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Clinical Trials Regulation

A new EU Clinical Trial Regulation (Regulation No 536/2014, referred to as 'CTR'), was adopted on 16 April 2014 and became applicable on 31 January 2022.

The CTR is designed to benefit patients and medical research in Europe by streamlining the approval of clinical trials across the EU Member States, while also maintaining the highest standards of safety for participants.

Key features of the new Clinical Trial Regulation include:

- Single submission and approval of mononational and multinational clinical trial applications through an EU 'Clinical Trial portal and database' (known as the Clinical Trial Information System (CTIS), hosted by the European Medicines Agency (EMA);
- Identical rules for conducting clinical trials throughout the European Union (EU);
- Increased efficiency of the approval process for clinical trials, with a lead 'reporting' Member State;
- Strictly defined timelines for assessment;
- Transparency rules requiring publication of assessment and inspection reports;
- A single fee per Member State.

In addition, manufacturing processes that come under the CTR Article 61(5) exemptions are required to be registered with the HPRA and to meet appropriate and proportionate requirements. Further information is available in the HPRA guide linked below.

This article is a brief introduction to the CTR and its implementation in Ireland. It should be read in conjunction with EU and national legislation, European Commission and EMA guidelines, in addition to the HPRA Guide to clinical trials conducted under the CTR in Ireland. The HPRA guide provides detailed information and a comprehensive list of references and resources.

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HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Transition

Key dates for transition to CTR are as follows:

From 31 Jan 2022	Application of CTR and go-live of CTIS
From 1 April 2022	Launch of application process for Article 61(5)
April to September 2022	Consultation process on national requirements for Article 61(5) processes
September 2022	Publication of national guidance setting out the appropriate and proportionate requirements for Article 61(5) processes
Up to 31 January 2023	Sponsors/applicants can submit new clinical trial applications under either the CTD (Directive 2001/20/EC) or the CTR
From 31 January 2023	New applications can be submitted under CTR only
Up to 31 January 2025	Substantial amendments to trials authorised under the CTD can be submitted for up to three years
By 31 January 2025	All ongoing clinical trials must transition to the CTR

Important changes to clinical trials

Clinical Trials Information System

The Clinical Trials Information System (CTIS) is an EU submission portal and database hosted by the EMA and designed to support the application of the CTR. All clinical trial applications under CTR and all communications between sponsors and Member States (MSs) take place through CTIS.

Sponsors, MSs, the EC and the public have access to different parts of CTIS, which went live on 31 January.

The EMA has published training material for CTIS. Further information is available on the HPRA webpage for the Clinical Trials Regulation.

Transparency

The CTR intends to increase the transparency of clinical trial activity in the EU by allowing stakeholders, including patients, to use CTIS to access information on trials conducted in the EU.

The clinical trial protocol, investigator's brochure, assessment report and inspection reports, if relevant, will be publicly accessible with certain exceptions relating to personal, commercially confidential data and confidential communications amongst Member States. Sponsor requests for deferral of publication of certain trial-related information will be subject to strict timelines as set out in the CTR.

Authorisation process

The sponsor will decide which Member States (MSs) to include in their application. These are referred to as 'Member States Concerned' (MSCs). The sponsor can also nominate an MSC to be the lead or 'Reporting Member State' (RMS).

Sponsors have the option of submitting their application in two phases up to two years apart and can add additional MSs as MSCs.

There are two parts to the assessment:

- Part I includes assessment of the protocol, investigator's brochure and investigational medicinal product dossier (IMPD). Assessment of these documents, within EU-mandated timelines, is led by the RMS, with MSCs providing comments.
- Part II includes assessment of the subject information and informed consent documents, the suitability of the investigator and of the trial site, indemnity and data protection. This assessment is done at national level by each national ethics committee.

Each MSC will consider the RMS's conclusion on Part I, and the ethics committee's opinion on Part II, and issue their single national decision via CTIS. A trial cannot be commenced in an MSC until the single national decision has been issued.

Risk-proportionate approaches and low-intervention trials

Risk-proportionate approaches, including the concept of 'low intervention' clinical trials, have been introduced in the CTR. Sponsors should indicate in the cover letter of the clinical trial application if they consider a clinical trial to be a low intervention trial and must provide detailed justification thereof.

Implementation in Ireland

National legislation

In Ireland, the CTR is directly implemented but certain aspects have been addressed in national legislation and guidance. The national legislation does not introduce requirements over and above those outlined in the CTR.

Trials authorised under the CTD (implemented nationally as SI No 190/2004) must transition to the CTR by 31 January 2025, when EU and national legislation will be repealed.

Coordinated review

In Ireland, a coordinated procedure for scientific and ethical assessment of clinical trials has been developed by the HPRA and the recently formed National Office for Research Ethics Committees (hereafter 'National Office', www.nrecoffice.ie), in conjunction with the Department of Health. The National Office has established two National Research Ethics Committees (NREC) to review clinical trials. This procedure is set out in national legislation.

The respective roles are as follows:

- The HPRA will be responsible for the scientific assessment (Part I) with input from the NREC on ethical matters.
- The National Office in conjunction with the NREC will be responsible for the Part II assessment.
- The HPRA will submit the single national decision for Ireland on a new application via CTIS, both on its own behalf and on behalf of the National Office and the NREC.

This coordinated procedure will lead to a timely single national decision

for Ireland on the scientific and ethical aspects of an initial clinical trial application. This is a positive development for sponsors conducting research in Ireland and for clinical trial participants.

