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HPRA MEDICINAL PRODUCTS NEWSLETTER

ISSUE 69

In this Issue

HPRA Website User Survey

We plan to redevelop the HPRA website as part of our new Strategic Plan for 2021 – 2025. As part of the initial planning process, we would like to ask you about your experience of using the HPRA website. Your feedback will help us improve our online communications and deliver a better web experience for our stakeholders.

Completing all questions in the survey will take approximately five minutes. However, some questions are optional. All feedback from our website users is welcome and we would value as much information as you can provide.

You can complete the survey using this link: Website User Survey.

Survey responses are anonymous. The information collected in the survey will only be used to improve and develop our online communications.

Human Medicines

Submitting a Request for Ireland to Act as Reference Member State in a Decentralised Procedure

The HPRA welcomes all requests for Ireland to act as Reference Member State (RMS) in Decentralised Procedures (DCP) for human medicinal products. Applicants should submit their request at least three months prior to the planned submission to ensure efficient processing.

All requests should be made using the RMS Common Request Form published on the CMDh website and submitted to RMS@hpra.ie. If using a reference product that has been authorised in the UK, please ensure your request is in line with CMDh guidance.

All requests received will be reviewed by the HPRA. Applicants will be contacted by email within 14 days of receipt of a completed RMS request form to indicate if a slot is available for the requested time. If a slot is not available, the HPRA will propose an alternate time. Once a slot has been offered, the applicant must indicate if they wish to accept within two weeks of the HPRA's offer email. If a response is not received within this period, the slot will be considered available for offer to another applicant.

Upon acceptance from the applicant of an agreed slot, a non-refundable booking fee of €1,000 will be required to secure the slot. The booking fee will be offset against the full application fee once the submission is received.

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Slots are allocated to a specific product and for a specific submission time. The applicant should confirm that the application will be submitted on the proposed date at least one month prior to submission. If the applicant wishes to change either one of those parameters, they must contact the HPRA immediately.

Scientific and regulatory advice does not form part of a request for Ireland to act as an RMS. However, advice is available through a separate procedure - national scientific and regulatory advice.

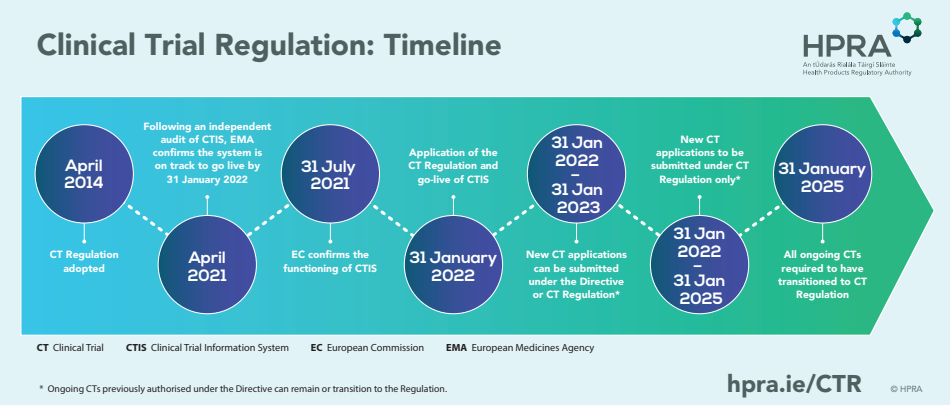
The HPRA holds a list of DCP requests in reserve in case a cancellation unexpectedly leads to a free slot. When free slots arise at short notice, the HPRA will proactively reach out to applicants with an offer of an earlier slot to maximise the optimal use of all the slots Ireland has to offer.

The HPRA publishes on its website the products that are imported to Ireland as unlicensed medicines. New product applications for these products are particularly welcomed and, where possible, will be offered a slot as a priority. For more information, please see our webpage on exempt medicinal products.

Azide Impurities – Reminder

All marketing authorisation holders (MAHs) for sartan-containing products are reminded of the CMDh letter to MAHs on the risk of azido impurity in sartan-containing medicinal products, which was published on the CMDh website following the April 2021 CMDh meeting. The information in this letter was also reiterated by direct correspondence from the HPRA on this issue. MAHs have been asked to review their products regarding a risk of contamination with azido impurities at the earliest opportunity. Responses should therefore be submitted without delay to facilitate potential regulatory actions by the HPRA and in other member states where appropriate. Similarly, MAHs who consider that no risk arises for their product should communicate this conclusion promptly to the HPRA.

Clinical Trial Regulation Progress



Please click on the image above to view in full size.

