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# HPRA MEDICINAL PRODUCTS NEWSLETTER

ISSUE 78

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# Human Medicines

## Decentralised authorisation applications for 2025

The HPRA is available to act as a Reference Member State (RMS) for new Decentralised Procedure (DCP) applications in 2025, in particular for generic medicines and products with limited alternatives in Ireland. Applicants planning to submit requests for DCP as RMS to the HPRA in 2025 should consult the new product applications page on the HPRA website.

We offer a slot-based booking system, where applicants will be given a suitable submission slot in an agreed month. To request your preferred slot, applicants are required to complete the request form in full and submit to RMS@hpra.ie. The request form is available on the CMDh website.

The HPRA's assessors and administrative staff are experienced in these procedures, and we operate a national scientific and regulatory advice process to review significant regulatory queries, or requests for scientific advice potentially impacting the submission in advance.

Please ensure relevant guidance is consulted prior to submitting regulatory queries. Due to the success of our slot request system, we have very limited availability remaining for 2024. However, we are operating a cancellation list for high quality applications which are ready to be submitted immediately if a slot becomes available.

## Nitrosamines

The HPRA is reminding marketing authorisation holders that they must maintain the quality of their product throughout its lifecycle. Marketing authorisation holders must continue to review their risk evaluation on the presence of nitrosamines as new information becomes available. This requirement is outlined in question 5 of the CMDh/EMA Q&A document on the CHMP opinion for Article 5(3) of Regulation (EC) No. 726.2004.

Marketing authorisation holders who previously submitted a 'Step 2 nitrosamine detected' template, resulting in a Scenario D outcome, are now required to carry out a calculation using the CPCA approach outlined in Appendix 2 of the Q&A. This calculation determines the acceptable intake (AI) for that impurity. Marketing authorisation holders must then resubmit their Step 2 nitrosamine detected template to nitrosamines@hpra.ie indicating which of the resulting scenarios A, B or C apply.

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If Scenario A 'nitrosamine detected above AI' applies, please also copy the Quality Defects and Recalls section of HPRA at HPRAqualitydefects@hpra.ie to determine the action required for the Irish market. This is required in addition to any discussions with the lead member state for that impurity.

Furthermore, the EMA is continually publishing nitrosamine acceptable intakes arising from new detections. Applicants should continue to evaluate the associated risk for their product and inform the Quality Defects and Recalls section of HPRA if nitrosamines above the acceptable intake are detected, for consideration of further market action.

# Transfer before authorisation

Where a marketing authorisation is transferred before authorisation, the new holder must notify the HPRA using the procedure below.

A transfer before authorisation must be submitted as a standalone application with all the required forms and supporting data. It is not acceptable to submit as part of the new application procedural documents.

## Making an application

To transfer a new authorisation, licence or registration, the proposed holder or another person acting on their behalf must apply, as per the HPRA's guide to electronic submission for human medicines. The application must contain the following documents:

1. A transfer application form and signed statements from the existing holder/applicant and proposed new holder which contains:
    - Application Form B for Transfer before Authorisation of a Marketing Authorisation for Human Medicines.
    - Fee Application Form for Human Products and proof of payment.
2. A revised module 1.2 application form, SmPC, labels and leaflet (only for transfers before authorisation).
    - Revised package leaflet with the new name and address of the holder. A Word version of the package leaflet is acceptable. Please note that the revised package leaflet mock-ups will not be subjected to review at this time. It is assumed that there is no change to the currently approved labels and package leaflet except for the change in name/address of the marketing authorisation holder.
3. A cover letter specifying the proposed transfer date.
4. Evidence of establishment in the European Union, e.g. certificate of incorporation or equivalent. This is only for companies or individuals not already holding an authorisation/ licence in Ireland.

The HPRA Receipts and Validation unit can provide the new (P)PA/DPR numbers in advance to facilitate the preparation of the application.

## Fees

An application for a transfer before authorisation is subject to an administrative fee. In the fee application form, the fee code 393 should be used for a single product and 393 x2 for two or more products in a range.

