February 2023

HPRA MEDICINAL PRODUCTS NEWSLETTER

ISSUE 73

In this Issue

Human Medicines

HPRA identifier for DHPCs and educational materials

A specific HPRA identifier has now been implemented for marketing authorisation holders for communicating important safety information. This identifier should be included at the top of the first page of Direct Healthcare Professional Letters (DHPCs) and cover letters accompanying educational materials that are distributed as part of a risk management plan and approved by the HPRA. The identifier highlights that these communications from marketing authorisation holders contain important safety information which has been approved by the HPRA and aims to distinguish them from other communications that may be received by healthcare professionals. The identifier is available to download from the HPRA website in various formats.

Clinical trials – deadlines, training and supports

Deadlines

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

- **New/initial applications** must now be made under the CTR via the Clinical Trials Information System (CTIS). This applies to all clinical trials including academic/non-commercial trials, and mono-national trials.
- **Substantial amendments** can be made to trials authorised under the Clinical Trials Directive (CTD) up to **30 January 2025**.
- All clinical trials will be regulated under the CTR from **31 January 2025**, and therefore ongoing CTD trials **must transition** to the CTR before this date.

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

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

CTR/CTIS training and supports

- Applicants can avail of training and supports from the HPRA and the EMA. Supports from the HPRA can be found on the CTR section of the HPRA website.
- EMA supports are available on the CTR and CTIS section of the EMA clinical trials webpage.
- It is mandatory to submit CTR clinical trials using the CTIS. Non-commercial sponsors can use the EMA Introductory guide CTIS for SMEs and Academia for guidance.
- Upcoming CTIS training and information events are listed on the information and events section of the EMA CTIS webpage.

Brexit update

On 20 April 2022, Directive 2022/642/EC of the European Parliament came into force. This directive amends Directives 2001/20/EC and 2001/83/EC regarding derogations from certain obligations concerning medicinal products for human use made available in the UK in respect of Northern Ireland, and in Cyprus, Ireland, and Malta. The objectives of amending Directive 2022/642/EC are to facilitate the continued supply of medicinal products and to maintain a high level of public health protection. To ensure uniform application of EU law in all Member States, the derogations applicable in Cyprus, Ireland and Malta will apply until 31 December 2024.

To ensure transparency, Directive 2022/642/EC stipulates that the competent authorities of Cyprus, Ireland and Malta and the UK in respect of Northern Ireland must publish on their website a list of the medicinal products marketed to which derogations have been granted.

The HPRA has compiled the list of products availing of these derogations which is available to download. Products are identified by the product name, product authorisation number and marketing authorisation holder. This list is required to be updated at least every six months. The HPRA last updated this list on 15 November 2022 and intends to update this again in April 2023.

The HPRA is also required to notify the European Commission of the medicinal products which hold derogations, specifying for each product, which derogations apply every six months. The next update is due on 20 April 2023. The Commission will be expecting to see a reduction in the numbers of derogations issued as we approach the December 2024 deadline.

Prior to the generation of these lists the HPRA requests that marketing authorisation holders review the products holding derogations to determine if these derogations are still required. If no longer required, marketing authorisation holders are requested to inform the HPRA of this by 31 March 2023, so they can be withdrawn and not reported to the European Commission or displayed on the HPRA website. This can be done by emailing brexit@hpra.ie.

The HPRA does not expect the derogation provisions permitted in Directive 2022/642/EC to be extended past 31 December 2024. As such, the HPRA will commence direct communication with marketing authorisation holders who hold derogations in Q4 of 2023 to determine the progress they are making towards achieving EU regulatory compliance.

Use of UK reference products for generic and hybrid applications

The HPRA has received queries regarding the use of UK reference products in generic or hybrid applications. For variations to update the product information, the HPRA applies the approach outlined in Q39 of the CMDh practical guidance on Brexit.

In effect, where the Summary of Product Characteristics (SPC), Product Information Leaflet (PIL) and label is being updated, the reference product of the initial MA application does not change, but the product information may be aligned to an EU/EEA reference product in the same GMA. Where this is not possible, other approaches to adaptation may be acceptable.

