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HPRA MEDICINAL PRODUCTS NEWSLETTER

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Human Medicines

Environmental risk assessment for human medicines

The EMAs Environmental Risk Assessment guidelines will come into effect on 1 September 2024. The development of these guidelines has been a long process with the concept paper for the initial revision guideline being published in 2016. A further draft revision was then published in 2018.

The HPRA has been involved in the drafting group since 2017 through our role in the Non-Clinical Working Party. We are also currently of this Working Party group having taken on the role at the end of 2021.

The HPRA is currently planning additional ERA training with other regulatory agency stakeholders to help industry professionals understand the guidelines. To read the guidelines in full visit the EMA website.

Implementation period for product information updates

For product information updates that are submitted by IA variation, the implementation date is when the company internally approves (to be ready for use in the company) the revised product information. The revised product information should then be used in the next packaging run. However, to assist companies transition to the revised product information, it is acceptable for batches that are currently in production at the time of the update, and where it may not be possible to substitute the revised product information, that the previous version of product information can be used.

Companies should be batch releasing only product with the revised product information as soon as possible, and no later than 6 months (the implementation period), after the implementation date. In exceptional circumstances, where batch release of product with the previous product information is required after the 6 months implementation period, the company should apply to the HPRA for a batch specific request where the acceptability of extending the implementation period will be evaluated.

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An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Clinical trials – Important dates and information

The HPRA would like to remind clinical trial sponsors of the following dates and deadlines in relation the Clinical Trails 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.

Sponsors of clinical trials expected to continue after 30 January 2025 must consider the time required for Member States to complete the authorisation procedure, which can take up to three months. To help streamline the process, Member States will implement, where possible, an expedited procedure for transitioning trials to the CTR.

An end of trial form should be completed to inform whether the clinical trial has been completed or never started.

Ongoing clinical trials do not need to be halted or ended during the transition from the Clinical Trials Directive (CTD) to the CTR.

Sponsors can avail of training supports to assist in making the transition from the CTR section of the HPRA website. The EMA also have a dedicated clinical trials section on their website where sponsors can find additional training and supports.

The application of the CTR strengthens Europe as an attractive location for clinical research. The regulation streamlines the processes for the application, approval, and supervision of clinical trials. In addition to this, clinical trial sponsors use the same system and follow the same procedures to apply for the authorisation of a clinical trial, no matter where they are located and which national competent authority (NCA) or national ethics committee they are dealing with.

The HPRA recently highlighted this message at the Health Research Board's, National Clinical Trials Office (NCTO), International Clinical Trials Day event held in UCD in May. The presentation also covered HPRA clinical trials activity, relevant EU updates and supports to sponsors related to trials across medicines, devices, and in vitro diagnostics.

'If you have any queries in relation to clinical trials or wish to engage with us on this topic, you can email clinicaltrials@hpra.ie

Applying for a national product or DCP authorisations in Ireland – Slot booking

The HPRA is transitioning towards a system of slot allocation (expected submission dates) for new national product and DCP authorisation applications. Applicants will be given a submission slot in an agreed month.

Submitting applications in an agreed month will help with planning and scheduling for timely assessment of applications. It will also help maintain access for products on the Irish and European markets.

To find out how to request a slot see the following guides:

- Guide to Submitting a Request for a New National Application Procedure for a Human Medicinal Product
- Guide to Submitting a Request for Ireland to Act as RMS in a DCP for Human Medicines

While the HPRA are adapting to this new process we will try to facilitate applications which require an earlier start date.

Due to the complexities of Article 10a applications ('Well established use' applications), applicants should obtain national scientific advice before submitting requests for such new applications. Further information can be found on our national scientific and regulatory advice page.

Furthermore, IE routinely participates as a Concerned Member State (CMS) in standard DCP procedures. A zero-day procedure as a CMS may be possible for medicines where Ireland is experiencing a critical shortage of a particular medicine.

Product information changes

The HPRA is reminding applicants that for on-going simultaneous variations impacting on product information, they are responsible for ensuring the final updated national texts are submitted to the HPRA once a variation is complete.

Applicants should also note that following the issue of all variations impacting product information, the updated SmPC and package leaflet will be published on the HPRA website. This product information normally takes 24 hours to update on the website.

Marketing authorisation holders are requested to check the final version of the SmPC and package leaflet when published or updated on the HPRA website to ensure the updated information is accurate.