Applications

A sponsor/applicant wishing to conduct a clinical trial in Ireland under the CTR should apply in CTIS. Applications should not be sent directly to the HPRA or the National Office. Proof of payment is required as part of the application dossier in CTIS.

Communications

All communications with the HPRA and the National Office relating to a clinical trial application or an authorised clinical trial under CTR should be sent via CTIS. Documents or responses should not be sent directly to the HPRA or the National Office, unless specifically requested. Responses from the HPRA or National Office will be sent via CTIS.

Language

An application to Ireland and all documents and communications before, during and after a clinical trial, must be in the English language.

Labelling

The labels for both IMPs and AxMPs must comply with the labelling requirements set out in Chapter X of the CTR. The labels must be now included in the application dossier. A list of information, which must be provided on the outer packaging and immediate packaging, is set out in Annex VI of the CTR.

The labelling text for investigational and auxiliary medicinal products, if any, must be in English. Other languages may be included. However, as far as possible, the full text for each language should be placed together on the label, rather than placing all language versions of each statement together.

Sponsor

Established in EEA

The sponsor of a clinical trial does not need to be located in an EU Member State, but Irish legislation continues to require that the sponsor, or the legal representative of the sponsor of a clinical trial in Ireland, must be established within the European Economic Area.

Delegation

The sponsor may delegate any or all of their trial-related duties and functions to another person or organisation. Any duties or functions delegated to a third party must be documented and specified in writing. The sponsor remains ultimately responsible for ensuring that the conduct of the trial and the data generated complies with the CTR and Irish legislation.

Co-sponsors

The CTR recognises that, in practice, there may be networks of researchers or research institutions conducting a clinical trial jointly and may be considered co-sponsors. However, to uphold the sponsor responsibilities in a clinical trial as per the legislation and ICH-GCP, where a clinical trial has more than one sponsor, they should all be subject to the obligations of a sponsor under the CTR. They can be delegated specific responsibilities of the sponsor by contractual agreement. This may be particularly relevant for non-commercial (academic) sponsors conducting clinical trials in Ireland.

Investigator

The NREC is responsible for determining the suitability of a clinical trial investigator and the quality of the facilities at the clinical trial site. Under Irish legislation, an investigator must be a registered medical practitioner or a registered dentist. The investigator and the sponsor may be the same person.

Subject information and the informed consent procedure

Irish legislation requires that the subject information and informed consent procedures should be in accordance with Chapter V of the CTR. The national legislation has introduced some changes to informed consent procedures, outlined below in brief.

Legally designated representative for incapacitated subjects

The definition of the 'legally designated representative' for an incapacitated subject has been expanded to include family members, or persons with a personal relationship with the subject, or if either one of these is not available or is unwilling to provide consent, a medical practitioner who is primarily responsible for the medical treatment of the proposed subject. In all cases, the person or medical practitioner acting as a 'legally designated representative' should be able to provide an interpretation of the will and preferences of the proposed subject.

Minors

In the case of a minor, a 'legally designated representative' (definition as above) should provide consent, but assent of the minor should also be obtained where a minor is capable of forming an opinion and assessing the information relevant to the clinical trial.

Emergency clinical trials

For clinical trials in emergencies due to sudden life-threatening or serious medical conditions, informed consent may be obtained and information provided on the clinical trial after the investigator's decision to include the subject in the clinical trial. This can be done provided that the decision is taken at the time of the first intervention on the subject, in accordance with the protocol, and if the conditions outlined in Article 35 of the CTR are fulfilled.

Simplified informed consent for cluster trials

Irish legislation makes provision for informed consent to be obtained by simplified means for clinical trials where groups of subjects rather than individual subjects are allocated to receive different IMPs. The IMPs must be used in accordance with the marketing authorisations, and the individual subject receives a standard treatment regardless of whether they accept or refuse to participate in the clinical trial, or withdraws from it. Therefore, the only consequence of non-participation is that data relating to them are not used for the clinical trial. Such clinical trials, which serve to compare established treatments, must be conducted in Ireland if they are authorised in Ireland – i.e., they are always mononational trials.

Prior interview – registered medical practitioner, dentist or nurse

Under Irish legislation, the interview performed prior to obtaining informed consent can be conducted by the investigator, or by a registered medical practitioner, registered dentist or registered nurse, who the investigator deems as appropriate to conduct the interview. This individual can take consent.

Clinical trial summary (end of trial) report

The sponsor is required to submit the results of the clinical trial via CTIS within one year from the end of the trial in all MSCs. The results should not be submitted to the HPRA.

The results comprise two summaries:

- A summary of the results;
- A summary written in a manner that is understandable to laypersons.

Fees

There will be a single fee per activity (e.g. new application or substantial modification) per MS. In Ireland, the fee should be paid to the HPRA, who then forward a portion of this fee to the National Office. Proof of payment of the fee should be submitted with the clinical trial application to CTIS. A small administrative fee will be charged to non-commercial sponsors.

Clinical trials transitioning from the CTD to the CTR will not incur a fee, but a fee will be charged for the next regulatory activity under the CTR, such as, for example, a substantial modification.

The HPRA and the National Office conducted a fee consultation in Q3 2021 and the outcome of the consultation process was published on the HPRA website. Fees for clinical trials are reviewed annually.

Safety reporting for clinical trials

Suspected Unexpected Serious Adverse Reactions (SUSARs) – changes

From 31 January 2022, dual reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) from clinical trials in Ireland authorised under the CTD to both the HPRA and Eudravigilance Clinical Trials Module (EVCTM) will no longer be required. Submission to EVCTM alone will be considered sufficient (as per 'final arrangements' as outlined in section 7.4.3 of CT-3).