For new applications, applicants are reminded of Q34, in which the use of a UK reference medicinal product in pivotal studies is no longer permitted unless the study was completed prior to the end of the Brexit transition period. HPRA Regulatory advice may be applied for in the case of detailed queries on this topic.

Information on the HPRA national scientific and regulatory advice procedure can be accessed through our website.

Nitrosamines

The CMDh and EMA have jointly updated the questions and answers document on nitrosamines. This document is an important resource for marketing authorisation holders to ensure they are up to date with recommendations and recently agreed nitrosamine limits. The document should be consulted regularly to determine further required actions.

The HPRA would like to highlight the new Q21 of revision 14. Where a new nitrosamine is detected (Scenario D), a request for an acceptable intake will be sent by the lead Member State to the Non-Clinical Working Party at the EMA. Until this limit is established, it states that marketing authorisation holders, with the agreement of the national competent authorities, may control impurities to a temporary acceptable intake (tAI) of ≤178ng/day (total nitrosamines). Applicants should submit nitrosamine Step 2 templates for each product by email to nitrosamines@hpra.ie as usual.

The HPRA Quality Defects team should be informed by email at HPRAqualitydefects@hpra.ie if batches reach levels of nitrosamine above this tAI limit, to discuss the required action for affected batches intended for Ireland. Furthermore, if a new nitrosamine is detected but remains below the class specific threshold of 18ng/day, this limit should be used in preference to request a substance specific acceptable intake limit. Similarly, the HPRA Quality Defects team must be informed of detections of known nitrosamines above the acceptable intake (Scenario A), to determine action for the Irish market. This is in addition to submitting the usual Step 2 templates to nitrosamines@hpra.ie and is required in addition to your communications with the lead Member State.

Swift scientific advice (quality sections of dossier)

The HPRA is now offering a swift scientific advice service to applicants. This new national advice procedure is in addition to the standard national scientific advice that is available for human medicines. Swift scientific advice concerns advice on the quality sections of a dossier and enables the provision of answers to applicant questions 30 days after the submission of the request for advice.

This new advice procedure has no requirement for a meeting between the applicant and the HPRA. This service intends to provide a simple mechanism for applicants to request clarification of the regulatory framework, or the interpretation of that framework, in relation to products in development or to proposed post-approval changes. When submitting a request for swift scientific advice, applicants should ensure the submission is of a suitable scope and contains adequate supporting information to be amenable to an advice procedure without a clarification meeting. The updated guide to national scientific and regulatory advice and the updated request form are available on the HPRA website.

Veterinary Medicines

HPRA welcomes extension to Brexit exemptions for veterinary medicines

The HPRA welcomes the European Commission's decision on the application of the EUs pharmaceutical acquis in markets historically dependent on medicines supply from or through parts of the UK other than Northern Ireland. The UK withdrew from the EU on 1 February 2020. However, in accordance with the EU/UK Withdrawal Agreement a transition period was agreed during which the supply of veterinary medicines from the UK into Ireland could continue in favourable terms without the need for full compliance with EU law. During the transition period, marketing authorisation holders were to make necessary arrangements to comply with EU legislation. That period was due to end on 31 December 2022, but in accordance with the Commission notice that period has been extended for a further final period until 31 December 2025. This additional period is to allow companies and operators in Ireland, Northern Ireland, Cyprus, and Malta to fully comply with EU law and to prevent shortages of veterinary medicines, particularly on the island of Ireland.

Marketing authorisation holders that currently benefit from these exemptions are required to engage with the national competent authorities to identify all relevant products so that the European Commission can be informed by 28 February 2023. By 30 September 2023, the marketing authorisation holders concerned will be required to provide a workplan charting how they plan to achieve full regulatory compliance with EU law within the timeframe given.

Change in fee system for veterinary medicines in the EU

On 13 December 2022, the European Commission published a proposal on fees charged by the EMA. The objective of the proposal is to ensure that the fees reflect better the underlying costs of the work done and coordinated by EMA. The proposal revises the entire current fee structure for centralised applications with a significant simplification of the fee structure. This includes a rebalancing of fees with fees for certain types of variations being abolished but increases in annual maintenance fees. While the proposal includes a significant increase in fees overall, special provision is made for immunological, and medicines for limited markets where a 50% reduction in the fee is proposed. Reductions in fees for small and medium sized enterprises are also proposed. The proposal also introduces a new annual maintenance fee in respect of veterinary medicines marketed nationally. This fee is intended to remunerate the EMA for pharmacovigilance activities.

