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HPRA MEDICINAL PRODUCTS NEWSLETTER

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Human Medicines

Nitrosamine limits

The HPRA would like to remind marketing authorisation holders (MAHs) of the updated approach to implementing acceptable intake (AI) limits for API derived nitrosamines (NDSRIs). These updates are outlined in the CMDH/EMA Q&A document on the CHMP opinion for Article 5(3) of Regulation (EC) No. 726/2004.

The Q&A documents are published on the EMA website. The CMDh provides a link in the nitrosamine impurities section of their website. In this section you can also find other guidance relevant to MR/DCP/national authorisations. Further information is also available in the July CMDh press release.

The Q&A document lists nitrosamines for which an acceptable limit has been agreed. It also outlines a methodology for (MAHs) to calculate an acceptable intake for a nitrosamine impurity where no limit is currently published.

As a matter of urgency MAHs must provide an **updated Step 2 nitrosamine detected response** for a nitrosamine without a published EU acceptable intake. This must be done by MAHs who have already submitted a **Step 2 Scenario D nitrosamine detected response/Quality defect report** for their product.

Where an acceptable intake (AI) has been published in Appendix 1 of the Q&A, this limit should be used to determine an updated Step 2 response and the associated scenario (i.e., exceeding AI, >10% AI to AI, below 10% AI), for your product.

Where no AI is published for the new nitrosamine, you have identified, please use the updated guidance to propose an AI. For example, you can use the Carcinogenic Potency Categorisation Approach (CPCA).

You also need to submit a Step 2 nitrosamine detected template. You must clearly identify whether the CPCA approach or other data has been provided in support of your proposed AI and the resultant scenario.

MAHs must use the updated guidance and the 'Template for the notification of step 2 confirmatory testing outcome: confirmation of nitrosamine detected'. These are available on the CMDh website in the nitrosamine impurities section.

Step 2 templates and supporting documentation should be emailed to nitrosamines@hpra.ie

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland
T: +353 1 676 4971 E: info@hpra.ie **www.hpra.ie**

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Where the level of the nitrosamine is above AI (Scenario A), also copy qualitydefects@hpra.ie in the email and ensure the following steps have been completed.

- Complete a quality defect report form.
- Use our guide to reporting and investigation of quality defects in medicinal products for human and veterinary use to help you complete the form.
- Ensure the Excel file submitted specifically highlights the results where nitrosamine levels above the AI limit are detected. Please provide results in ng/day as well as ppm (or ppb).

Reminder to MAHs to monitor CMDh website for relevant updates

MAHs for nationally authorised products, particularly those authorised the mutual recognition and decentralised procedures are recommended to monitor the CMDh website for information on their product portfolio.

The Co-ordination Group for Mutual Recognition and Decentralised Procedures-human (CMDh) was established under Article 27 of Directive 2001/83/ EC of the European Parliament and of the Council on the Union code relating to medicinal products for human use. The role of the CMDh is to examine any questions relating to a marketing authorisation of a medicinal product in two or more Member States.

These questions cover issues relating to new applications, variations, renewals, pharmacovigilance activities and currently Brexit related activities. The CMDh hold monthly meetings attended by representatives of the EU/EEA member states to discuss and resolve arising issues.

The outcomes of these meetings are published in the CMDh press release every month. The press releases are published on their website immediately after the meeting.

The CMDh publish minutes of the meetings approximately two months later. The minutes are explained further in 'procedural guidance,' 'advice to MAHs' and the 'recently published history' sections of their website.

Therefore, MAHs should regularly review the resources on the CMDh website in relation to their product portfolio and take any required actions according to the requested timeframe.

Clinical trials – deadlines for transition and guidance

New/initial applications must now be made under the Clinical Trials Regulation (CTR) via the Clinical Trials Information System (CTIS). This applies to all clinical trials including academic/ non-commercial trials, and mono-national trials.

Applicants should make themselves aware of the deadlines for trials authorised under the Clinical Trials Directive (CTD):

- Substantial amendments and other reporting obligations can be made to trials authorised under the CTD up to **30 January 2025**.
- By **30 January 2025**, any ongoing trials approved under the CTD will fall under the CTR. Therefore, any ongoing trials will need to be transitioned to CTIS and approved **before 30 January 2025**.

The HPRA recommends that sponsors submit transitions by the end of October 2024 at the latest. Sponsors can use the guidance available to assist with the transition.

- The European Commission have published a guidance document for the transition of clinical trials under EudraLex volume 10.
- The Clinical Trials Coordination Group (CTCG) adopted a best practice guide for multinational sponsors of transitional trials.
- Applicants can use the training materials provided under Module 23 of the EMA CTIS online training programme.
- Sponsors should raise a ticket with the CTIS User Support Service if they cannot find the trial they wish to transition in CTIS when searching by EudraCT number.

General guidance on the CTR and CTIS is also available on the:

- EMA website
- HPRA website
- EMA Introductory guide CTIS for SMEs and Academia for non- commercial sponsors

Veterinary Medicines

Expansion of the US-EU mutual recognition agreement on GMP inspections

Earlier this year, the mutual recognition agreement of pharmaceutical good manufacturing practice (GMP) between the European Union (EU) and United States (US) underwent significant expansion. This expansion included the GMP inspectorates for veterinary medicines from 16 EU national competent authorities, including the HPRA.

As a result of this expansion, the US Food and Drug Administration (FDA) and the HPRA can now mutually recognise each other's GMP inspections for veterinary product manufacturers. However, it is important to note that the requirement for EU importation testing will remain in place until the FDA recognises all EU member states.