EMA Confirms the Go-live Date of the Clinical Trial Information System

On 31 July, the European Commission confirmed in the Official Journal of the European Union that the go-live date for the application of the Clinical Trials Regulation (Regulation (EU) No 536/2014) and the supporting Clinical Trials Information System (CTIS) will be **31 January 2022**. Once the Clinical Trials Regulation (CTR) is officially implemented, the three-year transition period for trials to transfer from the Directive to the Regulation will commence. Sponsors are encouraged to familiarise themselves with this three-year transition period, which will allow initial clinical trial applications to be submitted under either the Directive or the Regulation up until 31 January 2023. Substantial amendments for trials that have been approved under the Directive can continue to be submitted and approved under the Directive up until the transition period ends on 31 January 2025. Sponsors are strongly encouraged to consider how and when they will migrate ongoing trials from the Directive to the Regulation and also how they plan to interact with the CTIS. The HPRA has updated its Clinical Trial Regulation time line graph accordingly and an updated version can be found above.

Clinical Trial Information System – Sponsor Webinar

On 29 July, the EMA held a CTIS webinar to assist sponsors in their ongoing steps towards transitioning to CTIS. Presentations were given by colleagues from both the European Medicines Agency (EMA) and the European Commission (EC) as well as from sponsor representatives. The webinar is available to view and sponsors are encouraged to consult the recording as part of their ongoing preparations. Presentation topics include "What is needed to work in CTIS" and "EMA training and support for sponsors" amongst others. Sponsors can also review the comprehensive EMA training materials relating to CTIS located on the EMA's CTIS online modular training programme webpage.

Clinical Trial Information System – Sponsor Handbook

On 28 July, the EMA published the Clinical Trial Information System (CTIS) Sponsor Handbook. The handbook will continue to be updated as new information becomes available and is a valuable source of information for sponsors who wish to access further guidance on key aspects of the incoming CTIS. If sponsors have questions regarding CTIS, they are encouraged to first reference the handbook, which was compiled by the EMA in tandem with representatives of industry stakeholders.

End of the Voluntary Harmonisation Procedure

In advance of the introduction of the Regulation, the end of the Voluntary Harmonisation Procedure (VHP) has been confirmed. In order to harmonise VHP processes, sponsors are advised that the last submission date, for both new trials and substantial amendments, is **15 October 2021**. While VHP trials are encouraged to transition to the CTR as soon as possible, sponsors should be aware that any amendments submitted between the end of the VHP procedure (beginning of December 2021) and the start of the CTR (31 January 2022) will be assessed under the Directive by the individual Member States.

The HPRA would like to take this opportunity to extend its gratitude to the Paul-Ehrlich-Institut (PEI) for this incredibly beneficial and productive initiative, which has seen Member States interact closely with regards to the assessment of clinical trials submitted via this process since 2009.

What Can Sponsors Do Now?

The HPRA has the following advice:

1. Sponsors are encouraged to review their current clinical trial portfolios and identify the trials they plan to submit under the Regulation. In preparation for submissions under the Regulation the HPRA, in tandem with the NREC, has launched the Clinical Trials Regulation-National Collaboration Project (CTR-NCP). Interested sponsors can read more about how to get involved in this initiative in the Guide to Clinical Trials Regulation - National Collaboration Project.
2. Sponsors should review their current portfolios to ensure that there are no outstanding submissions relating to the life cycle of any of their trials, for example, end of trial declarations or end of trial summary reports.
3. Sponsors of VHP trials should review any upcoming substantial amendments to determine if these can be submitted in advance of the end of the VHP procedure. This is to avoid individual assessment by the various Member States in the period before the commencement of the CTR.
4. Sponsors should consider how they plan to interact and manage their trials under the CTR and the associated CTIS, as both mark a significant departure from current processes.
5. It is strongly recommended that both commercial and non-commercial/ academic sponsors review the extensive and comprehensive training materials available from the EMA website and monitor both the EMA and HPRA websites for further updates.
6. Sponsors should keep an eye on the HPRA News and Events webpage for the opening of registration for the upcoming HPRA CTR information week planned for November.
7. CTIS interacts with various EMA existing databases and systems such as IAM (register users), OMS (search for organisations) and xEVMPD (search medicinal products). Sponsors must ensure that the relevant data is registered in these databases prior to submitting an initial clinical trial application. Sponsors who are unsure of their OMS registration status can review this on the EMA's Substance, product, organisation and referential portal.
8. An EMA account is required to access the CTIS restricted workspace and users of other EMA applications (e.g. EudraVigilance) can use these log in details to access this. Information specific to registering a Sponsor administrator can be located in the EMA CTIS online modular training programme with particular reference to module 3 and 19 and the accompanying step-by-step guides and video tutorials as well as the latest issue of the EMA CTIS Highlights newsletter. **Registration for high-level CTIS administrators is open as of September 2021.**
9. When considering user registration in CTIS organisations should also give some thought as to whether they wish to assume an Organisation-Centric or CT-Centric approach and more information regarding this can be located in module 7 of the EMA CTIS online modular training programme.