The proposal was discussed at a Council of Ministers working group meeting in late January, ahead of finalisation during the spring. The fee will be introduced by way of EU Regulation and will apply throughout the EU on its date of application.

Changes to the processing of Summaries of Product Characteristics by the HPRA

The HPRA would like to remind applicants and marketing authorisation holders of a change in how the Summary of Product Characteristics (SPC) is processed during the national phase of a marketing authorisation procedure. The HPRA takes the End of Procedure (EoP) SPC and publishes it directly to the HPRA website without any further manipulation or handling of the document. The objective of this change is to simplify internal processes and reduce administrative burden.

The EoP SPC is the 'common English text' that has been agreed between the applicant and Member States and does not include national-specific information, such as the name and address of the marketing authorisation holder, marketing authorisation number, date of first authorisation or date of revision of the text. This information is available on the HPRA website and is presented

together with the SPC document. The EoP SPC, together with the related national-specific product information on the webpage, constitute the authorised SPC.

Any questions relating to the new SPC process should be directed to vetinfo@hpra.ie.

Update on antiparasitic veterinary medicinal products for food-producing animals

The HPRA notes the announcement on 22 November 2022 by the Department of Agriculture, Food, and the Marine (DAFM) of a further extension of the transition period for the requirement of a veterinary prescription to dispense anti-parasitic medicines in Ireland. The DAFM has advised that the deferral is intended to provide additional time to complete the legislative process in respect of the new national legislation on electronic prescribing by veterinary practitioners. No final date for implementation has been given. The DAFM will announce an implementation date once the legislation is finalised in 2023.

This development does not have a material impact on the labelling requirements for the products involved, which now bear the prescription-only-medicine designation, in compliance with EU legislation as well as the 2019 HPRA report on this matter.

Recent updates to the veterinary pharmacovigilance section of the HPRA website

Considering the significant changes in legislation concerning veterinary pharmacovigilance following the introduction of Regulation (EU) 2019/6, the HPRA has updated the veterinary pharmacovigilance section of the HPRA website.

Information which is considered useful for and requested by marketing authorisation holders and applicants is now presented on a single page and includes links to useful resources including:

- EMA guidelines on veterinary good pharmacovigilance practices
- Adverse events and use of Veterinary Dictionary for Drug Related Affairs (VeDDRA) terminology
- Eudravigilance and user manuals for EVWEB and EVVET
- Signal management
- Video presentations on how to submit pharmacovigilance-related variations not requiring assessment (VNRAs) in the Union Product Database (UPD)

Concerning pharmacovigilance VNRAs, the HPRA understands that following the recent updates to the UPD and discussions at the Coordinating Group for Mutual Recognition and Decentralised procedures (CMDv), the technical grouping of category C.1, C.5 and C.6 variations is possible provided that the Reference Member State (RMS) is the same for all products included in the grouping and that any nationally authorised products included are also authorised in the RMS. This means that the same authority is the decision maker for all products that are included in the grouping.

In addition, the veterinary pharmacovigilance section of the HPRA website on adverse reaction/event reporting now includes three voiced-over video presentations providing useful information on:

- the role of animal owners in monitoring the safety and effectiveness of veterinary medicines and the importance of reporting adverse events
- pharmacovigilance and adverse event reporting for veterinarians, veterinary nurses, and animal healthcare professionals
- how to report an adverse reaction/event using the HPRA's online reporting form

Publication of information on newly authorised centralised veterinary medicines and updating of national product data in the Union Product Database

The HPRA understands that the EMA is no longer publishing information on newly authorised centralised veterinary medicines on their website. Instead, the information is uploaded by the EMA to the Union Product Database (UPD). The HPRA wishes to highlight this change to users, including those who use the EMA website to generate databases of authorised veterinary medicines for use in various applications nationally.