Sponsors should note that SUSARs for clinical trials authorised under the CTD are still required to be submitted to the ethics committee in line with the requirements of SI No 190/2004.

For clinical trials in Ireland authorised under the CTR, submission of SUSARs to EVCTM alone will be sufficient to meet the relevant regulatory safety reporting requirements.

Developmental safety update reports or Annual Reports

Developmental safety update reports (aka Annual Safety Reports, ASRs) for clinical trials authorised under the CTR should be submitted through CTIS, and should not be sent to the HPRA or the NREC.

Sponsors submitting ASRs for active substances for which they have at least one trial authorised under the CTR can submit through CTIS. Such a submission is sufficient to cover the HPRA's annual safety reporting requirements for that sponsor's clinical trials authorised under both the CTD and CTR.

ASRs for Clinical Trials under the CTD only are still required to be submitted to both the HPRA and the National Office, in line with the requirements of SI No 190/2004.

Implementing Regulation on coordinated safety assessment in clinical trials (EU) 2022/20

The Implementing Regulation on coordinated safety assessment in clinical trials was adopted by the European Commission on 7 January 2022 and has now been published in the European Commission official Journal (see: EUR-lex).

This Regulation outlines the legal framework for the implementation of coordinated safety assessment between Member States as mandated in Article 44 of the CTR. It defines the new role of safety assessing member state (saMS) and the new process of SUSAR screening. In future, the assessment of safety for active substances in clinical trials in more than one EU MS will be coordinated by the saMS, and the saMS may request further information from the sponsor following the identification of a safety concern in SUSAR or assessment.

Supervision of clinical trials authorised under the CTR

Corrective measures

The HPRA and the National Office, in conjunction with the NREC, will be responsible for the supervision of authorised clinical trials. In response to breaches of the CTR, the HPRA is empowered under national legislation to take corrective measures such as revocation or suspension of a clinical trial authorisation, or to require the sponsor to modify any aspect of the clinical trial. Unless immediate action is required, the sponsor and/or investigator will be given the opportunity to provide an opinion within a seven-day time limit (calendar days).

The HPRA may consult with the National Office, the NREC and with other MSs before taking a corrective measure. If a corrective measure is taken, the HPRA will notify the MSCs via CTIS.

Serious breaches

The CTR introduces a requirement for the sponsor to report serious breaches through CTIS without undue delay and within seven calendar days of the sponsor becoming aware of the breach. Serious breaches will be reviewed by the HPRA and, if necessary, by the National Office and the NREC. The HPRA will decide whether corrective measures are required. Regulatory actions may be taken by the HPRA if necessary. These include inspections and/or corrective measures.

HPRA guide

The HPRA published a guide to clinical trials conducted under the CTR in Ireland. Please read the guide in conjunction with the legislation, and the European Commission and EMA guidelines.

Queries

Please send queries to the relevant email address listed below.

Clinical trials authorised under the CTD: clinicaltrials@hpra.ie

CTR and CTIS: CTReg@hpra.ie

Ethical aspects: nationaloffice@nrec.ie

Human Medicines

Fees for variations – frequently asked questions

Recently, the HPRA has received an increased number of queries about variation fees through the submissions@hpra.ie mailbox. The information below provides responses to frequently asked questions. In addition, please consult the HPRA's guide to fees for human products to identify the correct fee category for authorisation applications.

Reduced fee

A reduced fee only applies for every third and subsequent product within a product range or where the changes do not impact the Irish product. For example, where a product range has four strengths, and the variation category B.I.Z. is applied for, the full fee is applied to the first two products and the reduced fee is applied to the remaining two products.

Bulk fee

Where there are multiple Type IB/II variations to one or more products (within an MA range) the bulk fee will apply.

Outgoing IA

The new outgoing type IA supplement fee only applies to variations for standalone Type IA applications where Ireland is the Reference Member State (RMS) and there are Concerned Member States (CMS) involved in the procedure. If there is no CMS involved in the variation, no supplement fee applies.

The supplement fee applies to each product range. For example, if multiple product ranges are applied for, a supplement fee will be charged per product range where another CMS is involved.

If a Type IB and IA variation is applied where Ireland is the RMS, no outgoing Type IA supplement fee applies to the Type IA variation but the outgoing type IB supplement fee will apply.

Veterinary Medicines

Implementation of Regulation 2019/6 – general update

Regulation 2019/6 applied throughout the European Union from 28 January 2022. The HPRA has been working over recent months to ensure that the changes to our work processes, guidelines and forms are in place to give effect to the new requirements. However, as new national legislation to complement the regulation is not yet available and we have been working to ensure go-live readiness for key processes, it was not possible to update all documents by the end of January. If you cannot locate a form or updated guidance on our website, email vetinfo@hpra.ie.

The Department of Agriculture, Food and the Marine (DAFM) has informed the HPRA that the new national legislation required to support the implementation of the new veterinary regulation will be made available in three parts, one of which will require an amendment of the primary legislation. While certain legislation is available from 28 January 2022, two components will be delayed until end of Q2 2022. Further information is expected to be available on the DAFM website. The DAFM has updated its list of questions concerning the changes to the prescription requirements for antiparasitics for food-producing animals. Although the requirement for a veterinary prescription has been postponed until 1 June 2022, the products concerned must be released from the site of manufacture in the new livery, which bears the prescription-only medicine supply route, from 28 January 2022.

The new European Union Product Database (UPD) has been operational from 28 January 2022. This database will contain information on all veterinary medicinal products authorised in the Community, including in other Member States and in Northern Ireland.

