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HPRA MEDICINAL PRODUCTS NEWSLETTER

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Human Medicines

Clinical trials – Important dates and information

Transition to the Clinical Trials Regulation

Applicants should make themselves aware of the following dates and deadlines in relation to the Clinical Trials Regulation (CTR).

- All clinical trials will be regulated under the CTR from **31 January 2025** and therefore ongoing trials authorised under the Clinical Trials Directive (CTD) must transition to the CTR in advance of this date.
- Sponsors should submit transition applications to the Clinical Trials Information System (CTIS) no later than **16 October 2024** to ensure review and authorisation.
- If a substantial amendment under CTD is required prior to transition, it should be submitted the HPRA by **30 June 2024**.

These dates apply to **all** clinical trials including academic/non-commercial trials, and mono-national trials. Sponsors can find further information and guidance in the European Commission's guidance document on transitioning to the CTR.

If a clinical trial has ended or never started, this must be declared by submitting a declaration of the end of trial form.

Training and supports

Applicants can avail of training and supports available from the HPRA and the EMA.

- Supports from the HPRA can be found on the dedicated CTR webpage.
- EMA supports are available on the CTR and CTIS section of the EMA clinical trials webpage.
- Non-commercial sponsors can use the EMA Introductory guide CTIS for SMEs and Academia for guidance when submitting a clinical trial through CTIS.
- Upcoming CTIS training and information events are listed on the information and events section of the EMA's CTIS webpage.

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HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Non-commercial clinical trial fees

As of 1 January 2024, non-commercial sponsors are no longer required to pay clinical trial application fees in Ireland.

The definition of a non-commercial clinical trial is based on the status of the sponsor which is defined in national law (S.I. No. 99/2022).

- A 'non-commercial sponsor' means a sponsor who has no commercial or financial interest in the outcome of the clinical trial.
- A 'non-commercial clinical trial' means a clinical trial conducted by a non-commercial sponsor which fulfils the following characteristics.
  - The ownership of the investigation data belongs to the non-commercial sponsor from the inception of the clinical trial.
  - The design, conduct, recruitment, recording of data and reporting of the results of the investigation remain under the control of the non-commercial sponsor.

This change is intended to support and facilitate non-commercial research in Ireland.

Details on all application fees can be found in the guide to fees for human products. Applicants should note there is no fee code for non-commercial clinical trials.

Swift written scientific advice- Quality and regulatory queries

The HPRA now offers swift written scientific advice to applicants. This is a new written national advice route in addition to the standard national scientific advice meetings that are already available. You can apply for swift scientific advice if you need guidance on quality or regulatory queries.

Swift written scientific advice has no requirement for a meeting between the applicant and the HPRA. It is intended to provide a simple mechanism for applicants to request written advice. Advice is issued 30 days after the validation of a request.

Your request for swift written scientific advice must include a brief overview and a list of questions. For each question raised, the applicant should state their position and provide a written summary. Depending on the complexity of the advice sought, the applicant may be informed if the scope or the number of questions in the advice is more suitable for the standard (meeting) scientific advice procedure.

Applicants can use our guide for national scientific and regulatory advice for guidance when submitting a request for swift written scientific advice. To apply for advice, applicants should submit a completed request form for national scientific and regulatory advice to scientifcadvice@hpra.ie.

Brexit and the Windsor Framework deadline of 31 December 2024

All marketing authorisation holders for human medicines are reminded that the exemptions granted, to allow a transition period for medicinal products impacted by the UK becoming a third country, expire at the end of the year. As a result, any companies relying on the exemptions, including UK based batch release and QC testing must bring their products into compliance or risk having their authorisation suspended. Companies that are having difficulties with compliance should contact the HPRA as a matter of urgency to consider any mitigating actions that may be taken.

In relation to the Windsor Framework, joint outer packaging with the UK for human medicinal products will no longer be feasible from the end of this year, although existing packaging can continue to be placed on the IE market. The HPRA will help facilitate companies who wish to move to multi-labelled packs and are happy to engage with companies on transitional provisions.

As many centralised products authorised through the EMA are currently jointly labelled with the UK, all marketing authorisation holders with centralised products using joint packs are asked to contact the HPRA outlining their plans to separate their packs from the UK market. Any companies who may have difficultly supplying the Irish market because of the Windsor Framework are asked to contact the HPRA as a matter of urgency. The HPRA will work with all marketing authorisation holders to ensure continued supply to the Irish market. We have also published a Q&A document on the implications of the Windsor Framework which is available on our Brexit latest information webpage.

Multilingual packaging pilot

The HPRA is reminding applicants for decentralised procedures (DCPs) of the importance of participating in the multilingual packaging pilot. This pilot allows applicants to agree a reduced text during the European phase of DCP procedures. The reduced text can then be applied to multilingual packs in the national phase and further discussions on reductions are not expected.

Multilingual packages can be discussed and prepared outside of the pilot for new and existing products. However, the HPRA considers it important to avail of the pilot opportunity to streamline their preparation. Multilingual packaging has important benefits, considering the limitations of Brexit and the Windsor agreement on joint packs historically shared with UK. The HPRA remains available to advise on issues regarding multilingual packs with IE.