Separately, the HPRA is planning to deploy a new application programming interface (API) in the coming months to allow automatic uploading of changes relating to national SPCs to the UPD. Pending this deployment, the information in the UPD in respect of product data from Ireland might not be fully up to date as we do not wish to update manually given the fact that the API will be available shortly. Therefore, the most up-to-date source of information on nationally authorised veterinary medicinal products is the HPRA website.

Veterinary medicinal products containing zinc oxide to be administered orally to food-producing species

On 19 June 2017, the European Commission decided that the marketing authorisation for all veterinary medicines containing zinc oxide that are administered orally to pigs must be withdrawn by 26 June 2022. The HPRA can confirm that the marketing

authorisations for the products concerned have been withdrawn in Ireland. The Commission's decision gave effect to the outcome of an EMA assessment of the benefit-risk balance of veterinary medicines containing zinc oxide. The assessment, which was conducted by the Committee for Medicinal Products for Veterinary Use (CVMP), concluded that the overall benefit-risk balance for the products concerned was negative, as the benefits of zinc oxide for the prevention of diarrhoea in pigs did not outweigh the risks for the environment.

Mock-up requirements following G.I.18 variations

The HPRA advises that mock-ups are no longer routinely reviewed following G.I.18 variations in line with updated HPRA policy. This policy was adopted alongside the New Veterinary Regulations, with the common objective of reducing the administrative burden for the applicant. The applicant is requested to implement the changes to the mock-ups in accordance with the changes agreed during the procedure. In the event of significant change(s) to the product information, the mock-ups should be submitted to the HPRA for review via a G.I.15 variation.

Compliance

Requirements for HPRA access to manufacturing sites where batch certification only takes place

The HPRA seeks to clarify requirements for holders of a manufacturing import authorisation where the authorised site is an office in a building shared with other businesses and the qualified person (QP) carrying out the batch certification activity is not permanently located at these premises.

The following requirements must be met by existing manufacturing import authorisation holders and intending applicants.

- The manufacturing authorisation holder must have a permanent physical site in Ireland. This site must have the necessary equipment and facilities to enable certification by the QP in accordance with the requirements defined in legislation and the EU GMP Guide. The site should be accessible at all reasonable times to the authorised officers of the HPRA.
- Records of batch certification and any supporting information relevant to QP oversight of the manufacture of the certified batches must be readily available at the site. The HPRA authorised officers need to be able to access those records at the site. If records are in an electronic format, the HPRA authorised officers must always have access to these records at the site through the company's equipment.
- There should be sufficient staff to support the batch certification activity. At the minimum, there should be a designated person at the site where batch certification occurs who can grant access to HPRA authorised officers in the event of an unannounced inspection. If the person operating at the site is not a QP, then this person must have sufficient knowledge of the pharmaceutical quality system (PQS) and at least have read-only access to records relevant to the batch certification activity to enable the HPRA authorised officers to review documents at the site. They must be continuously contactable and available to attend the site at short notice to assist HPRA authorised officers.
- Contact details for the site contact person should be in the Site Master File which is provided to the HPRA.

The HPRA will be contacting existing manufacturers where batch certification is the only authorised activity to verify that the arrangements outlined above are in place.

Adjusting our compliance management approach

On February 20203 the HPRA implemented a compliance management process that has been agreed at an EU level and is published in the EMAs Compilation of Union Procedures.

If the GMP or GDP compliance level at a manufacturing or wholesaling site is below the required standard on inspection, but does not meet the threshold for regulatory action, a company may enter into the compliance management process.

The aim of this process is to initiate early intervention to flag to the most senior levels within the company that there is an urgent need to improve compliance.

Manufacturers and wholesalers will be informed at the conclusion or in the immediate aftermath of an inspection if the deficiencies identified are being referred by the inspectors to a Compliance Regulatory Group (CRG) meeting where non-compliances are escalated and considered in the context of the compliance management process.

