramuscular/ subcutaneous injection	Adults and children: For the emergency treatment of hypoglycaemia
Glyceryl trinitrate sublingual spray	Sublingual spray	Adults: For the emergency treatment of severe angina attack
Medical gas mixture consisting of 50% nitrous oxide and 50% oxygen	By inhalation	Adults and children: Pain relief in emergency rescue situations
Naloxone hydrochloride 1mg/ml pre-filled injection	Intramuscular injection	Adults and children: For the emergency treatment of respiratory depression secondary to known or suspected narcotic overdose
Salbutamol 100mcg multi dose inhaler (pressurised inhalation solution)	Oral inhalation	Adults and children: For the emergency treatment of acute asthmatic attack

The HPRA is actively working with the Department of Health and relevant stakeholders, including the Pre-Hospital Emergency Care Council (PHECC) and the Pharmaceutical Society of Ireland (PSI), on the implementation of the legislation. Please monitor the HPRA website (www.hpra.ie) for further developments.

Human Medicines

Introduction of Educational Materials for medicines on HPRA.ie

As part of our strategy to enhance the safety of medicines and patient outcomes by effective risk management, and to respond to the increasing requirement for timely access to good quality information, the HPRA have commenced publication on our website of educational materials and tools which have been developed by Marketing Authorisation Holders (MAHs) as additional risk minimisation measures for their medicinal products and approved by the HPRA at national level. This will serve to promote public health by further facilitating the availability of these materials to healthcare professionals and patients and will complement the modalities already in use by MAHs. A specific webpage dedicated to educational materials can be found in the "Medicines" section of our website, under "Safety Information". MAHs who have HPRA-approved educational materials in place for their products are invited to submit copies of the latest version in suitable formats for publication on the HPRA website if they have not already done so. Further information can be obtained by contacting the HPRA at medvigilance@hpra.ie

Veterinary Sciences

Change to mock up submission to the HPRA

The HPRA continuously strives to improve our assessment procedures to ensure a more consistent and efficient process. As a result of one such initiative, the HPRA is now accepting mock-ups as a single pdf file, which incorporates the package leaflet as well as the smallest and largest pack sizes of the product to be marketed. There is no longer a requirement to submit the package leaflet as a separate pdf file to the other product packaging.

Clarification of changes to mock ups

On completion of a new veterinary medicinal product application, if the product is not to be marketed immediately in Ireland, it is possible to close the procedure in the absence of mock ups if the Marketing Authorisation Holder (MAH) so wishes.

In this situation, the MAH should notify the HPRA and a condition will be included in the Marketing Authorisation. When, in the future, the product is to be marketed, a national variation (type IB C.II.6.b) should be submitted to facilitate the assessment of the mock ups.

When a product is marketed and a variation impacts the product labelling, only the notified changes to the mock ups should be made and submitted for review. It is not appropriate to include any additional changes other than those directly related to the change applied for in the variation application.

Personnel changes

Ms. Michelle Sinnott left the HPRA at the end of 2015 to take up a new appointment. In her capacity as Personal Assistant to the Director of Veterinary Sciences, she will be replaced by Ms. Lauren Byrne (lauren.byrne@hpra.ie). Ms. Anne McNaughton, Scientific Officer, Pharmacovigilance has been appointed Pharmaceutical Assessor (Human Biologicals) and will be leaving the Veterinary Sciences Department early in 2016. We wish the colleagues well in their new roles. You can access an up-to-date organisational chart of the Veterinary Sciences Team on the HPRA website www.hpra.ie/homepage/about-us/our-structure/management-committee/management-teams.

Veterinary Sciences

Fee update

Following a review of our Veterinary Medicine fees in 2015, it has been agreed to discontinue applying fee code 568 & 548 (MRP/DCP applications which have 15 and over CMS) from 2016. Even if it is the case that at the time of writing (January 2016) government sanction for the overall fees for veterinary medicines is still awaited, we will apply this change with immediate effect, for the benefit of marketing authorisation holders.

Update to the product literature standard

In conjunction with our joint labelling partners, the Veterinary Medicines Directorate in the UK, we are pleased to announce that the format and layout of the product literature standard has been updated to ensure easier navigation. No additional requirements have been included in the update. Applicants are reminded that the product literature standard describes the national requirements for both Ireland and the UK and therefore the product literature standard should be consulted prior to the submission of mock ups submitted with any application type.

Update on legislative proposal for new EU Regulation

The first reading of the new European legislative proposal on the authorisation of veterinary medicinal products has been completed at the level of the Council Working Group. The Irish delegation at this forum is led by the Department of Agriculture, while the HPRA has been invited to be present in a support role to the Department. The proposed legislation is complex and far-reaching and will affect the processes under which veterinary medicines are authorised, supplied and used. It is expected to have major implications for, stakeholders and product users alike and will also have a significant impact on European regulatory authorities. Under the Luxembourg Presidency of the EU, Member States were requested to forward proposed amendments to the draft text; the HPRA has forwarded its proposals to the Department. As the process of elaboration is a co-decision process with the European Parliament, the HPRA understands that that body has also proposed a large number of draft amendments.