## Address for submitting applications

The HPRA accepts electronic submission of transfer applications and related information which is outlined in the Guide to Electronic Submissions for Human Medicines.

New applications should be submitted by CESP or email to submissions@hpra.ie

## Guide

For further details on the transfer process, refer to the Guide to Transfers of Marketing Authorisations, Parallel Import Licences and Dual Pack Import Registrations for Human Medicines.

# Clinical Trials Regulation transition period – Deadline approaching

The HPRA would like to remind clinical trial sponsors of the following dates and deadlines in relation the Clinical Trials Regulation (CTR).

- All ongoing clinical trials in the EU must be transitioned to the Clinical Trials Information System (CTIS) by **31 January 2025**.
- Sponsors should submit transitions to CTIS by **16 October 2024** at the latest to permit review and authorisation.
- An end of trial form should be completed to inform whether the clinical trial has been completed or never started.
- Any trials authorised under the CTD which are ongoing after **31 January 2025** and have not transitioned to the CTR will not be compliant with the regulations for the conduct of clinical trials in Ireland.

# Pre-CTA advice pilot

The HPRA is participating as a Member State Concerned in the ACT-EU pre-CTA advice pilot which is coordinated by the Clinical Trials Coordination Group (CTCG). It provides technical and regulatory support on the dossier of a CTA prior to its submission through the Clinical Trials Information System (CTIS).

The pre-CTA advice pilot will provide consolidated views of the Member States concerned on pre-submission topics. The scope of this pilot covers several areas such as advice on regulatory aspects of low interventional clinical trial status and submission of trials with decentralised elements or complex designs. More information on the ACT-EU pre-CTA advice pilot and how interested sponsors can apply is available in the pre-CTA advice pilot guidance for applicants.

# Use of medicinal products containing estragole in the flavouring

The HPRA wishes to alert authorisation and registration holders to the use of flavours which may contain estragole. Estragole is a natural constituent of several aromatic plants and their essential oil fractions. This includes anise, basil, chervil, cumin, fennel, hyssop, lemon balm, liquorice mint and tarragon. Estragole containing plants or their essential oils may be added to medicinal products as flavourings. For example, anise (also known as aniseed or star anise), fennel (bitter and sweet) and lemon balm.

The EMA's Committee on Herbal Medicinal Products (HMPC) published a statement on the use of herbal medicinal products containing estragole in 2005. Revision 1 of this statement was published in 2023. This revised statement outlines that levels of estragole should be reduced to a content below the guidance values of 0.05 mg/person per day for adults and adolescents and 1.0 µg/kg body weight for children. The revision also notes that exposure to estragole is not recommended in certain groups of patients.

In February 2022, the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh), in consultation with the EMA's Committee for Medicinal Products for Human Use (CHMP) agreed that the above-mentioned guidance values for estragole are applicable for all medicinal products, not just herbal medicinal products.

The HPRA requests that product authorisation and registration holders address the following:

- Review the composition of any flavours used in their products.
- If estragole is present in the flavour, the authorisation/registration holder must introduce appropriate measures and specifications for the product at an appropriate control point. These measures and specifications must ensure that the product complies with the limits outlined in the above guidance.
- The most appropriate stage for testing/control of estragole to take place should be considered, i.e. in the excipient or in the finished product.
- Reduction of the level of estragole in line with guidance values may be addressed in different ways, as outlined in the examples below.

**Example 1**

Immediate implementation in the finished product or excipient specification of a control for estragole in line with the guidance values or toxicologically justified limits, based on the maximum daily dose (MDD) of the product. This could include calculation of the estragole content based on the known level of estragole in the excipient or testing the finished product for the content of estragole.

**Example 2**

Reformulation of the product to remove or reduce the level of the concerned excipient so that the potential for the presence of estragole above guidance values in the maximum daily dose of the product is removed.

Other examples will be considered. All proposals must be robustly justified.