Thresholds for initiating compliance management: Factors of poor compliance history

- One or two critical deficiencies identified
- Number of major deficiencies raised during an inspection
- Non-compliance with previous commitments to critical or major deficiencies
- Repeated major deficiencies issued in successive inspections

Administrative Actions

The case management strategy may include administrative actions, such as:

- In person meetings with key personnel, cautionary letter issued to the manufacturer, wholesalers, or their associated marketing authorisation holder to outline specific compliance concerns, relevant company history, and the potential consideration of regulatory action in the event of continued non-compliance. Where appropriate, specific measures or milestones for future compliance assessment will be described in correspondence to the licence holder. Consideration may be given to public visibility of cautionary letters.
- Conditional approvals applied pending completion of corrective actions, for example GMP or GDP certificate restrictions which could include a reduced period of certificate validity, restrictions on use of specified facilities or equipment or capacity restrictions including blocking use of the GMP certificate to support new marketing authorisation applications or variations.
- GMP and GDP certificates issued as part of administrative action(s) will include a statement that indicates the site is under 'compliance management' and this will be visible to all EU competent authority users.

Following a period of increased monitoring if a manufacturer or distributor achieves the required level of compliance, the compliance management process will be closed, and the site personnel informed.

Registration of processes exempted under Article 61(5) of the Clinical Trial Regulation

Article 61(5) of the Clinical Trial Regulation (CTR) (EU Regulation 536/2014) provides an exemption from the requirement to hold a manufacturer's authorisation for the following processes, where they are carried out by authorised staff at a hospital, health centre or a clinic participating in the clinical trial.

1. Re-labelling or re-packaging of the investigational medicinal product (IMP)
2. Preparation of radiopharmaceuticals used as diagnostic IMPs
3. Preparation of an IMP in accordance with a doctor's prescription or in accordance with a pharmacopeial monograph.

The HPRA held a public consultation on the approach which will be adopted for registration of processes which are exempt from the requirement for a manufacturer's authorisation and the appropriate and proportionate requirements which should apply for the exempted processes. This consultation finished on 22 August 2022, and we would like to thank those who had submitted comments.

Register of exemptions

The EU (Clinical Trials on Medicinal Products for Human Use) (Principal) Regulations 2022 defines, at national level, where the above processes can be performed and by whom. These national regulations also describe the requirement for these processes to be included on a 'Register of Exemptions' which is maintained by the HPRA. If any of the above processes are being carried out with respect to a clinical trial being conducted under the CTR in Ireland, including trials that transition over to the CTR, then these processes should be included on the HPRA Register of Exemptions. The relevant application form and further information can be found on the CTR section of our website.

Appropriate and proportionate requirements

The HPRA has consulted stakeholders on application of the PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments as the appropriate and proportionate requirements, mentioned in Article 61(6) of the CTR, to be applied with respect to control the exempted processes. The implementation of these guidelines will only apply to the processes which are carried out under Article 61(5) and not to any other activities which may be taking place at the hospital, heath centre or clinic.

