

HPRA MEDICINAL PRODUCTS

NEWSLETTER

ISSUE
55

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Human Medicines

Contamination of herbal products with pyrrolizidine alkaloids.

Pyrrolizidine alkaloids are naturally-occurring, hepatotoxic constituents present in many plants. A number of reports have shown the presence of these alkaloids in herbal products, although they do not contain plants that produce pyrrolizidine alkaloids. It is reasonable to assume that this is caused by contamination with weeds during harvesting.

A [public statement on the contamination of herbal medicinal product with pyrrolizidine alkaloids](#) was published by the EMA's herbal medicinal products committee (HMPC) in May 2016. Some of the main points in this statement include:

- Confirmation that a value of 1 mcg of pyrrolizidine alkaloids per day is acceptable from a public health point of view during a transition period of 3 years.
- Reference to an analytical method which allows the quantification of 28 named pyrrolizidine alkaloids.
- Recognition that Good Agricultural and Collection Practice measures should be implemented or improved to reduce contamination of herbal medicinal products with pyrrolizidine alkaloids.

- Recognition that different member states are dealing with the issue in a number of ways, including the introduction of testing for herbs at particular risk of contamination with pyrrolizidine alkaloids.

Having considered the statement and reviewed available data, the HPRA is concerned about the risk of contamination with pyrrolizidine alkaloids in the case of products containing the following herbal substances: St. John's wort, passion flower, chamomile, lady's mantle, lemon balm, peppermint, sage, dandelion leaf and thyme.

The HPRA asks product authorisation holders and registration holders to institute testing for pyrrolizidine alkaloids in order to ensure that products containing the above herbal substances will comply with the transitional limit of 1 mcg per day. The herbal preparation and/or herbal product specifications should be updated accordingly by means of a variation.

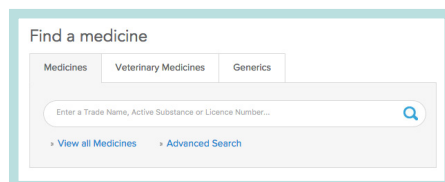


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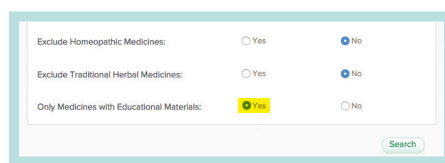
Enhanced access to educational materials on the HPRA website

Educational materials for medicines aim to minimise important risks and maximise the risk-benefit balance of a medicinal product. The content of educational materials aims to supplement the currently authorised product information for the medicinal product in order to support safe and effective prescribing and use. They are designed to fulfil specific risk minimisation objectives and focus on specific safety concern(s) in order to provide clear statements and concise messages describing actions to be taken in order to prevent and minimise these risks. Educational materials are developed by the Marketing Authorisation Holder (MAH) for a medicinal product when specifically recommended by a national competent authority (such as the HPRA) and these must be reviewed and approved by the HPRA prior to distribution to Irish healthcare professionals and patients.

HPRA approved educational materials have now been made more directly and easily accessible from the HPRA website using the 'Find a Medicine' search option on the homepage (www.hpra.ie).



For a full list of medicines that have educational materials, the advanced search option (under 'Find a Medicine' on the HPRA homepage) can be used once the box entitled 'Only Medicines with Educational Materials' is checked at the bottom of the page.



EudraVigilance updates and the move to E2B(R3) and centralised reporting

EudraVigilance stakeholders will be aware that preparations have been underway for some time to facilitate the move to the E2B(R3) standard and centralised reporting in 2017. The main IT development activities for the new functionalities of EudraVigilance are now complete and testing of these is underway. The new EudraVigilance system must undergo an independent audit before the move to centralised reporting; this is scheduled to take place in February 2017. It is planned to present the outcome of the audit to PRAC and the EMA Management Board in May 2017 and, subject to a positive audit outcome, the new functionalities of the EudraVigilance system will be released to all stakeholders in November 2017.

The new external testing system (XCOMP) is scheduled to 'go-live' in June 2017. All registered organisations

with a valid EudraVigilance Test account will be able to start sending E2B(R3) test files and to download E2B(R3) test data. This will provide organisations with a six month period to become familiar with the new system before it is launched in production.

To support stakeholders during this period of change, the [EudraVigilance website](http://www.eudravigilance.eu) has been redesigned and enhanced to publish important information on the new and existing EudraVigilance system – including a number of e-learning modules. Stakeholders should review the materials available and ensure their training plans incorporate all relevant modules. Before and after the go-live of the new system in November 2017, additional webinars will be organised by EMA to support stakeholders.

Article 57 database

The Article 57 database was established in line with the legal provision in Regulation (EC) No 726/2004, namely Article 57(2). It has now been functional for the purpose of notifications of changes to Qualified Person responsible for Pharmacovigilance (QPPV) and Pharmacovigilance System Master File (PSMF) information for over 1 year. As previously communicated, changes to the QPPV or in the location of the PSMF are no longer subject to a type 1 AIN variation. However, MAHs are reminded to keep this information up to date on the Article 57 database.

In addition, it should be noted that in the case of a transfer of a MA in one member state, the new summary of the pharmacovigilance system of the new MAH has to be submitted to all member states concerned as a type 1 AIN notification. This is in accordance with the [CMDh Q&A List for the submission of variations according to Commission Regulation \(EC\) 1234/2008](#) and is applicable even when using the Article 57 database. This is due to the necessity to submit 'proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC'.

Brexit and availability of veterinary medicines in Ireland



The HPRA is conscious of the potential impact of Brexit on the availability of veterinary medicines in Ireland. This is in the context of the efforts we have made over a number of years to achieve common labelling with the UK for many veterinary medicines on the market in this country and to incentivise the marketing of niche products here. As the smaller market for veterinary medicines, Ireland stands to lose most from any return to country-specific labelling. Moreover, given the fact that more than 75% of veterinary medicines

marketed here are intended to be used in food-producing animals and more than half of all produce from these animals is exported to the UK currently, any adverse effect on the agricultural sector is likely to impact significantly on the veterinary medicines sector nationally.

We hope to continue to work with the UK's Veterinary Medicines Directorate into the future, notwithstanding the many challenges that we will face. A limited survey of MAHs that was undertaken during the summer concluded that it was still too early to predict the impact on availability of veterinary medicines in Ireland, and that most MAHs have not yet internalised the implications for them. The HPRA hopes that MAHs will utilise the opportunities in the mutual recognition and decentralised

procedures to develop multi-language label packs which have both English and another EU language(s), in order to bring needed veterinary medicines to the market in Ireland. In any event, we urge MAHs to consider the implications of Brexit on the availability of veterinary medicines in Ireland and to communicate any issues or insights (jgb@hpra.ie). This will be of assistance to us as we work in collaboration with the Department of Agriculture, Food and the Marine to address any availability issues. It will also assist us at the HPRA in adapting our business model for the future.

Changes to Veterinary Sciences Department

Further to the election of Dr. David Murphy as chairman of the CVMP in June, David has vacated the Veterinary Assessment Manager role in order to focus on his European role. He has been given the title 'Veterinary Manager – CVMP' to reflect his new duties. However, he continues to serve as a member of the Veterinary Sciences Department management team. Pending the recruitment of a new Veterinary Assessment Manager (expected during the course of 2017), the day-to-day responsibilities of the role are being undertaken by the Director of Veterinary Sciences, Dr. J. G. Beechinor.

The HPRA would like to take this opportunity to advise of other staff changes and updates to teams:

Ms. Penelope Huggard joined the safety and efficacy assessment team as Veterinary Officer in December 2016.

Mr. Oisín McManus joined the pharmaceutical assessment team as Scientific Officer in October 2016.

We wish them well in their new roles. The current [organogram of personnel in the Veterinary Sciences](#)

Guide to which variation categories require the submission of updated mock ups

Many variation categories will result in changes and updates to mock ups. These changes may have a very small impact on the mock ups or may lead to a more substantial change. The HPRA no longer requires submission of mock ups in all cases and only requires mock ups for assessment for variations that have a substantial effect on the mock ups. A guideline document has recently been published on the HPRA website which details which [variation categories will require the submission of updated mock ups](#). The purpose of this document is to provide guidance on variations where mock-ups are required to be submitted to the HPRA following approval of a variation.

Changes to mock-ups: when is a notified change acceptable?

Changes to product packaging or package leaflets that do not affect the agreed QRD text, such as font size, layout, and legibility, do not require a variation. For example, a change to the barcode or logo (assuming same size), does not require a variation. To notify the HPRA of such a change, send an email to vetinfo@hpra.ie detailing the notified change and declare the absence of changes affecting the agreed QRD text, font size, layout, legibility. Once this email is received the notification can be automatically considered acceptable unless the HPRA notifies you otherwise. Please note that guidance as to whether or not a variation is necessary for alterations to mock-ups is provided in the [Product Literature Standard](#), which is available on the HPRA website. If you are in doubt about whether a variation is needed, please contact vetinfo@hpra.ie at the HPRA.

Veterinary Medicines

Reminder of mandatory use of eSubmission Gateway for veterinary submissions to EMA as of 1 January 2017

The HPRA wishes to remind stakeholders that as of 1 January 2017, the EMA eSubmission Gateway will become the mandatory submission channel for all veterinary submissions to the EMA.

Between January and March 2017, the EMA has advised that it will operate a flexible approach for submissions

of PSURs for cases where successful registration with Gateway is not possible for reasons outside applicants' control. The EMA has also advised that it will also maintain a flexible approach in case submission via Gateway/ Web Client is not possible due to unexpected technical failures of the system.

Compliance

PIC/S: Data integrity: Draft guidance published

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) has published a draft guidance for inspectors entitled PIC/S Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments. The guidance [has been published on the PIC/S website](#) and is available for public view.

The scope of the document covers the inspection of data integrity systems in operation at sites performing manufacturing (GMP) and distribution (GDP) activities. The content includes aspects covered in 'EMA Questions and Answers on Data Integrity' and 'MHRA Data Integrity Definitions and Guidance for Industry'. The guide is intended to provide an overview of key principles regarding data management and integrity as well as guidance on the interpretation of existing PIC/S GMP/ GDP requirements in current industry practice.

Basic expectations of data governance systems are outlined and fundamental concepts summarised. Organisational influences on successful data integrity management is highlighted. The importance of management understanding and commitment in an effective data governance system is emphasised. The guidance details the necessity for a combination of appropriate organisational culture and behaviours, and an understanding of data criticality, data risk and data lifecycle in order to effect good data

integrity management. It specifies that risk management should be utilised to determine the importance of each data / processing step.

To achieve success with data integrity, the guidance specifies a number of aspects that should be addressed by management:

- Code of ethics and policies – the company's general ethics and integrity standards need to be established and known to each employee, and these expectations should be communicated frequently and consistently.
- Quality culture – management should aim to create a work environment that is transparent and open, one in which personnel are encouraged to freely communicate failures and mistakes, including potential data reliability issues.
- Resource allocation – management should allocate appropriate resources to support and sustain good data integrity management such that pressures and workload do not increase the likelihood of errors or motivation to deliberately compromise data integrity. There should be provision to purchase equipment that is appropriate to the need, based on criticality of the data.

- The Quality Management System - this should be able to prevent, detect and correct weaknesses in the system that may lead to data integrity lapses. In the event that lapses are found, they should be handled as any deviation would be according to the quality management system.
- Regular management review of quality metrics related to data integrity - an effective review of data integrity control measures, including self-inspection, will demonstrate management understanding of the importance of the interaction of company behaviours with organisational and technical controls in respect of achieving good data integrity management.

The draft guidance contains detailed specific data integrity considerations for paper based systems, computerised systems and outsourced activities. The classification of data integrity findings and the remediation of data integrity failures is also included.

Participating authorities may comment on the document until 28 February 2017. The draft will be finalised and adopted thereafter. While it is not open to other stakeholders to comment, you should be aware of the content of the draft guidance as it is being implemented on a trial basis pending its introduction.

Submission of annual returns

Controlled Drugs

Manufacturers and wholesalers of controlled drugs are required to provide annual return submissions to the HPRA by 31 January each year. The submission of annual returns enables the HPRA to report to the International Narcotics Control Board (INCB) on the total quantities of controlled drugs imported, consumed and exported from Ireland. A notification was provided on 20 December 2016 to all manufacturers and wholesalers storing controlled drugs regarding the submission of the 2016 annual returns. These should be completed by the deadline and submitted to the HPRA on the appropriate spreadsheets.

The following lists include some useful tips for wholesalers and manufacturers to ensure that annual return submissions are completed correctly;

Wholesalers

- Read the guidance notes prior to completing the spreadsheets.
- Ensure the cover sheets are completed in full.
- Provide clarification in writing to the HPRA if the company does not have any narcotic or psychotropic substances to report.

Manufacturers

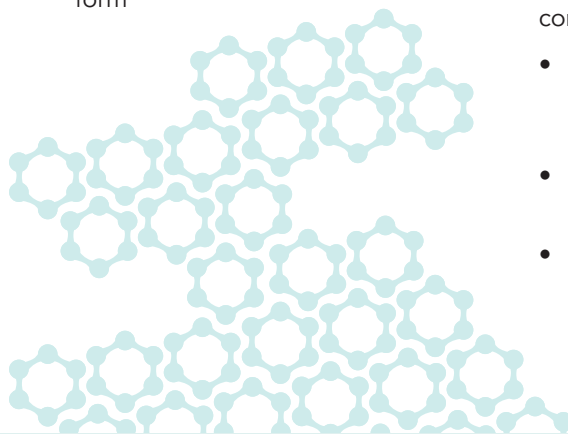
- Read the guidance notes prior to completing the spreadsheets.
- Ensure the cover sheets are completed in full.
- For each controlled drug, ensure the closing balance provided for the previous year corresponds with the opening balance of the current reporting year. If these figures do not reconcile, provide an explanation in the accompanying email.
- Check all endorsement information provided to the HPRA during the year prior to completing the total imports and total exports sections. If there are discrepancies, provide an explanation in the accompanying email.
- Remember to use conversion factors when reporting products or preparations that exist in the salt form

Precursor Chemicals

Precursor chemicals (also known as scheduled substances) are frequently used in the illicit manufacture of narcotic drugs and psychotropic substances. The HPRA is obliged to report annually to both the INCB and the European Commission on the import, export and legal uses of precursor chemicals as these relate to Ireland. In order to enable this, all precursor chemical operators are required to provide information annually to the HPRA about their transactions and annual usage. The annual return submission should be made to the HPRA by 31 January each year. A notification was provided on 20 December 2016 to all precursor chemical operators regarding the submission of the 2016 precursor chemical annual returns.

The following are some useful tips for precursor chemical operators to ensure that annual return submissions are completed correctly;

- Review the information in the precursor chemicals section of the [HPRA website](#).
- Read the guidance notes prior to completing the spreadsheets.
- Ensure the cover sheets are completed in full.



Notice regarding a fee increase for applications for medical device certificates of free sale

Following a recent consultation process relating to the introduction of fees for the regulation of medical devices, the fee applicable to submission of an application for a certificate of free sale for medical devices has increased to €250 per application (fee code 411) for a set of four certificates. .

The revised fee applies to requests for certificates submitted from 1 January 2017.

The fee in relation to a request for additional copies of certificates (more than four copies, fee code 413) remains unchanged at €23 per copy. Applicants

are reminded that additional copies of certificates can only be requested at the same time as the original request and not subsequently post issuance of the completed certificate.

Misuse of Drugs legislative amendments

As you may be aware, the Misuse of Drugs (Amendment) Bill 2016 was passed through the Houses of the Oireachtas in July 2016. The primary purpose of the Misuse of Drugs Acts 1977 to 2016 (the Acts) is to protect public health by bringing certain substances which are open to misuse, and known to be traded on the illicit market, under the scope of the Misuse of Drugs legislation, thereby aiding the law enforcement activities of An Garda Síochána and Revenue Customs. The amendments to the Acts will come into operation on foot of commencement orders and will enable the Minister for Health to introduce new regulations. The HPRA would like to inform industry of the implications that the amendments to the Acts and new Regulations will have for the licensing of controlled drugs.

New substances added

A number of substances that were previously not controlled will now fall under the scope of the Misuse of Drugs legislation. Some of the new substances intended to be controlled that may impact on stakeholders are listed below:

- Zopiclone
- Zaleplon
- Lisdexamfetamine
- Phenazepam

One of the consequences of these substances being controlled is that if your company handles any of these substances, or products containing these substances, you will have to obtain a controlled drug authorisation in respect of the activity performed (e.g. production or supplying).

For wholesale distribution authorisation holders, another potential consequence is the need to vary the company's authorisation to add the category of narcotic or psychotropic substances to the authorisation, if not present already.

With respect to companies that may require authorisation in relation to these proposed changes, the HPRA will work with these companies and use a pragmatic approach.

Regulations introducing changes to import and export licenses

You will be aware that, in 2013, a public consultation proposed a variety of amendments to the Misuse of Drugs Regulations 1988, as amended. It is anticipated that the Minister for Health will soon introduce Regulations to amend the current framework for some controlled drugs.

In essence, the new controls will require an import or export licence (as appropriate) for all substances listed

in Schedule 3 (including flunitrazepam and temazepam) and listed in Part 1 of Schedule 4 (which will include many benzodiazepines, zopiclone and zaleplon). A 'Letter of No Objection' will, therefore, no longer apply to the importation/exportation of these substances. The table below illustrates the impact of the changes.

Other changes

The Misuse of Drugs (Amendment) Bill 2016 also allows for the transfer of licensing functions from the Minister for Health to the HPRA.

In anticipation of the proposed changes, your company is asked to review the products handled to ascertain if any of the proposed changes affect the company in advance of the implementation of the Regulations.

Timetable for implementation

A timetable for implementation of the above changes is not yet available. The HPRA will provide further notification regarding this in due course.

Activity	Current requirements	New requirements
Each import or export of controlled drugs listed in Schedule 1, 2 or 3	Import or export licence (as appropriate)	No change
Each import or export of temazepam and flunitrazepam	Letter of no objection	Import or export licence (as appropriate)
Each import of controlled drugs listed in Schedule 4 part 1 (e.g. alprazolam, diazepam, nitrazepam, zolpidem)	Letter of no objection	Import or export licence (as appropriate)
Newly controlled drugs such as zopiclone and zaleplon	No requirement	Import or export licence (as appropriate)

Preventing falsified medicines from entering the supply chain: Have you played your part as an authorised wholesaler?

Qualification of suppliers of medicinal products: Why do you need to qualify suppliers?

In short, it is a requirement of the EU GDP Guidelines and the wholesale distribution authorisation (WDA). In reality, it is to ensure that the goal of providing high quality, safe and effective medicinal products to the patient is achieved. Nowadays the supply chain for a medicinal product is a complex system with many participants striving to achieve the same goal. However, if one participant in the supply chain does not follow the regulations and guidance available, this can have a detrimental effect on the goal and this is why knowing who is supplying your medicinal products is essential.

Qualifying your supplier

1. Identify all your medicinal product suppliers. This includes suppliers that are within the same global group or are considered affiliate entities.
2. Check that your supplier has the appropriate authorisation/registration (e.g. a wholesale distribution authorisation, a manufacturing authorisation or a broker's registration). It is good practice to check the European EudraGMDP database for authorisations and registrations of your suppliers. You should cross-check the following details: name, address, authorisation/registration number, authorised activities (procure, hold, supply or export) and the category(ies) of medicinal products that they are authorised to supply.
3. Check your supplier's compliance with the principles and guidelines of GDP. This can be checked by obtaining a copy of their GDP certificate or checking that no non-compliance report has been issued to the supplier. GDP certificates and non-compliance reports can be found on the EudraGMDP website.
4. Every effort should be made to independently check all the information provided to you by your supplier before you receive any medicinal products.

5. All supplier information should be periodically re-checked.
6. For new suppliers: 'due diligence' checks should be performed. This is an information gathering exercise and can be performed in many ways including but not limited to questionnaires or internet searches. Attention should be paid to the reputation of the supplier and also offers that seem too good to be true.

Procedures and documentation

It is important that you document all the checks that are performed, initially and periodically, in relation to supplier qualification. Make sure that all the steps you perform when qualifying and periodically rechecking your suppliers are in your procedure. Your procedure and any associated forms should be part of your quality system. Carrying out supplier qualification is one way to help prevent falsified medicines from entering the supply chain. Remember to stay vigilant and notify the HPRA of any suspicious activity.

Launch of the public consultations on the draft Commission acts on GMP

The European Commission has launched public consultations on two draft pieces of Commission legislation, i.e.

- *draft Commission Delegated Regulation laying down principles of good manufacturing practice for investigational medicinal products for human use and arrangements for inspections*
- *draft Commission Implementing Directive on good manufacturing practice for human medicinal products*

These were launched on the better regulation portal on 13 January 2017. The consultations, which can be accessed through the links below, will be open for comment until 10 February 2017.

Their purpose is to provide for separate implementing legislation for GMP for investigational medicinal products and human medicinal products. The existing GMP Directive for human medicinal products, 2003/94/EC, will be repealed.

Commission Delegated Regulation on GMP for IMPs:

http://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-203309_en

Commission Implementing Directive on GMP for human medicinal products:

<http://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-203200>

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