If a specification for the control of estragole is required but is not already in place, this is now overdue and must be included by variation as soon as possible.

Authorisation and registration holders with medicinal products containing estragole in the flavouring must contact regaffairs@hpra.ie and advise if the product complies with the published HMPC guidance values or not.

If the product does not comply, an appropriate action to bring the product into compliance must be proposed and agreed with the HPRA.

Applicants are reminded that the use of estragole-containing excipients or active substances in new product formulations should be kept as low as practically achievable, in line with the recommendations of the HMPC guidance.

# Veterinary Medicines

## HPRA Veterinary Medicines Information Day 2024 – Registration now open

We are inviting all marketing authorisation holders of veterinary medicines to attend our upcoming Veterinary Medicines Information Day on **24 October 2024**. This event will cover crucial developments related to the implementation of Regulation 2019/6 and associated national legislation, specifically impacting stakeholders in Ireland's animal health sector.

The event will be held at the Camden Court Hotel, Dublin, D02 W086, and will also be available online for those who cannot attend in person.

### Event Details

- **Date:** 24 October 2024
- **Location:** Camden Court Hotel, Dublin, D02 W086 (In-person) or Online
- **In-person Fee:** €100 per person (includes refreshments)
- **Online Fee:** €60 per person

### Why Attend?

- Gain insights into the latest developments in veterinary medicines regulation.
- Understand how these changes will impact your role and responsibilities.
- Network with industry peers and experts.

### Register Now

Early booking is essential for in-person attendance as spaces are limited.

To view the agenda and register to attend visit our event page.

## Important notice for marketing authorisation holders: Submission deadline for G.I. 18 variation applications

As of 1 August 2024, the HPRA has received a total of 801 G.I.18 variation applications, representing approximately 41% of all expected submissions.

To ensure timely processing and approval, the HPRA urges marketing authorisation holders to submit any remaining G.I.18 variation applications as soon as possible to ensure that applications can be processed in a timely manner.

These variations should be submitted so that the variation is finalised and implemented on labels and package leaflets before 29 January 2027. This is in accordance with the CMDv/ EMA Guidance on the details of the classification of variations requiring assessment according to Article 62 of regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations and Regulation (EU) 2022/839.

Applications will be processed in order of receipt. The HPRA requires that all remaining applications be submitted as soon as possible but for approval by 28 January 2027.

### Key reminders

- **Submission strategy:** Marketing authorisation holders are strongly advised to submit their applications as soon as possible to ensure they can be processed in time to allow implementation in the marketplace in advance of 28 July 2026.
- **Compliance requirement:** Products that do not meet the requirements of Regulation 2019/6 by the 2027 deadline cannot be placed on the market.

Acting early will help avoid potential disruptions to your market access. Please plan your submissions accordingly.

## Website development update

We're excited to announce that we are redeveloping our website to better serve our stakeholders. The new and improved site is expected to launch by the end of 2024.

As part of these changes, we are improving accessibility by limiting the use of PDFs and making our content more inclusive for those accessing our website using assistive technologies e.g. screen reader. Additionally, we are optimising the website for mobile devices for a more seamless experience on the go.

However, please note that as part of this update, we will no longer display our monthly product updates on the website. These updates typically include information on newly authorised veterinary medicines, withdrawals of existing products, and significant changes to marketing authorisations.

If you rely on these updates, please contact us as soon as possible by emailing Juliana.camargoteixera@hpra.ie. We will be happy to provide you with alternative ways to access this information.

# Recording suspected adverse events in animals following the use of human medicines

The HPRA would like to remind marketing authorisation holders on how to properly record suspected adverse events in animals following use of medicinal products for human use within the EudraVigilance Veterinary (EVVet) system.

According to section 2.3 of the guideline on veterinary good pharmacovigilance practices (VGVP) module any suspected adverse events involving medicinal products for human use should be recorded in the Union Pharmacovigilance Database (UPD).

