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## Human Medicines

### Follow-up of adverse reaction reports

The changes to reporting requirements in the EU which came into effect on 22 November 2017 have necessitated considerable process changes for all stakeholders. However, while many aspects of the reporting of adverse reaction reports has changed, the requirements around case follow-up have not been significantly impacted.

In accordance with Module VI of the Good Pharmacovigilance Practice (GVP) guidelines, which discusses the collection, management and submission of reports of suspected adverse reactions, Marketing Authorisation Holders (MAHs) should continue to follow-up on cases reported directly to them. Significant new information should be provided as a follow-up report. In accordance with GVP VI, for the purpose of submission of ICSRs, significant follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of a case, or could change its seriousness criteria. Furthermore, in accordance with GVP VI, National Competent Authorities (NCAs) may also involve MAHs in the follow-up of Irish reports received via

EudraVigilance. This may happen, for example, where example where important additional information is necessary for case evaluation or reconciliation, clarification is needed regarding inconsistent data within ICSRs, or where there is a need to obtain further information in the context of the validation of a signal, the evaluation of a safety issue, the assessment of a periodic safety update report, or the confirmation of a safety concern in a risk management plan. Where an MAH has downloaded a case from EudraVigilance and has amended the case to add details such as company comments, there is no requirement to resubmit this to EudraVigilance as a follow-up report.

The HPRA in turn will continue to follow-up on reports received directly from healthcare professionals and members of the public, as appropriate, sending any significant new information to EudraVigilance as a follow-up report. MAHs are not required to send any queries to the HPRA in relation to these cases once downloaded from EudraVigilance.

## Audits of type IA notifications: 2016/2017 Review

The HPRA conducts regular audits of Type IA notifications in order to confirm that they have been appropriately categorised and to ensure a consistent approach in the processing of new variations, both by industry and by the HPRA. As a result of the audits of Type IA notifications of 2016 (Q1-Q4) and 2017 Q1 and Q2, it was found that on average 33% of Type IA notifications reviewed in each quarter were deficient. The most common deficiencies identified were:

- 'EC Classification Guideline' page not submitted.
- Conditions applying to the chosen Type IA category not met.
- Documentation (as required by the variation category) not provided.
- Date of implementation not stated.
- Incorrect classification of Type IA notifications, where either the incorrect Type IA notification subcategory was selected or where the change was classified as a Type IA notification when a Type IB variation was required.

Therefore, in order to reduce the number of incorrect Type IA submissions, the HPRA would like to remind applicants of the following:

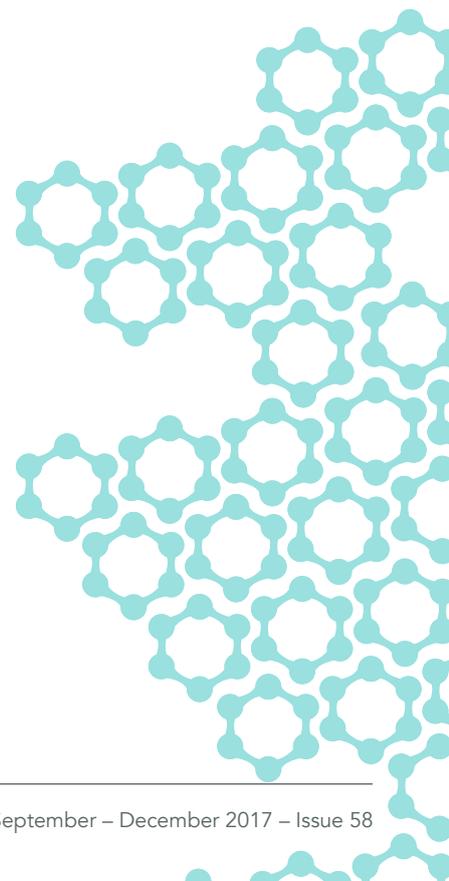
- All changes which fall under Type IA are listed in the 'EC Classification Guideline', along with a list of conditions and documentation requirements for each category. These conditions must be met and all necessary documentation

must be provided in order for the variation to be correctly classified as a Type IA. Otherwise, the variation is normally required to be submitted as a Type IB (default category) or as a Type II variation (where the proposed change could have a significant impact on the quality, safety or efficacy of the medicinal product). Careful consideration should be given to the list of conditions to ensure that the variation is appropriately classified as Type IA.