Veterinary Medicines

HPRA Information Day – Implementation of Regulation 2019/6 in Ireland (28 October 2021)

In advance of the application of the new legislation on veterinary medicines on 28 January 2022, the HPRA will host an information day for marketing authorisation holders and manufacturers of veterinary medicines on the implementation of the new requirements. The event will take place on 28 October 2021. This all-day event is focussed on the implementation of the new veterinary regulation as it affects stakeholders in the animal health sector who manufacture or supply veterinary medicines in Ireland. The programme for this event, will include speakers from the HPRA, the Department of Agriculture, Food and the Marine (DAFM) as well as industry, is available to view on the HPRA website. The aim of the event is to update and inform stakeholders on which processes are changing and how the changes will affect them. Ample time will be given for questions to discuss concerns that stakeholders may have.

The HPRA is planning to host the meeting as an online webinar. We regret that it has proved too difficult to hold an in-person event given uncertainties due to COVID-19. Nevertheless, we hope that the virtual meeting will allow participation by the greatest possible number of stakeholders. More details on this event, including details for registration, are available on the HPRA News and Events webpage.

Implementation of Regulation 2019/6 – Update

The HPRA is progressing with its project to implement the requirements of Regulation 2019/6 on the authorisation and monitoring of veterinary medicinal products. The HPRA provides a monthly update on progress on our website. We would encourage marketing authorisation holders to review their own operational processes to ensure that they are in line with new requirements. If you have any queries relating to the implementation of the new legislation, please email newvetreg@hpra.ie.

Applications for Veterinary Medicinal Products for Pets that Qualify for Registration under Article 5(6) of Regulation 2019/6

Article 5(6) of Regulation 2019/6 relates to veterinary medicines for aquarium and pond animals, cage birds, homing pigeons, terrarium animals, small rodents, ferrets and pet rabbits that are kept exclusively as pets. Qualifying medicines were previously exempted under national legislation (e.g. SI. No. 786 of 2007 and prior statutory instruments). However, this will change soon and they will be subject to registration by the HPRA when new national legislation is elaborated before 28 January 2022. The HPRA held a webinar on this topic on 14 May 2021. The webinar recording is available to view. On 29 July 2021, the HPRA published a draft guideline for the registration of qualifying medicinal products under Article 5(6) of Regulation 2019/6. It covers the criteria for registration, provides advice on the administrative aspects of the registration scheme and gives guidance on making an application. However, the HPRA is not in a position to accept applications until the necessary national legislation is available in early 2022.

Update on Implementation of HPRA Report - Method of Supply of Antiparasitic Veterinary Medicinal Products for Use in Food-producing Animals

The HPRA completed the changing of the legal method of supply for antiparasitic veterinary medicinal products for food-producing animals from Licensed Merchant (LM) to Prescription Only Medicines (POM) at the end of July 2021. As mentioned in the report itself and clarified during previous consultations, antiparasitic veterinary medicinal products for bees may continue to be marketed without a veterinary prescription. The HPRA is grateful to the animal health industry for the cooperation in managing this change, which will result in products with either LM or POM liveries co-existing on the market until 28 January 2022. The HPRA published a public notice in a number of newspapers during the week of 19 July 2021 to alert farmers and users to this development.

Marketing Authorisation Holders (MAHs) are reminded to:

- Co-ordinate the supply/importation of stock to ensure the introduction of the amended product labelling and literature as soon as possible. All antiparasitic products for food-producing species that are released for the Irish market must be compliant with the prescription requirement at the latest by 28 January 2022.
- Plan to avoid having large quantities of product in old LM livery in the marketplace in the second half of 2021.
- Inform retailers of the changes.

MAHs with any questions on this matter should contact vetinfo@hpra.ie.

Choosing between EU Authorisation Procedures

Regulation (EU) 2019/6 has opened up the centralised procedure to many types of new products. However, it can be difficult to know whether the complexities involved merit use of this procedure or whether a decentralised procedure is better suited to your needs. We are available to discuss regulatory pathways for new products with applicants.