If any errors are noted, the HPRA should be contacted as soon as possible to ensure the error is corrected.

Mutual Recognition and repeat use procedure – Proof of payment

Applicants are reminded that they can add additional concerned member states (CMS) to approved procedures. Requests to include additional CMS relative to the original procedure can be submitted at any time to the HPRA. This procedure is known as a repeat use procedure.

Requests for repeat use must be sent to RMS@hpra.ie approximately 90 days before submission to the CMS. The HPRA will then contact applicants outlining the next steps in the procedure. Applicants should note that proof of payment should accompany any returned pre-submission documents. For further fee information, please visit our medicines fees webpage.

Veterinary Medicines

G.I.18 VRAs – Guidance on submissions

Marketing authorisation holders have until 29 January 2027 to update the product information of existing products to comply with the requirements of Article 152 of Regulation 2019/6 in terms of format and content. This update is implemented by way of a G.I.18 variation requiring assessment (VRA) and the timing of submission should ensure that the variation is finalised and implemented before 29 January 2027 deadline.

The HPRA acknowledges the volume of work remaining and recognises the resource limitations for both marketing authorisation holders and national competent authorities (NCAs). To accommodate this, the HPRA along with colleagues in the European network have adopted core principles to facilitate the efficient processing of G.I.18 variations.

The scope of the G.I.18 variations will be limited to QRD alignment only. Alignment with recently published scientific guidelines or Article 13 labelling requests will not be permitted under the submission scope.

Marketing authorisation holders are requested to avoid the submission of grouped G.I.18 variations to avoid delays in approval. A standard 90-day timetable will apply for assessment. However, clock-stops will be reduced to 30 days for marketing authorisation holders to provide responses and 30 days for assessment of same responses.

The HPRA will adopt the use of a simplified assessment report with integrated PI document, where required editorial amendments will be tracked. As agreed with our European colleagues, the RMS will assume primary responsibility for the evaluation of the proposed G.I.18 alignment variation for products authorised by mutual recognition/decentralised procedures. Only in exceptional circumstances can a CMS comment on the submission.

The collaborative efforts of marketing authorisation holders and the HPRA in the practical application of these principles will facilitate the closure of these G.I.18 variations at the earliest possible stage.

These core principles will be communicated by way of a guidance document by the Coordination Group for Mutual Recognition and Decentralised Procedures for Veterinary Medicinal Products (CMDv) in due course. In the meantime, any queries relating to the submission/processing of G.I.18 variations should be addressed to vetinfo@hpra.ie

Implementation deadline for G.I.18 VRAs also applicable to products already in the distribution chain

The European Commission clarified at a meeting of the Standing Committee in February that, in accordance with Regulation (EU) 2022/839, batches compliant with the packaging and labelling requirements set out in the Regulation (EC) No 726/2004 and Directive 2001/82/EC, can continue to be released until 29 January 2027. Batches released thereafter must be compliant with the labelling and packaging requirements under Regulation (EU) 2019/6.

Introduction of "Umbrella" type variations

The submission of a single "umbrella" variation requiring assessment (VRA) which covers the main change along with any consequential variations not requiring assessment (VNRAs) or VRAs is now possible for products registered under mutual recognition, decentralised and national procedures. For the immediate future, applications will be limited to certain scopes.

An example of one commonly submitted VRA that will benefit from this new approach is the addition to the dossier of a finished product manufacturing site for finished product manufacture, primary and secondary packaging, and batch release. Such a change will now require the submission of a single VRA (F.II.b.1. z) in lieu of 1 x VRA (F.II.b.1.c) & 3 x consequential VNRAs (B.20, B.21, B.24.a).

Further information along with a full list of acceptable "umbrella" type VRAs is available within Q&A 4.20 of the CMDv's Q&A - List for the submission of variations according to Regulation (EU) 2019/6.

Introduction of super grouping and widened scope of technical grouping of VNRAs

Marketing authorisation holders are advised that the concept of "super grouping" has been introduced for Variations Not Requiring Assessment (VNRAs). This follows the publication of the 5th revision of the CMDv Best Practice Guide for Variations Not Requiring Assessment.