- Type IAIN notifications must be submitted immediately and Type IA notifications may be submitted within 12 months following implementation.
- The relevant page (s) of the 'EC Classification Guideline' including confirmation of compliance with all relevant conditions and documentation requirements must be submitted for each Type IA notification submitted. Conditions are not considered fulfilled unless they have been ticked on the submitted guideline page.
- Documentation requirements must be met in full; for example, the present and proposed sections of the application form, specifications, amended dossier pages, GMP certificates, etc., as required for each category of change. Updated label mock-ups and/or leaflet text must be submitted with the Type IA notification where there are changes to the label and/or leaflet.

- In line with 'Variations Guidelines' 2013/C 223/01, editorial changes should only be included if the variation applies to that part of the dossier. All editorial changes should be clearly identified in the present and proposed section of the application form along with a justification as to why the applicant considers them 'editorial'. The following amendments to the Module 3 may be considered editorial: adding headers for ease of use, punctuation changes and grammar corrections that do not alter the meaning of the text.

The EMA has published a ['Pre-notification check for type IA/IA<sub>IN</sub> Variations'](#) aimed at facilitating submission of complete and correct Type IA notifications. The HPRA recommends applicants to consult this checklist prior to submission of Type IA notifications.



## HPRA Veterinary science information day 2018

The HPRA is planning to host an Information Day on Wednesday 13 June 2018. The meeting will take place in the Hilton Dublin Airport, so as to facilitate those travelling. The purpose of this information day is to:

1. Update marketing authorisation holders and other stakeholders with respect to:
  - Brexit developments and HPRA preparations;
  - Developments on the new draft European Regulation on veterinary medicines.
2. Facilitate discussions between stakeholders on on-going and future regulatory developments.

3. Outline initiatives being developed in relation to communications and pharmacovigilance.
4. Allow an opportunity for stakeholders to network with HPRA personnel responsible for the authorisation and monitoring of veterinary medicines.

For details of fees and payment methods, please contact [events@hpra.ie](mailto:events@hpra.ie). There are reductions in fees for groups of three or more persons from the same organisation, as well as for not-for-profit organisations. For more information on this event, please contact [events@hpra.ie](mailto:events@hpra.ie). Please note that details of registration for this event will be available shortly on the HPRA website.

## Joint-labelling of veterinary medicines

The HPRA wishes to confirm that it strongly supports the use of joint-labelling with other countries, including the UK, even as the UK prepares to exit from the EU. As detailed in the HPRA Strategic Plan for 2016 - 2020, the availability of medicines is a key priority in the protection of public and animal health. The HPRA hopes that the new Regulation on veterinary medicinal products that is being finalised in Brussels currently will contain provisions which facilitate the maintenance of joint labelled veterinary medicinal products with the UK. The HPRA believes that the availability of joint labels has been a very significant factor in ensuring that Ireland benefits from access to needed medicines, through achieving minimum order thresholds for product manufacture that might not otherwise be met. Indeed, more than half of all veterinary medicinal products currently authorised in Ireland enjoy joint labels with the UK and this number is increasing yearly. In addition to joint labelling with the UK, we also encourage MAH's to develop multilingual packs, combining several languages on a single pack, wherever possible. We are happy to answer any queries on this topic which should continue to be sent to [vetinfo@hpra.ie](mailto:vetinfo@hpra.ie).

## Brexit update

The HPRA is continuing to meet with individual marketing authorisation holders on a voluntary basis to discuss and plan for Brexit. A number of marketing authorisation holders have indicated their wish to use the HPRA as Reference Member State for future procedures or for the HPRA to take over the position of RMS from the UK for existing products, post Brexit. We wish to thank those involved for their vote of confidence in our future. We are conscious of the impact of the current uncertainties around Brexit on marketing authorisation holders and understand that there may be a reluctance to make changes until more information about the precise nature of Brexit, as well as the impact of any transitional measures, is known. However, it is imperative for the HPRA

to be able to justify the business case for any increase in personnel to the Irish government, in order to gain the necessary approvals. Therefore we would urge marketing authorisation holders to engage with the HPRA as soon as possible, so that we can engage in a planned and sustainable expansion to meet the forecasted demands on the business. Please contact Ms. Grainne Flanagan in the first instance for an informal discussion of this matter ([grainne.flanagan@hpra.ie](mailto:grainne.flanagan@hpra.ie)).

An information item, which gives answers to common queries from industry on Brexit and which is updated periodically, is available on our [website](#).