The upload of legacy data to the UPD has been an ongoing challenge for all Member States and we are aware that there may be minor discrepancies in the data displayed in UPD. Please bear with us while we work over the coming months to correct any data issues. If major data issues are identified please contact us via newvetreg@hpra.ie providing the relevant details for us to review. If a marketing authorisation holder is submitting a VNRA and notices a product the HPRA is responsible for (i.e. in cases where the HPRA is the RMS, or when it is a nationally authorised product) is missing from the UPD, please notify newvetreg@hpra.ie.

Regular updates

The HPRA provides regular updates on Regulation 2019/6 in a dedicated website section: hpra.ie/NewVetReg

Pharmacovigilance changes

A number of significant changes to veterinary pharmacovigilance have arisen as a result of the implementation of the new veterinary Regulation (EU) 2019/6.

Pharmacovigilance System Master File (PSMF)

From 28 January 2022, a Pharmacovigilance System Master File (PSMF) must be in place for all new and existing veterinary medicinal products, including homeopathic veterinary medicines and veterinary medicines authorised in accordance with Article 5(6), which relates to specific species kept exclusively as pets. The PSMF replaces what was previously known as the Detailed Description of the Pharmacovigilance System (DDPS).

For new marketing authorisation applications submitted from 28 January 2022, the application dossier should include a summary of the PSMF. The format and content of the PSMF is set out in Commission Implementing Regulation (EU) 2021/1281 and described in the VGVP module titled Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files. Subsequent changes to a summary of the PSMF need to be made by way of an appropriate variation not requiring assessment (VNRA).

Periodic Safety Update Reports (PSURs)

From 28 January 2022, periodic safety update reports (PSURs) are no longer required under the new veterinary regulation. Consequently, only PSURs submitted to the HPRA before 28 January 2022 will be assessed, i.e. those submitted on or after 28 January 2022 will not be assessed. Consequently, marketing authorisation holders with a PSUR data lock point (DLP) of 27 November 2021 or earlier have had to submit those PSURs for assessment prior to 28 January 2022. Marketing authorisations with a PSUR DLP falling between 28 November 2021 and 27 January 2022 could also have been submitted prior to 28 January 2022 for assessment.

Signal management

Under Regulation (EU) 2019/6 marketing authorisation holders must carry out continuous signal management throughout the lifecycle of their veterinary medicinal product(s), based on adverse event reports received in respect of those product(s).

Guidance on veterinary good pharmacovigilance practices (the VGVP guideline) consisting of six modules, including one specifically addressing signal management, is available on the EMA's Pharmacovigilance webpage.

At least annually, marketing authorisation holders need to record the outcome of the signal management process and their conclusion on the benefit/risk balance for each of their products in the Union Pharmacovigilance Database.

It should be noted that the same pharmacovigilance requirements and obligations (including signal management) that apply to marketing authorisation holders also apply to holders of registrations of homeopathic veterinary medicines and veterinary medicines authorised in accordance with Article 5(6) of Regulation (EU) 2019/6, which relates to certain species kept exclusively as pets.

Additional information on the new requirements for veterinary pharmacovigilance was presented at a HPRA veterinary information day held in October 2021, and is available to view in the webinar recordings and Q&A documents published on the HPRA website.

Changes to HPRA requirements for mock-ups

As a result of the application of Regulation 2019/6 throughout the European Union from 28 January 2022, the HPRA has revised requirements for submission of mock-ups.

The HPRA will continue to review and approve mock-ups for new product applications before those products are placed on the market. However, the HPRA will no longer review mock-ups routinely for variation procedures and these will be completed based on the QRD texts, rather than approval of the mock-ups. In parallel, the HPRA will implement a surveillance programme whereby colleagues from the HPRA sample and analysis team will review labels taken from the marketplace and check for compliance with the approved QRD text. The primary driver for this change is to speed up completion and approval procedures. Further information relating to this change is available in an FAQ document on the HPRA's website.

Changes to product listings on the HPRA website

The veterinary area of the HPRA website will be changing over the course of 2022 to adapt to new requirements of the new veterinary Regulation 2019/6.

The first of these changes were implemented in January 2022 to the product listing part of the website. These changes are as follows:

- Publishing of the MAH address, in addition to the MAH name in the product record.
- Removal of the product strength.
- Updating 'Dosage form' to be aligned with SPOR mappings.

Further changes will take place over the coming months. We will provide updates as more changes take place.

Transition to new labelling requirements

Member States and stakeholders raised concerns regarding the European Commission's interpretation on 22 December 2022 that the Article 152 provisions of Regulation 2019/6 require that the packaging and labelling of veterinary medicines should be adapted to the new requirements as of 28 January 2022. Recognising these concerns, the Commission is taking urgent steps to address

the interpretation problems. The Commission is preparing a proposal for a legal act to set out a transitional regime for existing marketing authorisations in order to address the issues raised. The proposed legal act would allow marketing authorisation holders to continue placing veterinary medicines complying with the packaging and labelling requirements of Directive 2001/82 or Regulation 726/2004 on the market until 29 January 2027. The proposal would not affect the obligation to comply with the other relevant provisions of Regulation (EU) 2019/6 as of 28 January 2022. Once adopted, the legal act would apply retroactively, starting on 28 January 2022.

Submission of Mutual Recognition and Subsequent Recognition Applications

Prior to the initiation of a Mutual Recognition Procedure (MRP) or Subsequent Recognition Procedure (SRP; formally known as the Repeat Use Procedure), applicants are required to update the dossier for their already authorised product, in line with current regulatory requirements and introduce these changes by way of a variation application. In making the necessary dossier updates, applicants are reminded that the European Medicines Agency's Product information template v.9 supports the requirements of the marketing authorisation holders (MAHs) (Regulation (EU) 2019/6), which applied from 28 January 2022. As such, where required, the dossier (including product information) should be updated by way of a variation application (category G.I.17.a).

Processing of the Summary of Product Characteristics (SPC)

The HPRA would like to advise applicants that the HPRA will soon change how it processes the Summary of Product Characteristics (SPC) at the end of procedures (EoP). With the objective of simplifying internal processes, the HPRA intends to take the SPC document as agreed at EoP and publish it directly on the website without any further manipulation or handling of the document. Further information will be provided in due course on the veterinary section of the HPRA website.

Brexit and supply of veterinary medicines

The HPRA is pleased to note the Northern Ireland Protocol measures for veterinary medicines announced by the EU Commission on 17 December 2021. With this announcement, the European Commission's interpretive notice was extended and existing arrangements for veterinary medicines can remain in place until the end of 2022. Under these arrangements, a number of marketing authorisation holders (MAHs) have availed of exemptions as detailed in Commission Notice 2021/ C 27/08. Therefore, existing exemptions granted by the HPRA can be extended until 31 December 2022. MAHs wishing to extend their current exemptions are requested to confirm this by providing a copy of the original exemption to vetinfo@hpra.ie. The HPRA will then provide confirmation by email of extension until 31 December 2022. The confirmation can be shared by the MAH with wholesalers/distributors, as required. MAHs wishing to request new exemptions should complete the form available on the HPRA website.

The Commission stated that discussions on veterinary medicines with the UK government will continue over the coming months to identify permanent solutions that will safeguard the long-term continuity of veterinary medicines supply on the island of Ireland.

Irish language update

The Department of Agriculture, Food and the Marine (DAFM) has informed the HPRA that it is awaiting the final judgment from the appeal of the Order of the High Court in Dublin on the provision of bilingual packaging of veterinary medicines in the Irish and English languages on 25 June 2021. The case, which was first initiated in 2016, was heard on 9 December 2021 and judgement was reserved. It is not known what impact the judgment will have, given that Regulation 2019/6 allows the use of either Irish or English language labelling from 28 January 2022.

In an unrelated development, the Irish language derogation regarding Commission decisions on marketing authorisations submitted to the European Medicines Agency (EMA) expired on 1 January 2022. However, following discussions between the EMA and the European Commission in late 2021, product information in Irish will not routinely be required for centrally authorised medicines. Nonetheless, marketing authorisation holders (MAHs) for centrally authorised medicines that are established in Ireland have the right to submit product information in Irish if they choose to do so. Those not wishing to submit and receive such documents in Irish may waive their rights to communicate the information in Irish by contacting the EMA before 31 January 2022 and requesting a waiver. The waiver is valid for a period of three years, which can be renewed. For Commission implementing decisions, e.g. in respect of the outcome of Union interest referral procedures affecting veterinary medicines that are authorised in EU Member States, the Commission decision as well as the relevant annexes that are addressed to the Member States have been translated into Irish as of 1 January 2022. In cases where translation into Irish is required, the EMA will provide Irish translations of the QRD product information annex templates and the QRD reference documents. This new requirement applies irrespective of whether or not the products concerned are authorised for use in Ireland. Moreover, even if the information must be made available by the MAH to the EMA in Irish, there is no requirement to supply medicines bearing an Irish language label, carton or package leaflet.

Safety Features – end of 'use and learn' phase

The Falsified Medicines Directive (FMD) (2011/62/EU) brought in the requirement for certain medicinal products to bear safety features. The European Commission Delegated Regulation (EU) 2016/161 details the characteristics of the safety features, how medicine authenticity should be verified and by whom. The requirements set out in this delegated regulation came into effect on 9 February 2019.

In line with this requirement, all medicines required to bear safety features must have a 2D barcode and a tamper-evident seal on each pack. This requirement is an important patient safety initiative and relies on wholesalers, hospitals and pharmacies scanning the 2D barcode and investigating any alerts generated. Since 2019, the scanning system in Ireland has been in a 'use and learn' phase. This phase permitted wholesalers, hospitals and pharmacies to supply medicines that had generated alerts on scanning, provided there were no overriding concerns regarding falsification. This ensured the continuity of supply of medicines to patients while all stakeholders involved gained a better understanding of the scanning and alert system. The data generated from these scans throughout the 'use and learn' phase was, and remains, critical for identifying root causes of alerts and other issues that need to be resolved to allow for the ending of the 'use and learn' phase, with minimal disruption to the stakeholders involved and impact on supply to patients.

The National Safety Features Oversight Group, which comprises the Irish Medicines Verification Organisation, the Department of Health, the HPRA, the Pharmaceutical Society of Ireland, the HSE and the Private Hospitals Association, had outlined a phased approach consisting of seven phases to end 'use and learn', starting in Q3 2021 and ending during Q2 2022. Phase one and two, which required wholesalers to participate in a pilot programme to investigate any alerts generated and saw the red/green/amber colour-coded response for alerts turned on, were successfully completed in 2021.

Phase three and four, originally scheduled for 10 January 2022, were temporarily deferred to account for the impact of COVID-19 cases, the increased booster vaccination campaign, as well as staff shortages, on the stakeholders taking part. The dates for the remaining phases have since been revised (information below).

Revised implementation dates for Safety Features phases

Phase	Date	Details	Stakeholders involved
Phase 3 Use and learn ends for returns to wholesalers	28 February 2022	All alerts generated at wholesale level when scanning returns from customers must be investigated.	Wholesalers
Phase 4 Red, amber, green changes for pharmacies & hospitals	28 February 2022	Pharmacy and hospital FMD scanning software to display red, amber, green colour-coded responses (depending on outcome) when a pack is scanned.	Pharmacies Hospitals
Phase 5 Pilot of alert handling procedures with pharmacies, hospitals and wholesalers	14 March 2022	Wholesalers, hospitals and pharmacies to scan packs and investigate alerts generated but packs can be supplied as normal, provided there is no overriding concern regarding falsification.	Wholesalers Pharmacies Hospitals
Phase 6 Use and learn ends for wholesalers for all remaining activities	9 May 2022	All alerts generated at wholesale level must be investigated and suspected falsification ruled out before suppling customers or returning packs to saleable stock (FMD).	Wholesalers
Phase 7 End of use and learn for pharmacies and hospitals	30 May 2022	All alerts generated at pharmacy and hospital level must be investigated and suspected falsification ruled out prior to supply.	Pharmacies Hospitals

The Safety Features Oversight Group will continue to monitor progress during each phase to ensure that everything is in place to move to the next phase of the plan, including targeted communications with each stakeholder on details of what is involved for them.

All information relating to the implementation can be found on the IMVO website.

Integration of EudraGMDP and OMS

The European Medicines Agency (EMA) manages the EudraGMDP database, which holds a number of regulatory documents issued to EEA Competent Authorities, for example:

- Manufacturer's/importer's authorisation (MIA) for manufacturers of medicinal products for human and veterinary use;
- Registrations for manufacturers, importers and distributors of active substances;
- GMP certificates.

The EMA integrated the EudraGMDP database with a database called the Organisation Management Service (OMS) on 28 January 2022. The OMS is the EU repository of master data for organisation names and site addresses that appear on regulatory documents. From 28 January 2022, the HPRA can only issue documents on the EudraGMDP database for sites where the organisation name and address are available in the OMS database. The EMA has published information and a webinar recording on the integration of EudraGMDP and OMS.

The organisation name and address is already registered on the OMS database for many stakeholders. Stakeholders are advised to check if entries for their organisation exist in OMS and if they are correct. If details are incorrect or if there is no entry in OMS for your site, it is necessary to submit a change request to OMS at the EMA.

The HPRA cannot process any documents on EudraGMDP (MIA applications, MIA variations, Active Substance Registrations, GMP certificates) if OMS does not contain the correct details for an organisation, or the site where activities are carried out. If the HPRA encounters OMS details that appear incorrect or where details are absent, the company will be asked to submit a change request to the EMA. This could result in delays when issuing authorisations or processing documents on EudraGMDP.

Remote qualified person certification

Batch certification is a manufacturing operation specified on the manufacturer's authorisation and historically it was expected that the qualified person (QP) would be present at the authorised site when performing batch certification. Current national legislation governing the manufacturing of human medicines, investigational medicinal products and veterinary medicines permits the use of alternative premises from time to time, if approved in writing by the HPRA. This provision was used by the HPRA at the start of the COVID-19 pandemic to facilitate remote certification by QPs, and this information was communicated to QPs in March 2020. A number of QPs have operated remotely for some periods during the pandemic, in accordance with Irish government advice to work from home where possible.

The Government's advice has recently changed in accordance with the changing risk to public health presented by COVID-19. The HPRA has communicated during a number of seminars, including the QP Forum in September 2021, that it has implemented a formalised process to facilitate continued remote batch certification by QPs outside of the pandemic situation.

An MIA holder who wishes to apply for remote batch certification by QPs operating under its MIA should submit a technical variation as described in Appendix 4 of the HPRA Guide to New Applications and Variations to Manufacturer's Authorisations. To enable a transition period, where the HPRA has already granted approval for remote certification within the context of the COVID-19 pandemic, the QPs at that site may continue to conduct batch certification remotely under the conditions specified in March 2020. However, if the MIA holder intends to continue with remote batch certification beyond 30 April 2022, a variation to the MIA should be submitted to compliance@hpra.ie by 31 March 2022. The specific address where the activities would take place does not need to be identified.

However, in line with paragraph 1.1. of Annex 16 of the EU GMP Guide, batch certification must be carried out by a QP within the EEA, or Northern Ireland, in accordance with the provisions of the Northern Ireland Protocol. This remote activity can only be facilitated where secure electronic systems, meeting the requirements of Annex 11 of the EU GMP Guide, are employed. Where approved, the HPRA will include a clarifying remark on the authorisation stating 'Authorised operations include remote batch certification by a Qualified Person when operating within the EEA or Northern Ireland'.

QP duties at a manufacturing site may also include providing QP confirmation, as defined in Annex 16 of the EU GMP Guide. This is not a manufacturing or importation operation specifically identified on the MIA. Therefore, a variation to the MIA is not required in order to perform the QP confirmation activity remotely. It is expected that the same principles would apply to the control of this process and these controls will be reviewed during GMP inspections.

The above information was sent to QP contacts at Irish sites holding a manufacturer's authorisation on 27 January 2022. Please contact compliance@hpra.ie if any further clarification is required.

Supporting documentation required when applying to include a qualified person on an MIA

A candidate must meet specific education and experience requirements outlined in EU Directive 2001/83/EC and EU Regulation 2019/6 to be eligible to be named as a qualified person (QP) on a manufacturer's/importer's authorisation (MIA). Further detail is provided in the HPRA Guide to attainment of qualified person status in Ireland.