It is expected that a trilogue comprising representatives of the European Parliament, the Council and the EU Commission will meet shortly under the Dutch Presidency to discuss the many hundreds of amendments that have been proposed by Member States and Parliament. On finalisation of the text, which might not be completed by mid-year, the HPRA expects to host a HPRA Veterinary Medicines Information Day. The legislation foresees that there will be a two year period following the formal adoption of the Regulation in order to allow for its orderly implementation in the Community.

Use of animal test methods for regulatory testing of human and veterinary medicines

The HPRA, in our capacity as competent authority for the regulation of scientific animals in Ireland, is mindful of the requirements of Article 13 of Directive 2010/63/EU, which states that *'Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result is sought, not entailing the use of a live animal'*. The HPRA has therefore been in contact with various marketing authorisation holders to promote the uptake of validated (non-animal) tests for pyrogen and endotoxin testing specified in the European Pharmacopoeia and to point out that there is a legal requirement under national and European legislation that these alternative non-animal tests are used, unless there is scientific evidence that the alternatives are not suitable. Marketing authorisation holders should be aware of the legislation governing the 3Rs (replacement, reduction and refinement of animal tests) and ensure that validated non-animal tests are used in place of animal tests whenever possible. Queries in respect of this matter should be addressed to sap@hpra.ie.

Change to requirements regarding Applications for Certificates of Pharmaceutical Product and Certificates of Free Sale for medicines authorised by the HPRA

Having considered representations from marketing authorisation holders and manufacturers, we have modified the requirements for applications for certificates of pharmaceutical product (CPPs) and certificates of free sale (CFSs) for medicines that are the subject of marketing authorisations (MAs) granted by us.

Previously, a CPP or CFS issued by the HPRA could only reflect the information that was contained in the most recent version of the MA as granted by us. However, as a result of the amended variations legislation relating to MAs, an application for a CPP or CFS, can now contain information which is the subject of a recently submitted Type 1A ('do and tell') variation or a future Type 1A variation application (in line with the approved timelines). The certificates application form (F-0181) has been revised to take account of such variations and these must be covered by a declaration as per the new Appendix III to the form.

The nature of the information that differs from that in the most recent version of the MA, and which can be documented in a CPP or CFS, is set out below:

- Composition pages which are to be attached to the CPP can reflect changes in the name or amount of the inactive ingredients (also called 'excipients'). These also include changes to polishes or coatings.

  Note: Changes to the active ingredients are not acceptable in any circumstances.

- A list of the manufacturer(s) of the product can also be attached to the CPP. These can include listings of manufacturers involved in primary/secondary packaging and/or batch release and which are the subject of Type 1A variations.

Note: Changes to the manufacturer(s) making the actual dosage form and which is/are already listed in the actual CPP document cannot be accepted.

Revised notes on the draft CPP template and the export certificate application form have already been put in place and these are currently available on our website. www.hpra.ie

Applicants are reminded that no change to the details in the MA can be included in the CPP/CFS without the completion of the declaration in Appendix III on the application form and, if not already the case, the relevant Type IA variation(s) must be submitted within the prescribed timelines to ensure that the marketing authorisation information is updated.

Failure to adhere to the above requirements may result in future applications for export certificates being invalidated.

For clarification or further information please contact the Licensing Section, Compliance Department on 01-6764971.

Importation of Controlled Drugs

The International Narcotics Control Board (INCB) grants estimates to Ireland that determine the maximum quantity of controlled drugs the State may acquire through import and/or manufacture in a given year. The HPRA must ensure that these estimates are not exceeded throughout the year and do so by monitoring the quantities requested for import. All organisations importing controlled drugs are reminded to refrain from requesting amounts in excess of the required quantity. The impact of doing so would be for Ireland to exceed its estimate which would necessitate application to the INCB for an increase.

The effect would be to cause delays for all importers and manufacturers of the controlled drug in question which, ultimately, could have a direct impact on patients. In addition, the HPRA should be informed of any increase or decrease in demand for a controlled drug as soon as possible.

Once a consignment has been imported/exported, licences and letters of no objection (LONOs) should be returned to the HPRA within seven days.

Exporting Controlled Drugs

When exporting controlled drugs from Ireland, the application to the HPRA for an export licence must be accompanied by an import licence from the country of destination. Such import licences for controlled drugs will now be accepted in electronic format.

The electronic copy should be submitted via Eudralink to controlleddrugs@hpra.ie. For Eudralink registration and information please contact the Eudralink helpdesk eudralink@ema.europa.eu.

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

On the 2 October 2015, the European Commission submitted, to the European Parliament and the Council, its Delegated Regulation supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use. Article 121c (1) of Directive 2001/83/EC provides that delegated acts prepared pursuant to that Directive should enter into force only if no objection has been expressed either by the Parliament or the Council within a period of two months. That period may be extended by two months at the initiative of the Parliament or of the Council. The period was extended in this case and the Delegated Regulation is currently undergoing scrutiny by the Parliament and the Council.

The delegated regulation may be accessed through the following links:-

http://ec.europa.eu/transparency/regdoc/rep/3/2015/EN/3-2015-6601-EN-F1-1.PDF

http://ec.europa.eu/transparency/regdoc/rep/3/2015/EN/3-2015-6601-EN-F1-1-ANNEX-1.PDF

Subject to no objection being raised by the Parliament or the Council, the publication of the Delegated Regulation in the Official Journal of the European Union is expected by mid-February 2016. The regulation will enter into force on the twentieth day following that of its publication in the Official Journal and it will apply from three years after publication in all Member States with the exception of Belgium, Greece and Italy where it will apply from nine years after publication.

It is anticipated that the publication of the Delegated Regulation will be accompanied by the publication of a Question and Answer (Q&A) document on the Commission website and of the implementation plan for the introduction of the safety features on centrally authorised products on the European Medicines Agency (EMA) website.

The HPRA will continue to liaise with stakeholders in respect of this matter such that all are ready for implementation by the due date.

Sale or supply of traditional herbal medicinal products (THMPs) that are the subject of transitional protection

Only THMPs that have been granted a certificate of traditional use registration by the HPRA or that are the subject of transitional protection, pending a decision to accept or refuse the application to register as a THMP, can be lawfully sold or supplied in Ireland.

Concerning those products that are covered by transitional protection, it must be noted that, upon granting of a certificate of traditional use registration, the product concerned is no longer covered by transitional protection and, as such, must only be sold in the format registered for the market in Ireland. Consideration will be given to the need to allow for the run-down of stock already in the supply chain and the transitioning to the registered packaging as part of the application process. Where an application for registration of a THMP is refused, the HPRA will determine the appropriate market actions required in relation to any of that product remaining on the Irish market.

Revision to Annex 16 of the EU GMP Guide: Certification by a Qualified Person and Batch Release

Annex 16 has been revised to reflect the globalisation of the pharmaceutical supply chain and the introduction of new quality control strategies. The new format covers four main areas; (1) the process of certification, (2) relying on GMP assessments by third parties, (3) handling of unexpected deviations and (4) the release of a batch.

The revision allowed for the clarification of existing arrangements and should aid with more consistent interpretation of the GMP requirements, including those relating to sampling that is performed at third country manufacturing sites. This revision implements ICH Q8, Q9 and Q10 documents, and interpretation documents, such as the manufacturing and importation authorisation (MIA). The inclusion of the EMA's reflection paper on the proposed solution for dealing with minor deviations from the detail described in the Marketing Authorisation, the so called 'QP discretion paper', and the extension of the principle to GMP deviations is an important update to Annex 16.

The revised annex, which comes into operation on 15 April 2016, may be accessed through the following link:-

http://ec.europa.eu/health/files/eudralex/vol-4/v4_an16_201510_en.pdf

Quality Defect Investigations – Guidance in relation to Reporting and Information Gathering

Notifying Suspected Quality Defects in medicines to the HPRA

We have a number of means available to facilitate reporting of a suspected quality defect in a human or veterinary medicine to the HPRA. These include our online reporting system at www.hpra.ie, along with telephone and email.

The online reporting system is mainly designed for healthcare professionals (HCPs) and members of the public to report suspected quality defects. It is not expected that MAHs or manufacturers would use the online system to report suspected defects to the HPRA, as the level of information required from them tends to be more extensive than for HCPs and members of the public. It is preferable that MAHs and manufacturers would submit their notifications by email, to qualitydefects@hpra.ie

Defect issues may be reported to us via telephone, particularly in the case of urgent or potentially serious cases. Phone contacts (including out-of-hours contact details) for the HPRA Quality Defects team are available on our website, https://www.hpra.ie/homepage/about-us/contact-us.

Such calls should be followed up, in writing, via email.

Guidance on Content and Timeframe for Submission of Information on a Quality Defect issue by MAHs or Manufacturers

An email notification should include information on the medicinal product (name, strength, pharmaceutical form, etc.), batch number and a clear and full description of the defect.

Further information which should be available and communicated to the HPRA during the initial phase of a quality defect investigation includes the following:

- Number of units in affected batch(es)
- Distribution details of affected batch(es) in Ireland:
  - No. of units in the affected batch(es);
  - No. of units received into Irish primary wholesaler;
  - Date of first distribution by primary wholesaler;
  - No. of units distributed by primary wholesaler;
  - No. of units currently at primary wholesaling facility;
  - Date of last distribution by primary wholesaler (if applicable).
- Similar quality defect reports received relating to the same batch(es)

Further details on the particulars to be submitted with a defect notification are laid down in the 'HPRA Guide to Reporting of Quality Defects in Medicinal Products for Human and Veterinary Use', which can be found at the following link: HPRA Guide to reporting of quality defects.

When additional information is requested by the HPRA from a manufacturer or MAH regarding a suspected quality defect case, this should be provided as soon as possible. This is to allow the case to progress efficiently and without undue delay. Typically, it is expected that the information should take no longer than 2-3 days to compile.

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