Applicants can find further information and guidance in the latest version of the CMDh Best Practice Guide on Multilingual Packaging which is available on the CMDh website under 'Application for Marketing Authorisation'.

Veterinary Medicines

Alignment of product information with version 9.0 of the QRD templates

Article 152 of Regulation (EU) 2019/6, states that marketing authorisation holders have until 29 January 2027 to update the product information of existing products to comply with the requirements of the regulation.

The update is implemented by way of a G.I.18 variation requiring assessment. This involves a one-off alignment of the product information with version 9.0 of the QRD templates i.e., a major update of the QRD templates in accordance with Regulation (EU) 2019/6, for veterinary medicines placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004. The timing of submission should ensure that the variation is finalised and implemented before 29 January 2027.

Up to the end of December 2023, G.I.18 variations have been submitted for 26% of veterinary medicines authorised by the HPRA. That leaves 74% of authorised product variations to be submitted and processed, with packaging changes to be implemented by the deadline.

Given the volume of work remaining and the resource limitations for industry, the HPRA requests that all marketing authorisation holders put a plan in place for submission of the required variations and implementation of resulting packaging changes. This plan should include consideration of the time needed for processing of variations by the HPRA.

Where possible, efforts should be made to phase submissions with a view to distributing workload across what remains of the transition period. However, the HPRA is happy to receive G.I.18 variations as soon as they are prepared. Once validated, they will be processed according to established timetables.

Any queries relating to the submission or processing of G.I.18 variations should be sent to vetinfo@hpra.ie.

HPRA Information Day on implementation of Regulation 2019/6 in Ireland

The HPRA is planning to host an Information Day for marketing authorisation holders of veterinary medicines on the implementation of the Regulation and associated national legislation towards the end of 2024. It is expected to be an all-day in-person event.

The event will focus on developments related to the implementation and how it has affected stakeholders in the animal health sector in Ireland. The programme for this exciting event, will include speakers from HPRA as well as presentations from the Department of Agriculture, Food, and the Marine and various representatives from the animal health industry.

The event is currently being developed in consultation with stakeholders. Ideas and suggestions are welcome and should be sent to vetinfo@hpra.ie before 31 May 2024. More details on this event, including confirmation of the date and details for registration, will be available on the HPRA website by 28 June 2024.

Implementation of Article 107 of Regulation 2019/6

Article 107 of Regulation 2019/6 outlines specific regulatory measures to control antimicrobial resistance when using antimicrobial medicines.

- Article 107 prohibits antimicrobial use for prophylaxis other than in exceptional cases. In these cases, antimicrobials must only be administered to an individual animal or a restricted number of animals when the risk of an infection or of an infectious disease is very high and the consequences are likely to be severe.
- Article 107 allows antimicrobials to be used for metaphylaxis only when the risk of spread of an infection or of an infectious disease in the group of animals is high and where no other appropriate alternatives are available.

The HPRA provided further information to marketing authorisation holders on Article 107 at a webinar in November 2023.

The HPRA is now in the process of reviewing the indications for authorised antimicrobial products for compliance with Article 107 of the Regulation. Where required, consideration is being given how best to coordinate the implementation of changes to the product SPCs and package leaflets. Several of the products concerned are authorised under the decentralised and mutual recognition procedures which will require consultation with other Member States.

The goal is to ensure that the process of updating these products to comply with Article 107 is updated within the same general timeframe of similar products. This means that communication of the changes to veterinary practitioners and stakeholders can be optimised and that products with more restrictive indications are not disadvantaged against similar antimicrobials on the market. Further details on this will be available on the HPRA website over the coming months.

Implementation of fee increases for veterinary medicines

The HPRA has received notification from the Department of Agriculture, Food, and the Marine that the sanction of HPRA fees for veterinary medicines by the Minister for Agriculture, Food and the Marine is no longer required. This is following the revocation of the Animal Remedies Act, 1993.

This means that the HPRA will apply any changes to annual fees for veterinary medicines in the same timeframe as for

human medicines. These are usually applied on 1 January of each year following the fee consultation in the previous quarter. The fees for veterinary medicines for 2024 were updated on 1 January 2024 and are available in the guide to fees for veterinary products.

National legislation on veterinary medicines

The HPRA understands that national legislation implementing electronic prescribing is expected to be signed by the Minister for Agriculture, Food, and the Marine shortly.

In addition to this, a new Statutory Instrument (SI) is also expected to be signed. This will replace SI No. 36 of 2022 and is intended to correct several inaccuracies and introduce some editorial amendments. For further information, you contact the Department of Agriculture, Food, and the Marine.

Review of impact of Regulation 2019/6 on the HPRA's Veterinary Sciences Department

Like marketing authorisation holders, the HPRA's Veterinary Sciences Department has been significantly affected by Regulation 2019/6 and associated national legislative changes. While Regulation 2019/6 was intended to reduce the administrative burden, including within national competent authorities, the opposite has been our experience.