The HPRA Guide to new applications and variations to manufacturer's authorisations provides guidance on supporting documentation that must accompany an application to add a QP

to the MIA. Applicants must submit the following details:

- A copy of qualification certificates issued by a relevant third-level institution to support educational requirements. Qualification certificates for primary degrees and associated master's degrees or higher diplomas that collectively constitute the education requirements should be submitted.
- A copy of the proposed QP's Curriculum Vitae
- The current email address for the proposed QP
- A summary of training, relevant to the role of QP, performed at the manufacturing site concerned. This should include details of training on the company quality system and product-specific training. Where all relevant training on the curriculum has not been completed at the time of application, a statement should be included confirming that this will be completed prior to commencement of the batch certification activity by the proposed QP.

In submitting this information electronically, titles of supporting documents should reflect the content (e.g. 'John Smith CV' rather than 'attachment 1'). If supporting documents are submitted together as a single pack, individual documents should be hyperlinked through a table of contents. CVs should include the name and address of the manufacturing site where experience was obtained and detail if that site held an MIA at the time. The CV should clearly indicate the candidate's job title(s) and include a brief overview of the scope of each position held. The duration of experience in each role should be clear, e.g. the CV should include the start and end month for each position such that the total duration of experience can be calculated.

Where qualifications have been obtained outside of the Republic of Ireland, the applicant must provide proof (e.g. in the form of a letter or other documentary evidence) from the competent authority in the EEA member state where the qualifications were obtained that the qualifications fulfil the QP educational requirements as defined in EU Directive 2001/83/EC and EU Regulation 2019/6. If a candidate has acted in the role of QP in another EEA jurisdiction, evidence of QP status should be submitted, e.g. a copy of the relevant MIA listing the candidate as a QP, or a letter from the competent authority in the Member State confirming QP status.

English translations are required for all supporting documentation where relevant.

Registrations for active substances used in veterinary medicines

Regulation (EU) 2019/6 on veterinary medicinal products, which legislates for the authorisation, use and monitoring of veterinary medicines in the European Union, came into effect on 28 January 2019, and applies in all EU Member States from 28 January 2022.

The Regulation requires manufacturers, importers and distributors of active substances used as starting materials in veterinary medicines, who are located in Ireland, to register for an active substance registration (ASR) with the HPRA from 28 January 2022. Registration requirements apply to entities that physically and/or financially import, procure and/or supply* active substances.

Manufacturers and importers

Manufacturers and importers of active substances located in Ireland are required to register the manufacturing or importation activities carried out for each active substance supplied for use in a veterinary medicine. The HPRA will conduct inspections of active substance manufacturers and importers on a risk basis. Manufacturers of veterinary medicines who are importing active substances from third countries are also required to register as importers. Information about registering is available in the HPRA guide to registration requirements for active substance manufacturers, importers and distributors in Ireland.

Distributors

The European Commission implementing regulation (EU) 2021/1280 on good distribution practice for active substances in veterinary medicines, provides a comprehensive overview of the requirements that must be met to register for an ASR for active substances used in veterinary medicines. It is recommended that all entities looking to apply for an ASR for veterinary active substances review both the Regulation 2019/6 and Implementing Regulation (EU) 2021/1280. Key requirements are highlighted below:

An entity applying for a veterinary ASR for distribution should have:

- A quality system to ensure that the objectives of good distribution practice are achieved, clearly setting out the responsibilities, process and risk management principles for all of the activities that form the distribution chain;
- Adequate premises, installations and equipment, in order to ensure proper storage and distribution of active substances used as a starting material in veterinary medicines;
- Procedures that describe all distribution activities that affect the identity, traceability and quality of the active substances used as starting materials;
- A designated person to be responsible for the quality system at each location where distribution activities are performed;
- Procedures in place for the management of complaints, returns and recalls and, regular self-inspections.

Entities that currently do not have a quality management system should review the HPRA guide to quality system for general sale wholesale distributors.

As stakeholders may be aware, a registration process is already in place for the manufacture, importation and distribution of active substances used in human medicines. As a result, the following HPRA guidance documents and forms have been updated to include active substances for veterinary medicines within their scope.

Guides

- Registration requirements for active substance manufacturers, importers and distributors in Ireland
- Managing changes to registrations of active substance manufacturers, importers and distributors

Application form

- Application for registration of manufacturer, importer or distributor of active substances

Following the approval of an ASR for active substances used in veterinary medicines, the ASR holder will be required to communicate to the HPRA on an annual basis to confirm there has been no changes or to highlight any changes to the information provided in the registration form. Changes that may have an impact on the quality or safety of the active substances that are manufactured, imported or distributed should be notified immediately.

Email queries to compliance@hpra.ie.

* *Procure means obtaining, acquiring or purchasing active substances. Supply means all activities of providing selling or donating active substances to another entity.*

Risk-based cross-contamination control

Approaches to cross-contamination control and related GMP inspection findings were presented in the HPRA's Medicinal Products Newsletter Issue no. 69.

This article focuses on the application of Quality Risk Management (QRM) principles as the basis of cross contamination control strategies in finished product manufacturing sites. This risk-based requirement is reflected in the following EU regulatory guidelines and documents:

- Chapters 3 and 5 of the EU GMP Guide (Eudralex Vol.4 Part I)
- Annex 15 of the EU GMP Guide
- EMA guidance document 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 Questions and answers document EMA/CHMP/CVMP/SWP/246844/2018: Questions and answers on implementation of risk-based prevention of cross-contamination in production and "Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities"

A QRM process should be used to assess the cross-contamination risks presented by products manufactured in shared facilities. The outcome of this QRM process should then form the basis of the technical and organisational measures implemented at the site to control the risks. These requirements are reflected in Chapter 3 Paragraph 3.6, and Chapter 5 Paragraphs 5.20 and 5.21 of the EU GMP Guide.