Purely national marketing authorisation (MAs) in different Member States or mutual recognition/decentralised products with different reference Member States (RMSs) can now be combined under a single submission. Much like the current work-sharing procedure, marketing authorisation holder must contact the proposed "lead-RMS" to confirm acceptance to act as Lead-RMS at least 14 days before the intended submission date. Examples of acceptable super grouping can be found in the CMDv Best Practice Guide.

Regarding technical grouping, all products (MRP/DCP and purely national) of one decision making authority and

one marketing authorisation holder may be grouped in one submission provided that all VNRAs in this submission apply to all products identically. In addition to this the data and documentation submitted must be the same.

With the increased functionality of the Union Product Database (UPD), the scope of technical grouping has been widened. Examples of acceptable technical groupings are available in the best practice guide.

Update on the joint labelling initiative

The HPRA and the Veterinary Medicines Directorate (VMD) have successfully operated a bilateral joint labelling procedure for over 20 years. This was challenged in recent years with the UK's withdrawal from the European Union (EU) and the subsequent implementation of Regulation (EU) 2019/6. These challenges resulted in significant changes to requirements for the labelling and package leaflets of veterinary medicinal products authorised in the EU.

However, following a revision of UK national legislation, the VMD has advised that their national product information templates can be used by applicants when applying for initial national Marketing Authorisation (MA) applications or when updating the product information of existing MAs under a G.I.18 Variation Requiring Assessment (VRA). The UK product information template v.3 has harmonised the UK labelling requirements with the EMA annotated version 9 QRD templates, which are applicable in Ireland. The VMD are accepting applications using product information template v.3 as of 29 April 2024.

Ahead of the revision of the UK legislation, the interim position as agreed by the HPRA and VMD in June 2023 will still apply for a transitionary period. Further details on this position are available in the Joint HPRA/VMD Guide to Acceptable Texts for Joint Labelling for Veterinary Medicinal Products for use in Ireland and the UK.

Marketing authorisation holders are reminded that the HPRA will not accept requests under Article 13 for additional information on the label other than those detailed in the joint HPRA/VMD guide unless under exceptional circumstances. Therefore, if a marketing authorisation holder wishes to retain/obtain joint labelling, it is strongly advised that no additional information is requested under Article 13.

This welcome development will ensure the continued availability of veterinary medicinal products on both the Irish and UK markets.

Provision of labelling mock-ups for joint assessment

In the second half of 2023, the HPRA communicated to stakeholders that, as part of a revised process, mock-ups for newly granted marketing authorisations would be reviewed under a separate G.I.15z variation. This process expediated the issuance of marketing authorisations and facilitated the co-ordination of a mock-up review with product launch for the concerned marketing authorisation holders.

Recently the UK Veterinary Medicines Directorate (VMD) adopted the same approach. On the completion of new marketing authorisation applications (MAAs) in the UK and IE and where marketing authorisation holders advise that they wish to obtain a joint UK/Ireland label, the HPRA and VMD will require the submission of a G.I.15z VRA to both agencies to facilitate joint assessment of mock-ups prior to marketing.

The streamlining and enhancement of the joint labelling process following the completion of new MAAs will lead to more efficient timelines and greater predictability for marketing authorisation holders.

SPC harmonisation - Action for generic/hybrid MAHs of Domosedan Solution for Injection

As part of 2023 SPC harmonisation exercise of the Coordination Group for Mutual Recognition and Decentralised Procedures for Veterinary Medicinal Products (CMDv), the procedure for Domosedan 10 mg/ml Solution for Injection for horses and cattle concluded on 2 May 2024.

Marketing authorisation holders of all generic/hybrid products have until 1 July 2024 to submit a variation requiring assessment to align the SPC (concerning target species, clinical information referred to in point (c) of Article 35(1) and withdrawal period) of their product.

In the case of hybrid marketing authorisations, where parts of the SPC have been supported by product-own data (for example additional target species or a withdrawal period), the information in the SPC based on product-own data will not be harmonised. More information can be found in the CMDv's best practice guide for the harmonisation procedure of the SPC of generic/hybrid veterinary medicinal products.

Any questions relating to the submission of the required variation, where the HPRA is an RMS (MRP/DCP) or NCA (NAP) for the affected products, should be sent to vetinfo@hpra.ie.