## Response to HPRA survey on Irish language information

Following the initiation of judicial review proceedings against the Irish Minister for Agriculture, Food and the Marine, contending that the labelling and packaging of veterinary medicinal products should be in both the Irish and English languages, the HPRA initiated a survey of marketing authorisation holders in September 2017 to ascertain the effect of such a requirement. The HPRA received a 51% response rate to the survey. The HPRA wishes to thank all those who took the time to complete the survey. The HPRA is not a direct party to the Court case and awaits the development and hearing of the Court case on this matter, which is expected to be heard in the High Court during the course of 2018. The overall result of the survey is as follows:

1. Percentage of products on the market currently with joint / common UK/ Ireland labelling: Approximately 50% of companies have > 80% of products with common labelling, with only 20% of companies having unique labelling for Ireland. The remainder (30% of companies) have common labelling for some or many of their products.
2. If Irish is made a compulsory language, 92% of respondents stated that it will have a negative or a significantly negative impact on their company.
3. If Irish is made a compulsory language, 71% of respondents opined that it would have a negative impact or a significantly negative effect on availability in Ireland; the remainder responded that there would be no, or in the opinion of 4% of companies, a positive impact.
4. With regard to the effect of such a requirement on the price of veterinary medicines, 78% of responders opined that it would increase the cost of individual products and the remainder advising that they did not think that it would affect pricing.
5. With regard to any other impact or comments, the 45% of respondents restated their concerns on availability and cost. Some 15% of them cautioned against possible adverse impact on readability while a further 14% considered that they did not see any added benefit of such a requirement.

## Updating the SPC as a result of a variation

The HPRA would like to remind applicants that when updating an SPC as a result of a variation, only the SPC section(s) directly affected by the variation should be changed.

Updates to other SPC sections including minor and editorial changes, are not appropriate and cannot be approved during assessment unless previously agreed or requested by the RMS.

When prior agreement has been obtained these proposed additional minor/editorial changes must be clearly highlighted on the application form and a full track changed version of the SPC submitted with the variation application package.

Other changes to the SPC, not related to the variation applied for will require submission of a separate variation application.

## Staff changes in the Veterinary Medicines Team

Dr. Paul McNeill was appointed Veterinary Assessment Manager with effect from 1 December 2017. Dr. Rhona McHugh was appointed Executive Assessor, Pharmaceutical Quality Team, with effect from 1 January 2018. Dr. Rachel Horan, Scientific Officer, and Dr. Darragh O'Hanlon left the HPRA to take up opportunities in the private sector.

We wish all well in their new roles.

The up-to-date organogram of personnel in the Veterinary Sciences Department is available on the [HPRA website](#).

## Cosmetic Products Notification Portal

[Regulation \(EC\) No. 1223/2009](#) on cosmetic products requires that responsible persons of cosmetic products submit information relating to the cosmetic products they place, or make available, on the European market through a portal called the [Cosmetic Products Notification Portal \(CPNP\)](#).

In addition, where distributors take a cosmetic product already on the EU market, and translate, on their own initiative, any element of the labelling of that product in order to comply with the national law, they must also notify the cosmetic product to CPNP. In respect of this limited situation the distributor does not take on the role of the responsible person.

### How do I access CPNP?

CPNP is a free-of-charge, online notification system created for the implementation of Article 13 of [Regulation \(EC\) No. 1223/2009](#) on cosmetic products. In order to access the CPNP the user needs to firstly create an account on both of the following systems:

1. [EU Login](#)

The European Commission Authentication Service (formerly known as 'ECAS') provides the user with access to different applications and services offered by the European Commission.

2. [The DG Sanco Authentication Authorisation System \(SAAS\)](#)

This system provides the user with a profile and access rights based on their organisation and role for a specific European Commission application, in this case, CPNP.

Once that is completed you can log into [CPNP](#).

### What information am I required to submit to CPNP?

Before placing any cosmetic product on the EU market, the responsible person must electronically submit the following information to CPNP:

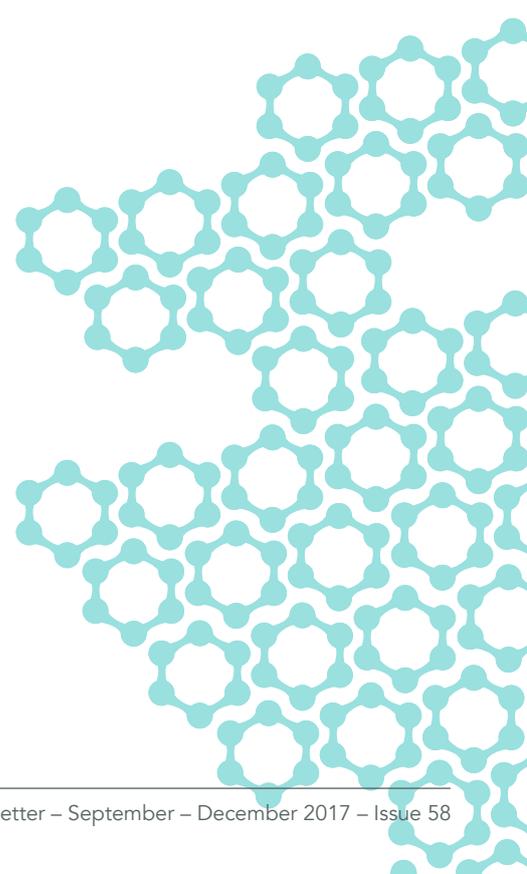
1. Category of cosmetic product;
2. Cosmetic product name or names, ensuring it enables its identification;
3. Name and address of the responsible person where the Product Information File is made readily accessible;
4. Country of origin in the case of import;
5. Member State in which the cosmetic product is to be placed on the market;
6. Contact details of a physical person to contact in the case of necessity;
7. Presence of substances in the form of nanomaterials;
8. Identification of the substances in the form of nanomaterials, including the chemical name (IUPAC) and other descriptions;
9. Reasonably foreseeable exposure conditions of the substances in the form of nanomaterials;
10. Name and the Chemicals Abstracts Service (CAS) or EC number of substances classified as carcinogenic, mutagenic or toxic for reproduction (CMR), of category 1A or 1B, under Part 3 of Annex VI to Regulation (EC) No 1272/2008;
11. Frame formulation allowing for prompt and appropriate medical treatment in the event of difficulties. A 'Frame formulation' is a formulation which lists the category or function of ingredients and their maximum concentration in the cosmetic product or gives relevant quantitative and qualitative information whenever a cosmetic product is not covered or only partially covered by such a formulation.

When a cosmetic product has been notified to CPNP, there is no need for any further notification at national level within the EU. Nevertheless, it should be noted that the successful notification of a cosmetic product to CPNP does not mean that it is being correctly marketed as a cosmetic product, nor does it mean that it meets all of the requirements of Regulation (EC) No. 1223/2009.

### Useful links:

- [Cosmetic Products Notification Portal \(CPNP\) - Article 13 User Manual](#)
- [Cosmetic Products Notification Portal \(CPNP\) - Article 16 User Manual](#)
- [Frequently Asked Questions on CPNP](#)

For further information relating to the requirements for cosmetic products in the EU, including those relating to the responsible person, distributors and the product information file, please see the HPRAs website [HPRAs website](#). For any queries contact [cosmetics@hpra.ie](mailto:cosmetics@hpra.ie).



## Understanding and using CosIng – the Cosmetic Ingredient Database

CosIng (Cosmetic Ingredient Database) is the European Commission online database that provides information about cosmetic ingredients contained in the cosmetic product legislative framework. Access to, and information about, CosIng is available free of charge on the European Commission website. The CosIng database is useful for consumers, distributors, manufacturers, importers and responsible persons searching for more information about cosmetic ingredients as it provides easy access to regulatory information about ingredients listed in annexes II - VI to Regulation (EC) No. 1223/2009 on cosmetic products.

It should be noted that the listing of an ingredient in the CosIng database does not mean it has been accepted or approved for use in a cosmetic product and the information it contains should always be cross-checked against the regulations.

The database also links to scientific opinions of the Scientific Committee on Consumer Safety but such opinions are restricted to those published on the internet.

Useful information available for each ingredient on the CosIng website includes:

- International Nomenclature of Cosmetic Ingredients (INCI) name
- Description of the ingredient
- International Non-proprietary Name (INN)
- Ph. Eur. Name
- CAS #
- EC #
- Chemical/IUPAC Name
- Cosmetic Restriction(s)
- Other Restriction(s)
- Function(s)
- SCCS opinion(s)

CosIng can be used to search for an ingredient by the common name, the INCI name of a substance or the chemical/IUPAC name. The database includes data since the adoption of the Cosmetics Directive on the approximation of the laws of the Member States relating to cosmetic products (76/168/EEC) in 1976 and Regulation (EC) No. 1223/2009 on cosmetics products.