The aim of this process is to further enhance cooperation and harmonisation between the EU and the US and ensure the quality and safety of veterinary medicines.

HPRA veterinary medicines webinar

The HPRA is hosting a special webinar on Wednesday 1 November 2023. The event is for marketing authorisation holders supplying veterinary medicines in Ireland. The webinar will address how national and European regulatory developments on veterinary medicines affect you.

The webinar aims to:

- Explain recent changes impacting the regulation of veterinary medicinal products in Ireland
- Reflect on how changes to the EU platform and processes affect how marketing authorisation holders engage with the regulatory system
- Consider the next steps in the implementation pathway
- Inform stakeholders about where to find relevant information

The webinar will take place between 11.00 am and 1.00 pm GMT. The webinar will be free of charge, but you will need to register in advance. Details of registration are available on the HPRA website. There will be a questions and answers session during the webinar. However, if you have any questions you wish to be answered, you can submit these beforehand to veterinarywebinar@hpra.ie.

New classification of supply routes in Ireland

With the introduction of new national legislation on 11 July 2023, there have been changes to the supply routes of veterinary medicines.

As a result of this veterinary medicines will now fall into one of four supply categories and are denoted with the following abbreviations.

- **Subject to veterinary prescription** may be identified with the abbreviation POM.
- **Prescription only exempt** products may be denoted by the abbreviation POM(E).
- **Licensed retailer** products may be denoted by the abbreviation LR.
- **Companion animal medicine** products may be denoted by the abbreviation CAM.

As per Regulation 2019/6, the supply category must be indicated on the package leaflet of the medicine.

The HPRA has reassigned all products previously denoted VPO or VPO1 to the POM category. Products that were previously labelled as LM are being moved to LR category on the HPRA's website. Changes to the product labelling and package leaflet are expected to be introduced during the ongoing process of labelling changes required by Regulation 2019/6.

New legislation on veterinary medicines

On 11 July 2023, the Veterinary Medicinal Products, Medicated Feed and Fertilisers Regulation Act 2023 (No. 21 of 2023) was enacted. The Act encompasses the following provisions.

- The **establishment of a new national database** to record veterinary prescriptions.
- The **introduction of new regulations** governing veterinary medicines and medicated feeds, including aspects related to their retail and advertising,
- There are **changes to the supply classification** for veterinary medicines in Ireland,
- The **Animal Remedies Act 1993 is revoked** as part of this new legislation.

The HPRA is currently consulting with the Department of Agriculture, Food, and the Marine (DAFM) to determine the timelines for implementing labelling changes to existing products.

New statutory instruments are also expected to be developed to cover the supply and use of veterinary medicines in Ireland. This includes the development of a national database to record veterinary prescriptions.

Provision of labelling mock-ups

To expedite the issuance of new product authorisations, the HPRA has introduced a streamlined process that separates the approval of label mock-ups from the granting of marketing authorisations.

Under this new approach, the marketing authorisation will be issued once the procedure is finished. The review of mock-ups will now be managed separately through the G.I.15z application.

Applicants can submit the G.I.15z variation for mock-up approval as soon as they are available. These enhancements are expected to lead to more efficient timelines and greater predictability for MAHs. This will ensure that mock-up reviews are coordinated with product launch.

Compliance

Electronic certificates of pharmaceutical product and free sale now available

The HPRA is pleased to launch the issuance of electronic versions of the certificate of a pharmaceutical product and the free sale certificate. This applies to both medicinal products and cosmetic products. Printed versions of documents with a wet signature will remain in place for those applicants who require this service.

The application process will remain the same, you should note on the updated application form that you wish to receive an electronic version of the certificate and any attachments that may be requested.

The Summary of Product Characteristics (SPC) used will be the latest version published on the HPRA website. The HPRA do not accept an SPC submitted by the applicant. They can note the requirement on the CPP draft.

The certificate will be emailed back to the applicant's email address. This service is now live. For queries relating to this initiative please email exportcerts@hpra.ie.

Manufacturer's / Importer's Authorisation (MIA) pre-submission process

The HPRA has introduced a pre-submission process for companies who intend to apply within the next 6 months for an MIA for the manufacture of human and veterinary medicines and investigational medicinal products.

A company can make a request for pre-submission meeting for MIA. The form is less detailed than the MIA application form and will facilitate discussions during the pre-submission phase. The completed form and request for a meeting should be sent to compliance@hpra.ie.

The HPRA objectives for providing pre-submission advice relating to MIA applications are:

- Assist a company so that their application can have a successful outcome within the required legislative timeline.
- Discuss key project milestones related to the development of the pharmaceutical quality system and the high-level qualification activities related to the premises and equipment.
- Obtain advanced notice of future applications to help ensure availability of inspection resources.

The meetings will be held online and are scheduled for one hour. Personnel from the HPRA's inspection team will be included in these meetings. The company will be asked to provide a presentation in advance, and they can ask questions in relation to the MIA application process. There will also be an opportunity to clarify any essential aspects that need to be in place at the time of inspection.

An MIA application form will be provided to the company when they confirm that they are ready for an inspection within 4 weeks.

An earlier regulatory review meeting to discuss GMP facility design can also be arranged. An in-person meeting with GMP inspectors would normally include a review of qualification and validation activities during the building of a new facility or significant upgrading of an existing site. Further details about this are available in our guide to scientific and regulatory advice for GXP activities.

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