Where the marketing authorisation holder of a veterinary medicinal product (VMP) is notified of an adverse event that involves both a VMP and a medicinal product for human use, they are required to include detailed information for the medicinal product for human use in the suspected adverse event report.

Marketing authorisation holders should follow the guidance in section 2.2 of the EudraVigilance veterinary – best practice guide when recording medicinal products for human use into EVVet.

When completing the 'Registered name or Brand name' field, the name of the medicinal product for human use should be manually entered by selecting 'Add Product X as a new product'. Be sure to include '(H)' after the product name to indicate that it is a human medicinal product e.g. Aspirin (H). The example below is how this entry should appear.


Using this approach will help accurately identify reports involving the use of human medicinal products. Properly collecting and recording this information in the UPD enables national competent authorities to monitor and address potential safety concerns effectively.

# New regulation on Substances of Human Origin (SoHO)

## About the new regulation

On 17 July 2024 Regulation 2024/1938 of quality and safety for substances of human origin intended for human application was published in the Official Journal of the European Union. Substances of human origin (SoHO) means any substance collected from the human body.

These new rules will replace the current rules for blood (Directive 2002/98/EC) and tissues and cells (Directive 2004/23/EC). A three-year implementation period will apply.

Regulation 2024/1938 applies to SoHO intended for human application and SoHO used to manufacture products regulated by other EU legislation, (such as medicinal products, medical devices, advanced therapy medicinal products and investigational medicinal products) and intended for human application.

The types of products covered by these new rules has been expanded. Previously unregulated substances such as, faecal microbiota and human breast milk, are now included.

The Regulation aims to improve harmonisation, simplify cross-border exchange and improve access to SoHO across the EU.

It also aims to improve the protection of citizens that donate SoHO by verifying donation frequency for living donors of SoHOs that can be donated repeatedly and frequently (e.g. plasma or stem cells).

The Regulation includes use of expertise from the European Centre for Disease Prevention and Control (ECDC) and the European Directorate for the Quality of Medicines and HealthCare (EDQM) of the Council of Europe. Their expertise will provide authoritative technical guidelines to help the sector meet the required safety and quality standards. Both expert bodies will use their capacity and experience to adapt the guidance in line with scientific progress and frequently changing threats.

From August 2027 entities conducting any of the activities listed below that affect the safety and quality of SoHO will have to register using a new process with the HPRA and submit annual activity data.

- SoHO donor registration
- SoHO donor history review and medical examination
- Testing of SoHO donors or of persons from whom SoHO are collected for autologous or within-relationship use
- Collection
- Processing
- Quality control
- Storage
- Release
- Distribution
- Import
- Export
- Human application
- Clinical-outcome registration

Entities currently authorised as tissue establishments or blood establishments will be contacted by the HPRA to discuss the registration process.

Entities that carry out activities that have a greater impact on safety and quality (i.e. processing and storage, release, import or export) will have to fulfil additional requirements to be authorised as a SoHO establishment. These entities will also be inspected.

The HPRA will develop guidelines to include the registration process, how to maintain compliance and other relevant information as part of the implementation plan and will actively engage with stakeholders during this transition period.

The European Commission has prepared a Question and Answer Document on the new Regulation.

## How this regulation affects medicinal products

Regulation 2024/1938 will apply to SoHO collected as starting materials to be used to manufacture products regulated by other EU legislation. This will apply to:

- SoHO donor registration
- SoHO donor history review and medical examination
- Testing of SoHO donors
- Collection
- Release

This Regulation will also apply to the storage, distribution, import and export of SoHO when carried out up to and including their distribution to a manufacturer regulated by other EU legislation. This means that there will be closer interaction between this regulatory framework and other related frameworks and ensures coherence without gaps or overlaps.

## When will these new rules take effect?

The new rules will come into force from 7 August 2027. However, an extra year has been provided for certain transitional provisions. Visit the HPRA website or sign up for website alerts to be kept up to date during the transition period.

## Contact us

If you have any queries in relation to the new Regulation you can email compliance@hpra.ie.

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