CosIng can be accessed through the following link:

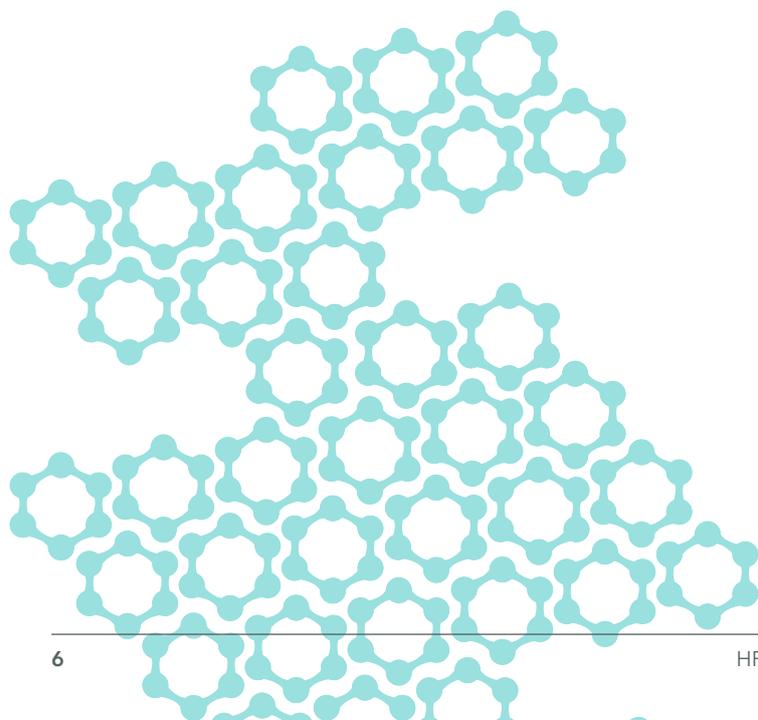
[https://ec.europa.eu/growth/sectors/cosmetics/cosing\\_en](https://ec.europa.eu/growth/sectors/cosmetics/cosing_en)

Furthermore, a manual on how to use CosIng can be accessed through the following link:

[http://ec.europa.eu/growth/tools-databases/cosing/layout/Cosing\\_Manual.pdf](http://ec.europa.eu/growth/tools-databases/cosing/layout/Cosing_Manual.pdf)

Notes:

1. CosIng is not considered 100% accurate. For example, the European Commission may not update CosIng immediately after new updates to the annexes of the Regulation and therefore the ingredient should always be checked in the most up to date Regulation.
2. If an ingredient is assigned with an INCI name and appears in the inventory section of the CosIng database it does not mean it can be used in a cosmetic product or that it is approved for such use; the use of any ingredient in a cosmetic product must be supported by a safety assessment of the product which should be performed by a suitably qualified safety assessor.



## Temperature mapping in storage areas for medicinal products

The purpose of this article is to highlight key considerations when conducting the temperature mapping of a storage area for medicinal products. A temperature mapping exercise must be conducted, whether the storage area or unit is temperature controlled or not. The term 'storage area' includes all areas where medicinal products are stored or temporarily held, including goods in, goods out, returns, quarantine, controlled drug rooms, etc. The temperature requirements of the storage area should be based on the temperature requirements of the products to be stored. It is expected that a temperature mapping study is completed prior to the commencement of storage of medicinal products in that area. To that end, key considerations for a temperature mapping study are described below:

1. Temperature mapping exercises should firstly incorporate a risk assessment of the storage area to identify those areas which may experience fluctuations or extremes of temperature, e.g. skylights, windows, doors, air handling units, height of shelving, etc. A documented protocol for the mapping study should be generated in advance of the exercise. This should document the methodology for the study, including the reasoning for the number of temperature probes used and the location of the probes – this should be based on the outcome of the risk assessment. At a minimum, it is expected that probes are placed in areas where the medicinal product will be stored and in those areas identified as posing the highest risk.
2. The length of the temperature mapping exercise should be specified in the protocol. It is recommended that, for an uncontrolled storage area, the study is carried out over a minimum of

seven consecutive days in order to reflect routine activity levels in the area, fluctuations in airflows and temperature differences between day and night. Studies of a shorter duration may be justified for controlled environments having limited fluctuations. These justifications should be documented in the protocol and supported with evidence. At a minimum, readings from the temperature monitoring probes should record maximum/minimum readings on a daily basis; however, continuous temperature monitoring readings are preferable. For clarity, the relocation of temperature monitoring probes throughout the storage area over a number of days is not considered a temperature mapping exercise.