Currently, the HPRA has some limited availability regarding requests to act as Reference Member State for new decentralised procedures and mutual recognition procedures. If you are considering launching a new product in the EU and wish to access relevant experience from an English-speaking regulatory agency, please contact vetinfo@hpra.ie.

Update on Irish Language Case

In respect of proceedings relating to the provision of bilingual packaging of veterinary medicines in Irish and English languages brought against the Department of Agriculture, Food and the Marine (DAFM) in 2016, the High Court in Dublin gave its Order on 25 June 2021. The Court noted the judgment of the European Court of Justice that the Directive 2001/82/EC language requirement for the labelling of veterinary medicines had been incorrectly transposed into Irish national law, and ordered that the national legislation be amended. The HPRA understands that DAFM has since filed an appeal to the Order. The HPRA will continue to monitor developments in this case.

Staff Changes in the Veterinary Sciences Team

There have been a number of staff changes within the Veterinary Sciences Department in recent months. The following personnel have either left the department or have given notice of intent to do so: Dr Bairbre Sharkey, Dr Penny Huggard, Dr Orla Marron, Dr Joey DeCourcey, Ms Shannon Kieran, Ms Dearbhail NíChúirc, Ms Orla NíDhúbhda and Ms Megan Byrne. The HPRA wishes them all the best in their future careers. Recruitment has commenced to fill the vacancies created. The up-to-date organogram for the Veterinary Sciences Department is available on the HPRA website.

Compliance

Understanding the Definition of a Cosmetic Product: Claims and Uses

Products placed on the Irish market as cosmetic products must meet the definition as stated in Article 2 of the European Cosmetics Regulation (EC) No. 1223/2009:

'any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours'.

Notably, the definition states that the product must be made of a substance or mixture that is placed in contact with the external parts of the human body and the definition specifically identifies those parts. Also, the definition considers the intended purpose or use in respect of a substance or mixture applied to those parts. With that understanding, claims made in relation to a cosmetic product or its ingredients, for example, on the labelling, advertising or marketing materials; including those made on websites, social media, blogs, interviews or other such promotional activities (list not exhaustive), must be consistent with the definition as outlined above.

Medicinal claims, whether explicit or implied, or an intended use that is of a medicinal nature, are not permitted for cosmetic products. Similarly, products that exert or are presented as exerting a pharmacological, metabolic or immunological action in order to restore, correct or modify a physiological function would not be in line with the definition of a cosmetic product. To that end, products which, explicitly or implicitly, claim to cure, alleviate or prevent disease are medicinal products or medical devices subject to how the medicinal benefit is achieved. Please refer to the following sections of the HPRA website for more information:

- Classification of Medicines
- Classification of Medical Devices

The abovementioned definition of a cosmetic product refers to placing the product in contact with the external parts of the body (including the epidermis) with a view to having cosmetic effects on those parts of the body. Therefore, in general the HPRA considers that products intended to be systemically absorbed and/or to have effects at depths below the epidermis or, for example, to act on muscles, would not be appropriate to place on the market as cosmetic products.

Furthermore, Article 2 of Regulation (EC) No. 1223/2009 states:*'...a substance or mixture intended to be ingested, inhaled, injected or implanted into the human body shall not be considered to be a cosmetic product'*. Therefore, any product that is intended for use by injection, including if administration by injection

could be implied or facilitated by how the product is packaged or presented, would not meet the definition of a cosmetic product.

The justification for all claims made about a cosmetic product must be recorded in the Product Information File in order to meet the requirements of Regulation (EU) No. 655/2013 (the claims regulation). The approach of the *Technical Guide for Cosmetic Claims,* published in 2017, should also be applied. More guidance about making cosmetic products available on the Irish market is available from the HPRA and European Commission websites at the following links:

- For those manufacturing cosmetics, importing cosmetics or selling cosmetics of their own brand name: http://www.hpra.ie/homepage/cosmetics/regulatory-information/making-importing-or-selling-cosmetic-products-in-ireland
- For distributors or retailers: http://www.hpra.ie/homepage/cosmetics/regulatory-information/selling-cosmetic-products-in-ireland
- For links to the relevant European legislation and guidance: https://ec.europa.eu/growth/sectors/cosmetics/legislation_en

Any queries in relation to this topic should be sent to cosmetics@hpra.ie.

Updates to Active Substance Registrations – When to Notify Manufacture of a New Active Substance

The manufacture of new active substances is required to be included on the manufacturer's active substance registration (ASR). Different notification requirements ensue depending on the significance of the introduction of the new active substance to manufacturing activities.