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

The HPRA will host an Information Day on Thursday 14 October 2024 for marketing authorisation holders of veterinary medicines on the implementation of the Regulation and associated national legislation. The planning for this all-day in-person event is ongoing. The event will be focussed on developments related to the implementation and its effects on stakeholders in the animal health sector in Ireland. The event will run as a hybrid event, with limited availability for in person attendance at a Dublin city centre venue.

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.

Publication of veterinary medicines shortages on the HPRA website

The HPRA has recently began publishing information in relation to shortages of veterinary medicines. This information is relevant vets, pharmacists, and licensed retailers who need up-to-date information about medicines currently available to treat animals.

The HPRA publishes an updated list on a periodic basis, as new information becomes available. The list includes information provided by marketing authorisation holders to the HPRA or to the Department of Agriculture, Food, and the Marine.

To view the list of veterinary medicines shortages, visit our veterinary shortages page. We have also published an additional page about veterinary medicinal shortages which includes information about the HPRA's role in veterinary shortages and how shortages are managed in Ireland.

Compliance

Importation of exempt medicinal products by the holder of a Wholesale Distribution Authorisation (WDA)

An 'exempt medicinal product' (EMP) is a medicine that does not hold a marketing authorisation for the Irish market but may be supplied to Irish patients under certain conditions. These conditions are set out in paragraph 2 of Schedule 1 of S.I. 540 of 2007 Medicinal Products (Control of Placing on the Market) Regulations 2007.

This legislation states that an EMP may be sold or supplied 'in response to a bona fide unsolicited order, formulated in accordance with the specifications of a practitioner for use by his individual patients on his direct personal responsibility, to fulfil the special needs of those patients'.

Paragraph 2 of Schedule 2 of the Medicinal Products (Control of Wholesale Distribution) Regulations 2007 also details the requirements for Wholesaler Distribution Authorisation (WDA) holders with respect to the wholesaling of EMPs.

Before the Medicinal Products (Control of Placing on the Market) (Amendment) Regulations 2019 (S.I No. 218 of 2019) was introduced in May 2019, only the holders of Manufacturer's Authorisations (MIAs) in Ireland could import EMPs directly from non-European Economic Area (EEA) countries. However, this amendment now permits wholesalers to do so on the provision that the **products sourced from non-EEA countries are only for supply to patients in Ireland**.

This means that WDA holders that physically import EMPs under their WDA are responsible for ensuring that these products remain in the Irish market and are not onward supplied outside of the State. Therefore, companies that import EMP products under their WDA should only supply entities that are entitled to supply an EMP to the public in Ireland, e.g. retail pharmacy businesses, hospital pharmacies, registered medical practitioners etc.

The only exception to this may be where the WDA entity that has imported the EMP supplies it to another WDA holder in Ireland that is part of the same parent company. In that regard, adequate control and oversight is expected to ensure that the further supply of the imported EMP is only within the State.

GMP records for receipt of materials

The GMP inspectorate continues to see a trend in deficiencies observed during inspection of records for receipt of deliveries. These deficiencies include incomplete records for label verification against an approved supplier list and other delivery documentation, as well as inaccuracies between the supplier of the material and the approved supplier in the company quality system.

To facilitate a review of processes and ensure compliance, the HPRA is reminding manufacturers of specific GMP related requirements in the EU Guide to GMP.

- Chapter 4, paragraph 4.22 stipulates there should be written procedures and records for the receipt of each delivery of each starting material (including bulk, intermediate, and finished goods), primary, secondary, and printed packaging materials.
- Paragraph 4.23 of Chapter 4 also details specific checks that should be included in receipt records.
- Chapter 5, paragraph 5.30 also stipulates that there should be a record of receiving checks on each delivery. Like the requirements outlined in Chapter 4, this paragraph stipulates that 'for each delivery of starting material the containers should be checked for integrity of package, including tamper evident seal where relevant, and for correspondence between the delivery note, the purchase order, the supplier's labels and approved manufacturer and supplier information maintained by the medicinal product manufacturer.'
- Section 7.2, of Part II, requires labels of containers be examined upon receipt.

In relation to imported products, section 5 of Annex 21 gives further clarity on the documentation needed for imported products. These documents include freight and customs documentation, listing both the site of origin and site of physical importation.

Records review

Manufacturers and batch certification sites are required to ensure that the material receipt process and management of associated records meet the GMP requirements outlined. They should also ensure that records are available for review during regulatory inspections.

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