In 2018, the EMA published a Questions and Answers guidance document (EMA/CHMP/CVMP/SWP/246844/2018) that expanded on certain aspects of the QRM approach to cross contamination control and cleaning validation/verification requirements. Notably, Q&A no. 7 outlines requirements for analytical testing at product changeover following completion of cleaning validation. It clarifies that analytical testing is expected at each product changeover unless otherwise justified through a robust QRM process. This process should consider at a minimum the repeatability of the cleaning process (e.g. manual or automated cleaning), the hazard posed by the product, and whether visual inspection can be relied upon to determine the cleanliness of the equipment at the residue limit justified by the Health-Based Exposure Limit (HBEL).

Q&A no. 8 clarifies requirements for conducting visual inspection of cleaned equipment. It outlines that manufacturers should establish the threshold at which the product is readily visible as a residue. Given one of the criteria to be considered in the QRM process as per Q&A no. 7 is whether visual inspection can be relied upon at the residue limit justified by the HBEL, it is implied this threshold should be established for all products manufactured in shared facilities. Q&A no. 8 also provides detail on how visual inspection should be documented and how personnel should be trained and qualified for this task.

Deficiencies have been issued in recent inspections in relation to these requirements. Examples are listed below:

- There was no documented quality risk management process that considered the repeatability of the process, the hazard posed by the product or whether visual inspection could be relied upon to determine the cleanliness at the maximum acceptable carryover (MACO) limit to justify not performing analytical testing at each changeover.
- The threshold at which product was readily visible had not been established.
- There was no periodic analytical verification of manually cleaned equipment.

Responses to deficiencies cited in GMP inspection reports

This article aims to clarify the expected level of detail to address GMP inspection deficiencies in order to promote a 'right first time' approach for responses submitted to the HPRA.

Guidance in inspection report cover letters

All inspection reports are accompanied by a cover letter, which outlines the expectations for responses addressing the deficiencies identified in the report. Each deficiency should be documented individually, reflecting the wording in the inspection report. The company can include comments on a deficiency if necessary to provide further clarity or context.

The cover letter specifies that a corrective and preventative action (CAPA) approach be applied to the deficiencies as follows: *Following the assignment of actions to each deficiency, an assessment should be performed to identify other areas potentially impacted and actions assigned as appropriate. All actions should be assessed for effectiveness in line with quality risk management principles.*

The corrective action should address the specific deficiency cited to ensure there is no potential impact to the batch, product or process directly implicated. It is also necessary to carry out a holistic assessment to determine potential risks and impacts to other batches, products or processes at that time or in the future and to ensure that appropriate preventative actions are identified and implemented.

The responses should include appropriate target completion dates for both the corrective and preventative actions. The target completion dates should be realistic and appropriate given the potential risk involved. In general, the expectation is that shorter timelines are assigned for any critical or major deficiencies identified. Where longer target completion dates are necessary, for example, when capital expenditure is required, these should be justified.

Common issues in responses and CAPA plans

Common issues in relation to inadequate responses and CAPA plans are listed below:

- A procedure update is proposed to address the specific issue but no actions are identified to verify that the procedural changes are effective.
- The response includes a corrective action to address the specific issue but no preventative action is included to ensure that the issue does not reoccur in relation to other batches, products, processes etc.
- The specific deficiency is addressed, but a holistic review is not conducted to identify potential systemic inadequacies, i.e. very specific actions are proposed which do not assess potential impact on other processes or systems.
- An appropriate CAPA is not included for every element of the deficiency and no justification is provided in that regard. This applies primarily to deficiencies, which comprise multiple sub-parts. The response provided should address each sub-part of the deficiency.
- Generic wording is used to address the overall deficiency. This is repeated for each sub-part of the deficiency, even though it may not address the specific sub-part involved.
- Target completion dates are not appropriate and/or justified.

Examples of responses that required additional details to be submitted

To illustrate some of the above points the following examples are included.

- A deficiency was identified with respect to deviation investigations conducted at Company A. There was no evidence of the appropriate use of root cause analysis during deviation investigations. In addition, checks for recurrence were not executed in a consistent manner and documented in appropriate detail. Previous CAPA effectiveness was not assessed where recurring deviations were identified.
  - *Company A responded to indicate that it intended to update its procedure on Deviation Investigation to address the deficiencies cited. The response was deemed inadequate because measures to monitor the effectiveness of the updated procedure, ensuring that suitable levels of root cause analysis and appropriate checks for recurrence were conducted going forward, had not been included.*
- A deficiency was cited at Company B with respect to the content of cleaning validation protocols and reports, which did not include swab locations.
  - *The company's response focused on corrective actions for the specific protocols but no systemic action was identified to prevent a recurrence.*
- A deficiency was cited as there was no permitted daily exposure (PDE) data for some of the active pharmaceutical ingredients (APIs) handled at Company C.
  - *The company responded that the additional PDE data had been generated since the inspection. The company response did not confirm if maximum acceptable carry over (MACO) calculations had been recalculated using the additional PDE data and if it had been established whether or not there was an impact on the established site cleaning validation limits.*
- A deficiency was issued to Company D because a number of named procedures had not been reviewed as per the standard periodic review schedule.
  - *Company D did not include a review of other quality system procedures within its CAPA plan to identify if other documents were potentially impacted by the same issue.*

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