Immediate notification

Immediate notification of the manufacture of a new active substance is required if it differs from active substances already listed in the manufacturing operations of the company's ASR. Examples include:

- Introduction of highly potent, sensitising active substances;
- Introduction of new technology or significant process changes.

Annual notification

An annual update can be used to include new active substances in the registration if the synthetic processes, processing equipment and cleaning or containment measures are similar to active substances already included in the registration.

The HPRA's Guide to Managing Changes to Registration for Active Substance Manufacturers, Importers and Distributors gives further examples of changes requiring immediate notification and those that are required to be communicated by annual update. The guidance outlines supporting information to be submitted, including details of process validation studies performed or planned. Where the manufacture of an active substance meets the criteria to be communicated through an annual update, the update should be made after the completion of successful process validation. The application forms are available via the following links:

Immediate notification

Annual notification

Active substances under development or manufactured only for use in clinical trials do not need to be included in the ASR.

Queries should be sent to compliance@hpra.ie.

Cross-contamination Control and GMP Inspection Findings

Use of Permitted Daily Exposure (PDE) Limits in Cross-contamination Control

Requirements for using health-based exposure limits (HBELs) and toxicological evaluations to support maximum allowable carryover limits for products manufactured in shared facilities are specified in Chapters 3 and 5 of the European Commission Guide to GMP. The primary method of conducting the toxicological evaluation is through the determination of a PDE value. This represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at, or below, this dose every day for a lifetime. The EMA documents below provide guidance as to how this value should be determined:

- EMA/CHMP/CVMP/SWP/169430/2012: Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
- EMA/CHMP/CVMP/SWP/246844/2018: Questions and answers on health-based exposure limits and cross-contamination

The annex to guideline EMA/CHMP/CVMP/SWP/169430/2012 outlines how the PDE determination strategy should be documented and summarised for presentation during GMP inspections.

Maximum Allowable Carryover (MACO) Residue Calculations

One common approach to determine the MACO of a residue into the next product using the PDE value is to multiply the PDE value by the next product minimum batch size and divide by the maximum therapeutic daily dose of the next product. The minimum next product batch size gives the highest concentration of the contaminant within the batch. The maximum therapeutic daily dose of the next product reflects the maximum possible amount of contaminant that could be ingested by the patient per day.

Attention should be given to the units for this part of the calculation; these should be consistent for both the numerator and the denominator. The batch size and maximum therapeutic daily dose of the next product can be expressed in either weight or the number of individual dosage units.

If the next product batch size and maximum therapeutic daily dose are expressed in weight, the value used for the next product maximum therapeutic daily dose should reflect the weight of the entire dosage unit. Using the weight of the active pharmaceutical ingredient (API) only rather than the entire dosage weight results in an overestimation of maximum allowable carryover limit by a factor equivalent to the concentration of the API within the dosage unit. As any residual contaminant would be present in the entire drug product formulation of the next product, it is the entire dosage weight of the next product that is representative of what would be ingested by the patient.

Deficiencies Cited during Inspection of Calculations used in Cleaning Studies

Using the weight of API rather than the entire dosage weight of the next product in MACO calculations has been cited as a deficiency during inspections of cleaning studies.

Other calculation based deficiencies cited during the review of cleaning studies include the following:

- The volume of rinse solution used was not taken into account in the determination of the acceptance criteria for rinse samples.
- The rinse volume outlined in the calculation to determine the acceptance criteria for the rinse sample did not reflect the actual rinse volume used.
- The value used for the total shared equipment surface area did not include all relevant shared product contact surfaces.
- The surface areas of certain swab locations were less than the required surface area for swabbing (e.g. 25cm^2); this resulted in the acceptance criteria being disproportionately high relative to the samples taken for these locations.
- Swab recovery studies were not performed for all types of surfaces swabbed.
- The recovery factor identified in swab recovery studies was not applied in the determination and reporting of swab results.
- The validated limit of detection and limit of quantification were above the residue limit acceptance criteria.
- A veterinary manufacturing site used a human (50kg) bodyweight to scale the PDE value, which was not reflective of the worst-case target species and not in line with the requirements of the EMA's *Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.*
- An active substance manufacturing site applied the maximum allowable carryover limit for the product as the acceptance criteria for individual pieces of equipment within the equipment train; this resulted in the acceptance criteria for the total cumulative carryover residue in the equipment train to be overestimated by a factor equivalent to the number of individual pieces of equipment within the train.

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