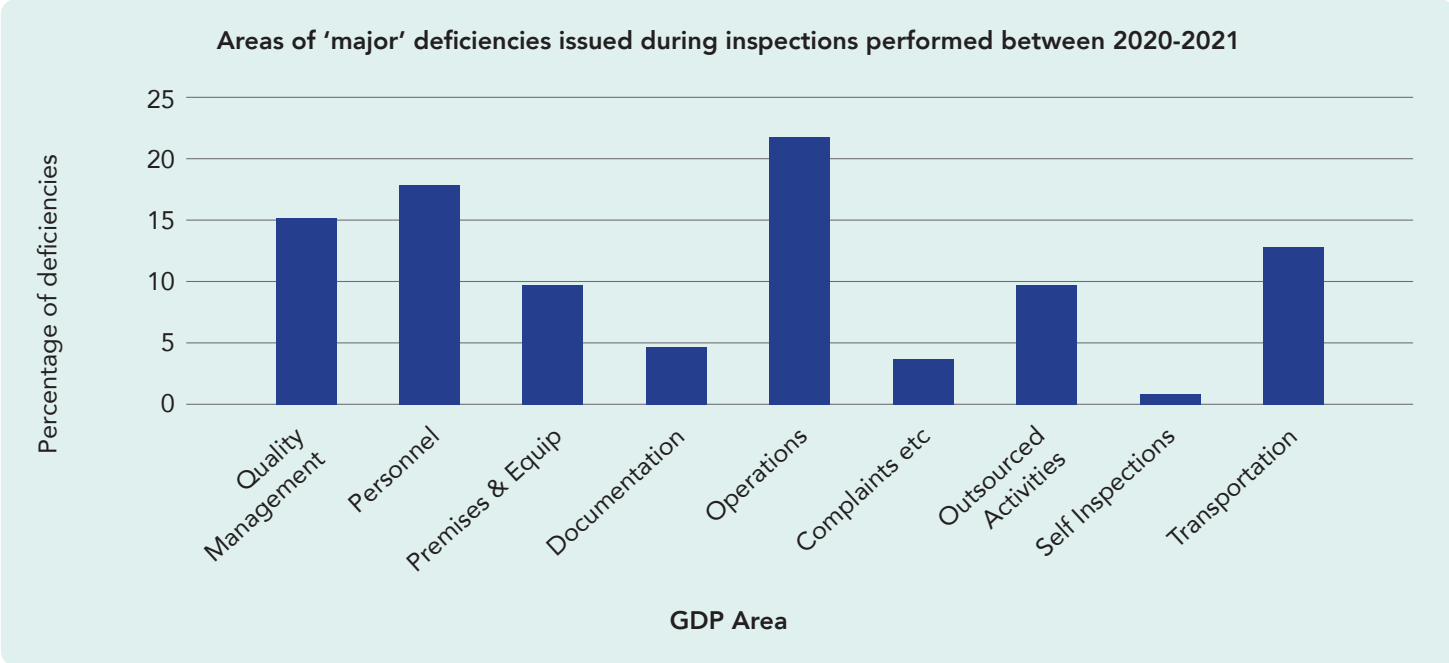
The extent to which these requirements apply will depend on the risks associated with the process. The processes should be assessed by the registrant against the requirements described in these guidelines. Controls other than those described in these guidelines, which the registrant has justified within its quality system to provide an equivalent level of protection for clinical trial subjects and integrity of the clinical trial data, may be acceptable. Higher risk processes, such as those involving aseptic manipulations of a dosage form, will be expected to closely adhere to these guidelines, in particular Annex 1, unless there is strong documented justification supporting an alternative approach.

The Minister for Health may publish further information on the appropriate requirements to be applied for those processes exempted under Article 61(5) of the CTR.

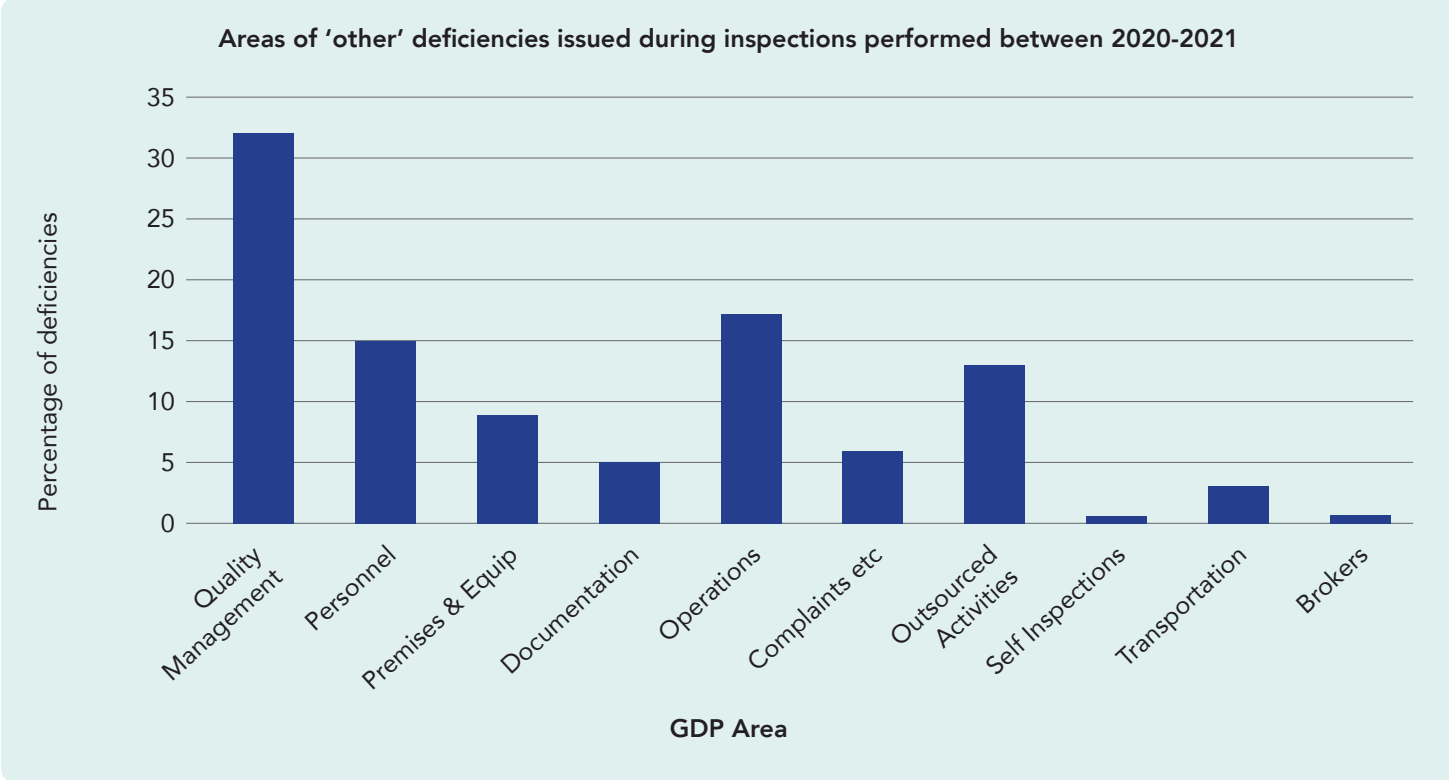
Common deficiencies issued to wholesale distributors