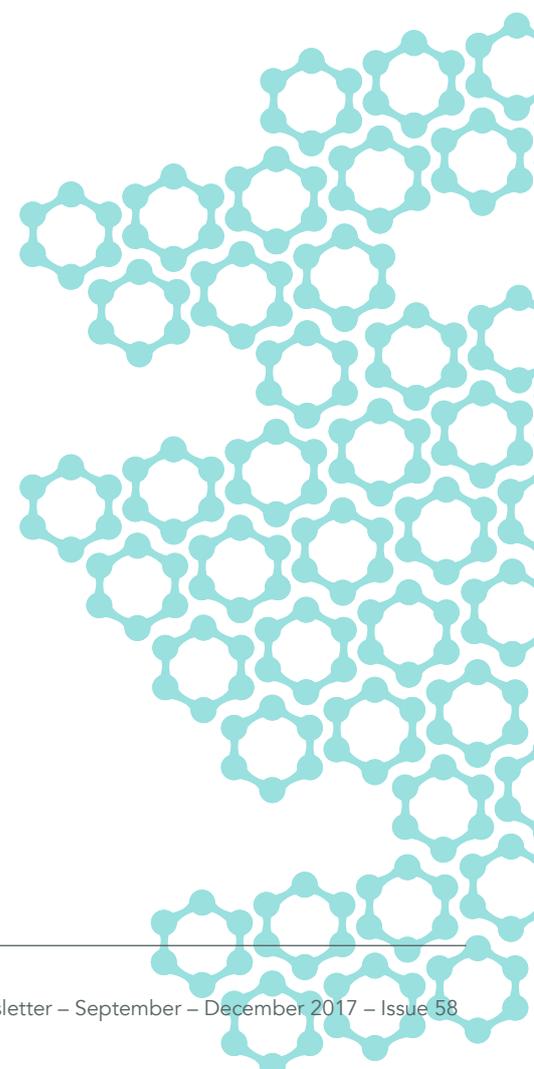
3. The initial exercise should be conducted in an empty state and again with products present (i.e. in a partially full or in a full state). Dummy products can be used to simulate product packaging. The exercise should initially be repeated seasonally, i.e. a winter mapping exercise and a summer mapping exercise, unless it can be demonstrated that the storage area or unit is not affected by seasonal variations. Based on the mapping results, temperature control systems may be implemented or modified and the area remapped. The location of product storage may also be changed and the area remapped again, as appropriate, or the area may be deemed unfit for storage of medicinal products. After any structural change to the storage area the need to re-map should be assessed.

The results of the study should be documented, analysed and a summary report generated. This report should contain all of the temperature readings throughout the study, as well as a summary of the maximum

and minimum readings. Conclusions and recommendations should be documented, identifying and justifying the numbers of, and areas where, the temperature monitoring probes will be placed for ongoing monitoring. These positions should be based on the results of the study and the areas where products will be stored.

Further suggested reading:

- WHO Technical Report Series no. 961, 2011, Annex 9: Model guidance for the storage and transport of time and temperature sensitive pharmaceutical products.
- 'Temperature mapping of storage areas' Technical supplement to WHO Technical Report Series, No. 961, 2011.



# Compliance

## 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 21 December 2017 to all manufacturers and wholesalers storing controlled drugs regarding the submission of the 2017 annual returns. If your company has not yet completed and returned the submissions to the HPRA, please complete the submissions on the appropriate spreadsheets and return them as soon as possible.

## Submission of annual returns – 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. Annual return submissions should be made to the HPRA by 31 January each year. A notification was provided on 21 December 2017 to all precursor chemical operators regarding the submission of the 2017 precursor chemical annual returns. If your company has not already provided this information to the HPRA, it is asked to do so as soon as possible.

## Precursor chemical regulatory update

A notification was sent to stakeholders on 12 December 2017 with a number of updates regarding precursor chemicals. If your organisation deals with precursor chemicals and was not in receipt of this notification please contact [controlleddrugs@hpra.ie](mailto:controlleddrugs@hpra.ie).

## Misuse of Drugs legislative amendments

Four new substances have been added to Schedule 1 of the Misuse of Drugs Regulations 2017 with effect from the 24 November 2017.

The four substances are as follows:  
U-47700  
EPH  
MPA  
XLR-11

Ireland is required to subject these substances to national control on foot of obligations as a party to the UN Conventions of Narcotic Drugs 1961 and Psychotropic Drugs 1971. An annual licence is required to perform activities with these substances in addition to an import or export licence (as appropriate) for the importation/exportation of each consignment.

## Safety features and the impact on wholesale distribution authorisation (WDA) holders

### What is a safety feature?

A safety feature consists of two elements placed on the packaging of a medicinal product by the manufacturer:

- (1) a unique identifier, which is a two-dimensional (2D) barcode, allowing the identification and authentication of the individual pack on which it is printed; and
- (2) an anti-tamper device.  
The requirement for safety features will apply mainly to prescription-only medicines, with some limited exceptions.

Commission Delegated Regulation (EU) 2016/161 details the characteristics of the safety features, how medicine authenticity should be verified and by whom. The obligations for wholesalers detailed in the legislation will apply, as of, 9 February 2019.

### How will the verification system work for wholesalers?

In specific circumstances as set out in the above mentioned Delegated Regulation, wholesalers will be required to scan the unique identifier (i.e. the 2D barcode) of medicines that pass through their warehouses. Wholesalers are not obliged (but can) verify the integrity of the anti-tampering device also.

When scanned, the details embedded into the 2D barcode will be checked against details in a national repository or hub, or the European hub if the product was not originally intended for the Irish market. When the wholesaler scans the barcode on a pack, if the details are not found in the repository/hub, an alert will be generated leading to an investigation to find out if the pack is falsified.

### When will a wholesaler need to scan a pack of medicinal product?

A wholesaler is required to scan the 2D barcode and verify the authenticity of the pack of a medicinal product if he does not receive the pack directly from the manufacturer or marketing authorisation holder or from the wholesaler designated by the marketing authorisation holder to store

and distribute the medicinal products covered by his marketing authorisation. (Such a designated wholesaler is known as the 'primary' or 'nominated' wholesaler). The repository system will maintain a listing of 'nominated' wholesalers.

Wholesalers must also verify medicinal products returned to them by persons authorised or entitled to supply medicinal products to the public (e.g. a pharmacy) or returned by another wholesaler.

A wholesaler must verify and decommission the unique identifier in certain scenarios, including the following:

- products to be distributed outside of the European Union;
- products which have been returned and are not to be put back into saleable stock;
- products which are intended for destruction;
- samples for competent authorities; and
- products to be distributed to certain customers, other than pharmacies, which are not required to verify and decommission products, such as, dispensing doctors, nursing homes and prisons.

Verification of the unique identifier is not required if the medicinal product changes ownership but remains in the physical possession of the same wholesaler, or, if the product is distributed within the Republic of Ireland between two warehouses belonging to the same wholesaler or the same legal entity and where no sale takes place.

### What systems do wholesalers need to scan packs of medicinal products?

In order to meet these legal obligations, wholesalers will need to install software systems to create a connection (via an internet connection) to the national hub. The Irish Medicines Verification Organisation (IMVO) manages this national hub and will work directly with the providers of

these systems (and internal software developers in wholesalers, if required) to provide wholesalers with the software development kit (SDK) and the support they may need to create an interface between their IT systems and the hub.

The IMVO will have an onboarding process for wholesalers that connect to the IMVO repository but wholesalers will not be required to pay any fees for this to the IMVO. Further information regarding the onboarding process for wholesalers is available by contacting the IMVO. <http://www.imvo.ie/>

### Batch tracking

Wholesalers are reminded that chapter 4 of the GDP guidelines for medicinal products for human use states that batch tracking must be in place for medicinal products bearing the safety features. It states the following: 'Records must include at least the following information: date; name of the medicinal product; quantity received, supplied or brokered; name and address of the supplier, customer, broker or consignee, as appropriate; and batch number at least for medicinal product bearing the safety features'.

### What should wholesalers do now?

Wholesalers need to review their current processes, suppliers, customers and types of products they distribute to determine what products need to be verified, or verified and decommissioned, prior to onward distribution. Wholesalers should also review how best to introduce batch tracking, if they are not already doing so. For some wholesalers, this may require significant change and, as such, wholesalers are strongly encouraged to begin planning now to ensure they are ready to meet their legal obligations in 2019.

Further information on Safety Features is available from the link below:

[https://ec.europa.eu/health/human-use/falsified\\_medicines\\_en](https://ec.europa.eu/health/human-use/falsified_medicines_en)

## GMP guidance for consultation

A revised draft of Annex 1 to the EU GMP Guide, on Manufacture of Sterile Medicinal Products, has been issued for public consultation; this will run from 20 December 2017 to 20 March 2018. Guidance on how to provide comments is provided on the European Commission's website and can be accessed via the following link: [https://ec.europa.eu/health/humanuse/quality/developments/pc\\_2017\\_12\\_sterile\\_medicinal\\_products\\_en](https://ec.europa.eu/health/humanuse/quality/developments/pc_2017_12_sterile_medicinal_products_en)

This consultation is being carried out in parallel with a consultation process being run by PIC/S and the WHO. Both of these organisations were involved in the drafting process for the revision of Annex 1.

## Update on regulatory oversight of outsourced storage of stability samples

It has been decided to formalise our approach in relation to outsourcing storage of stability samples. Manufacturers that outsource the storage of stability samples relating to medicinal products for human use, investigational medicinal products or veterinary medicinal products are not required to name these sites as contract storage sites on the Manufacturers' / Importer's Authorisation (MIA) held by the manufacturer. A site that carries out storage of stability samples is not required to hold a GMP certificate for this activity in Ireland.

Responsibility for ensuring that storage of stability samples is carried out correctly in accordance with ICH and EU GMP (Chapter 7) requirements lies with the manufacturers which are outsourcing this activity. HPRAs inspectors will review controls applied during GMP inspection of the contract giver's site. Contract givers in this situation could include authorised manufacturers of medicinal products or registered manufacturers of active substances.

## New regulatory approach for contract laboratories

There are a number of independent laboratories located in Ireland which carry out testing of medicinal products on behalf of manufacturers. Until recently these contract laboratories could apply to the HPRAs for a Laboratory Approval; this was independent of any variation by a manufacturer to name the site as a contract laboratory on its Manufacturer's / Importer's Authorisation (MIA). Sites holding a Laboratory Approval underwent routine GMP inspections and, pending a successful outcome, GMP certificates were issued.

The HPRAs are changing this process such that it will no longer issue a Laboratory Approval and a listing of approved laboratories will no longer be available on the HPRAs' website. Those sites which currently hold a Laboratory Approval have been contacted in this regard.

Contract laboratories which carry out specific testing\* in relation to medicinal products will continue to undergo GMP inspections and assuming a satisfactory outcome, GMP certificates will be issued by the HPRAs for these sites. (\*See the HPRAs' guidance on application for a MIA for information on the specific types of contract laboratories which are required to be named on an MIA and which must hold a GMP certificate for this purpose.)

If a manufacturer is intending to use a new contract laboratory, it should submit a variation application to the HPRAs to add the contract laboratory to its MIA, specifying the type of testing which it intends to outsource. If the proposed laboratory does not hold a GMP certificate, the HPRAs will make arrangements for inspection directly with the contract laboratory and fees associated with the inspection will be charged to it. Pending a satisfactory inspection, the resultant GMP certificate will be used as the basis of approval of the variation to the contract-giver's MIA.

## Brexit: transfer of responsibility for EU batch certification and wholesaling activities

### EU Batch Certification

With the forthcoming exit of the UK from the European Union, companies may be considering relocating the responsibility for batch certification of products from the UK to Ireland. This may involve either i) transfer of batch certification responsibility to an existing manufacturer or ii) establishing a new manufacturing site responsible for this function.

If the company intends to transfer this responsibility to an existing manufacturing site, i.e. one already holding a Manufacturer's / Importer's Authorisation (MIA) it will be necessary to determine if any variations to this MIA are required (e.g. to cover batch certification of the particular product type or to add contract manufacturers / contract laboratories). Please refer to the HPRA website for guidance on applications for variations to an MIA and this will assist in determining what variations may be required to the MIA concerned. These variations may be progressed in advance of any variations to the Marketing Authorisations for the products concerned.

If the company intends to establish a new site in Ireland that will be responsible for batch certification of the products concerned, then an application for an MIA should be submitted in accordance with the guidance provided on the HPRA website:

<http://www.hpra.ie/homepage/medicines/regulatory-information/manufacturers/applications-for-a-manufacturing-authorisation>

### Wholesaling Activities

Brexit will also have an impact on wholesaling activities. Companies may consider transferring wholesaling activities of medicinal products from the UK to Ireland given that supply from the UK to the EU will be deemed third country importation post Brexit. These wholesaling activities may be transferred to an existing Wholesale Distribution Authorisation (WDA) holder in Ireland or a new WDA application may be submitted.

Should the activities be transferred to an existing WDA, the categories on that WDA should be reviewed to ensure any new products to be wholesaled are appropriately covered by the existing WDA. Where they are not, the appropriate variations should be submitted. Please refer to the HPRA website for guidance on applications for variations to a WDA and this will assist in determining what variations may be required.

If the company intends to establish a new wholesaling site in Ireland, then an application for a WDA should be submitted in accordance with the guidance provided on the HPRA website:

It should be noted that post-Brexit, any medicinal product supplied to the UK from Ireland will be considered exportation, therefore the scope of existing Irish wholesaler authorisations may need to be changed to include the activity 'export'.

Applications and guidance regarding new applications for, and variations of, a wholesale distribution authorisation is available on the HPRA website:

<http://www.hpra.ie/homepage/medicines/regulatory-information/wholesalers-and-distributors>

In order to facilitate timely scheduling of inspections and completion of the inspection process, any new applications for an MIA or a WDA should be submitted 6 months before the Brexit date \* (\* note this date may be adjusted to reflect any agreed post Brexit transition period). The HPRA also encourages intending applicants to make early contact with the Compliance Department by emailing [inspect@hpra.ie](mailto:inspect@hpra.ie) prior to submission of the application itself.