Moreover, whilst the Veterinary Sciences Department have been at the forefront in leading assessments across the various EU procedures, it is uncertain how frequently those procedures will be used by industry in the future. This will be due to the expected impact of the new EMA fees from January 2025.

Another challenging issue arising from Regulation (EU) 2019/6 is the new Union Product Database (UPD), which is critical to the operation of the Regulation. The iterative nature of the development of the UPD means that it has been a complex process requiring continuous adaptation of HPRA processes due to the increase in workload.

The process of uploading HPRA data from our national database was expected to be an automatic one, that would allow seamless updates from variations processed nationally to be carried through to the UPD. However, given the problems encountered, we have had to settle for a semi-automatic batch upload system, with additional checks needed to ensure correct data upload.

Some of the changes such as updating the Summary of Product Characteristics (SPCs) and associated package leaflets of all veterinary medicines under the G.I.18 category of variations requiring assessment are expected to be one-off or time limited. Other changes such as changes to the pharmacovigilance monitoring system are here to stay.

Furthermore, the European Commission is still in the process of drafting several implementing and delegated acts. This means that the final impact on both the animal health sector and the HPRA is not yet fully known.

The HPRA has continued to adapt our risk assessment policies to focus resources where they have most impact. However, there is a need to understand the full effect on the business model, given that is has now been over two years since the Regulation was applied.

The HPRA has initiated a project to evaluate the impact of Regulation 2019/6 on the HPRA's Veterinary Sciences Department business model and ensure the following.

- The strategy maximises HPRA's value to stakeholders, including animal health companies, the national veterinary sector, the wider agricultural sector, and the scientific animal protection sector.
- The strategy can be delivered in a self-sustained manner.

The HPRA will update stakeholders further on this matter in due course.

Updating the adverse events section of the product information

The EMA has recently updated their questions and answers document on describing adverse events in the product information and package leaflet. Marketing authorisation holders should review this guidance prior to submitting a G.I.18 variation requiring assessment to ensure that the product information submitted is consistent with the recommendations included in the document above.

Where possible, adverse events should be described using lower level VeDDRA terms. These are available from the Combined VeDDRA list of clinical terms for reporting suspected adverse events in animals and humans to veterinary medicinal products.

Marketing authorisation holders are also reminded that when updating the package leaflet as part of a G.I.18 variation requiring assessment, section 7 (adverse events) should be written in 'user friendly' terms. This means that the terms can be easily understood by the public in accordance with Article 14.3 of Regulation (EU) 2019/6. Examples are provided in the EMA's questions and answer document mentioned above.

Deadlines for submission of sales data on veterinary medicinal products to the Union Product Database

As per Article 58(12) of Regulation (EU) 2019/6, marketing authorisation holders are required to submit the annual volume of sales for each of their veterinary medicinal products to the Union Product Database (UPD). The deadline for submitting the data for 2023 is **29 February 2024**. After

this, the deadline to provide annual volume of sales will be set as the end of February of the following year.

The EMA hosted a webinar in April 2023 on submitting the volume of sales data for veterinary medicinal products. This included a demonstration on how to submit sales data to the UPD which can be accessed on the EMA's event page for the webinar.

When preparing to submit volume of sales data, marketing authorisation holders must ensure that all data is correct and accurate. However, in the case that there is any missing or incorrect packaging information relating to one or more of their products in the UPD, this must be notified to the relevant Competent Authority without delay.

- For centrally authorised products, users should contact the EMA.
- For nationally authorised products, users should contact the relevant National Competent Authority.
    - To correct common data, users should contact the RMS.
    - To correct national data, users should contact the CMS.

For those products where the HPRA is the relevant competent authority, the appropriate contact email is vetinfo@hpra.ie.

For more details on common or national data, please refer to Annex 1 of Chapter 2 of the Vet EU Implementation Guide.

Compliance

Chemicals now scheduled as Category 1 Precursor Chemicals

The chemicals listed below were scheduled as Category 1 Precursor Chemicals in 2023. A full list of Precursor Chemicals and which Category they fall into is available on our categories of precursor chemicals webpage.

- Diethyl (phenylacetyl) propanedioate (DEPAPD)
- Ethyl 3-(2H-1,3-benzodioxol-5-yl)-2-methyloxirane-2-carboxylate (PMK ethyl glycidate)
- N-phenylpiperidin-4-amine (4-AP)
- Tert-butyl 4-anilinopiperidine-1-carboxylate (1-boc-4-AP)
- N-phenyl-N-(piperidin-4-yl) propenamide (norfentanyl)

If you are an operator that places any of these chemicals on the market in the European Union, or if you are a user of any of these chemicals in Ireland, it is your responsibility to ensure that you are appropriately authorised for these activities.

Likewise, if you are an operator that imports or exports any of these chemicals to/from Third Countries, it is your responsibility to ensure that you are appropriately authorised for these activities.

To learn more about the licensing requirements for Precursor Chemicals for trade within the EU, and for trade between the EU and Third Countries, visit our licensing and registration of operators webpage.

Queries can be sent to controlleddrugs@hpra.ie.

HPRA
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Health Products Regulatory Authority