A review of all deficiencies resulting from 102 Good Distribution Practice (GDP) inspections performed between 2020 and 2021 were undertaken. There were 328 'major' deficiencies, 665 'other' deficiencies found; however, no critical deficiencies were issued during this period. The deficiencies identified were grouped together under the relevant chapters of the EU GDP Guidelines.

Examples of the most frequently occurring deficiencies for both 'major' and 'other' deficiencies are shown in graph 1 and graph 2.



Graph 1: GDP areas of 'major' deficiencies issued



Graph 2: GDP areas of 'other' deficiencies issued

The four chapters with the highest occurrence of deficiencies were Quality Management, Operations, Personnel and Outsourced Activities and it was evident during this review that several deficiencies were recurring within these areas (Table 1).

Table 1: The highest occurrence of deficiencies issued

Quality Management	• Change controls and risk assessments were not handled correctly or not raised when required; for example, changing the RP on the company WDA or the introduction of a new QMS. • SOP deficiencies such as: – RP oversight was often not detailed in procedures. – RPs were not approving SOPs. – Incorrect definitions or incorrect information included in SOPs. • Bona fides were not being completed on a routine basis, or being completed using the incorrect authorisation and licence.
Operations	• The RP had not approved the bona fides or there was no RP oversight. • Both the financial and physical route of supply was not qualified by the company. • The company had not verified all the details of the WDA such as the supplier/customer address, authorised operations, authorised medicinal categories. • Bona fides were not being completed on a routine basis, or were completed using incorrect authorisations and licences.
Personnel	• No evidence of a signed role profile for the RP or the RP role profile was deficient. • No evidence of annual refresher GDP training for RP/DRP. • The RP/DRP were not trained on updated HPRA guidelines.
Outsourced Activities	• Technical Agreements were deficient because: – they were not periodically reviewed. – they did not capture the requirements of the GDP guidelines. – they did not include requirements to report temperature excursions. – they did not incude training requirements or RP oversight requirements. • Audits not performed/Audit Reports deficient in that there was not enough detail included in the report.

Responsible person (RP) oversight was identified as a theme of concern throughout the findings of the review. For any wholesaler, the role of RP is critical within the operation and comes with important required responsibilities. The RP should have appropriate experience and knowledge to carry out this role. Management is expected to support this role by ensuring that the RP has the authority, resources, and full understanding of the wholesaling operations to fulfil their duties. The company should be able to demonstrate this during an inspection.

Guidance in respect of the duties/role of the RP is available from the HPRA Guide to Good Distribution Practice of Medicinal Products for Human Use.

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority