

HPRA MEDICINAL PRODUCTS

NEWSLETTER

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67

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Human Medicines



Brexit Updates (pages 1–4)

The Brexit transition period ended 31 December 2020 and the HPRA would like to take the opportunity to thank stakeholders for their extensive work in preparing for this event by ensuring regulatory compliance and robust supply chains. With the conclusion of the transition period, the HPRA continues to support applicants to maintain medicines availability through regulatory interactions, agreement of multilingual packages, of batch specific requests, publication of HPRA guidance and links to other available guidance.

The Commission ‘Withdrawal Notice’¹ (references included at the end of this section) outlines the expectations around the legal situation as of the end of the transition period including applicable rules in Northern Ireland. Furthermore, a Commission Notice² outlining certain exemptions that the competent authorities of Ireland (IE), Malta, Cyprus and the United Kingdom (UK) with respect to Northern Ireland UK (NI), are permitted to apply in respect of products supplied to their markets was published in December 2020 (latest version is dated 25 January 2021).

These exemptions, which are detailed further below (and further elaborated on page 3), are in summary:

- Allow continued batch release in the UK;
- Allow continued QC testing in the UK;
- Remove the requirement to decommission EU product under the Falsified Medicines Directive going to the UK.

To avail of these exemptions, a marketing authorisation holder must apply to the HPRA using the [application form](#). In particular, please note that the deadline for the application to continue QC testing must have been received by 30 January 2021.

Please find more information in this [European Commission communication](#).

Non-Compliant Marketing Authorisations following the Brexit Transition Period

From 1 January 2021, for medicines placed on the market in the EU, the following entities or activities may no longer be located in the UK (batch control, batch release and importation may take place in Northern Ireland):

- Marketing authorisation holder (MAH);
- Batch control site(s) for finished product (unless a time-limited exemption has been agreed – please see section ‘EU Commission permitted flexibilities to facilitate supply of medicines to the Irish market’ for details of these time-limited exemptions);²
- Batch release site(s) for finished product (unless a time-limited exemption has been agreed see section entitled ‘EU Commission permitted flexibilities to facilitate supply of medicines to the Irish market’ for details of these time-limited exemptions);²
- Products from Great Britain must be imported into the EU/EEA/ Northern Ireland by sites holding a manufacturer’s/importer’s authorisation (unless a time-limited exemption has been agreed, see section ‘EU Commission permitted flexibilities to facilitate supply of medicines to the Irish market’ for details of this time-limited exemption).²

If these activities have not been transferred to the EU/EEA, (or UK(NI) as appropriate) then the MAH must no longer place new batches of their medicinal products onto the Irish market. In order to give MAHs some time to rectify any remaining non-compliances, the HPRA will not be taking immediate action to suspend authorisations that are not regulatory compliant. MAHs are advised however to rectify remaining non-compliances as soon as possible as the HPRA will take appropriate regulatory action on authorisations that are not compliant in due course. Further practical guidance has been issued by CMDh for MR/DCP products in relation to Brexit⁷ and also specific to where Northern Ireland is a Concerned Member State (CMS).⁸ European Medicines Agency (EMA) guidance is also available.^{9,10}

Companies are also reminded that they are required to move their pharmacovigilance system master file and the qualified person for pharmacovigilance to the EU/EEA and update the article 57 database. The HPRA is currently reviewing this and will communicate further on this matter.

If you have queries in relation to achieving regulatory compliance or how the above requirements apply to your authorisation, please consult the [Brexit section of the HPRA website](#) or contact us directly at brexit@hpra.ie.

Marketing Authorisation Holder Transfer

For any marketing authorisation where the holder is based in the UK, this must now be transferred to a holder based within the EEA (an MAH cannot be located within Northern Ireland). To transfer the MAH from a UK holder to one based within the EEA, the HPRA transfer procedure must be used¹¹. As part of this process, a new product authorisation number will be issued for the product.

It is possible to transfer the MAH while there are ongoing/open variations. When the transfer is issued, the new MA holder details will transfer onto the open/ongoing variations.

An updated package leaflet is required to be submitted with a transfer application so that this can be displayed on the HPRA website. The package leaflet should reflect the new MAH details. A Word version of the package leaflet is acceptable.

NOTE: The HPRA transfer procedure was modified³ to assist companies with their Brexit-related activities e.g. for Brexit-related transfers MAHs are allowed up to six months to implement such packaging changes following issue of the transferred authorisation and, in any case, no later than the 1 October 2021. In addition, the HPRA no longer requires stock to be recalled from wholesaler level six months following the issue of the transferred authorisation / licence / registration.

Please find more details of the HPRA MAH transfer procedure in the HPRA ‘Guide to transfers of marketing authorisations, parallel import licences and dual pack import registrations for human medicines’¹¹.

Multilingual Labelling and Joint Labelling with the UK

The HPRA would like to remind stakeholders that we are willing to work with companies to develop multilingual packaging. Details on developing multilingual packaging are available on the HPRA website.⁴

The HPRA continues to accept the marketing of products that carry a joint label with the UK as per section 6.3 of the EU Commission notice on the *Withdrawal of the UK and EU rules for medicinal products for human use and veterinary medicinal products*¹.

The HPRA will accept joint labelling with the UK if the product information is the same in the UK as in Ireland and the product labelling and package leaflet is fully in line with the summary of product characteristics as authorised in Ireland. Administrative information such as the UK MAH name and address, marketing authorisation number, and site of batch release can be included on the joint labelling subject to it being distinguishable from IE information, and there being sufficient space to ensure legibility of the product information.

Article 41 of the Withdrawal Agreement

Under Article 41 of the withdrawal agreement, a medicine, which is certified by a Qualified Person and has been released in the UK for sale or supply before 11 pm on 31 December 2020, can be supplied to the Irish market after the transition period ends. The receiving site in Ireland, which must be appropriately authorised (e.g. an authorised manufacturer or wholesaler), must perform checks on all shipments of medicine received to which the provisions of Article 41 apply.

In accordance with the Northern Ireland protocol, there will be no change to the existing regulatory requirements for the supply of batches of medicines, certified by a qualified person at a manufacturing site and released for sale or supply in Northern Ireland, to the Irish market. Further details are available on our [website](#).

Registration of New Sites of Batch Release and/or Quality Control Testing Sites

If the site(s) of batch release and/or quality control testing have been transferred from Great Britain to the EU, the corresponding type IA_{IN}/IA variations must be submitted as per the timelines indicated in the CMDh 'Practical guidance for procedures related to Brexit for medicinal products for human use approved via MRP/DCP'.⁷ The relevant variation category is: B.II.b.2 *Change to batch release arrangements and quality control testing of the finished product*.

As stated above, in order to facilitate IE/UK joint labelling, the HPRA has no objection to the manufacturer(s) responsible for batch release for the Great Britain market being listed on the leaflet along with the manufacturer(s) responsible for batch release for the EU market, with the Great Britain site being clearly designated as being for Great Britain only. This allowance is on the basis that, according to EU law, EU batch release can only occur from sites within the EU 27 or UK (NI) after 31 December 2020 (unless a time-limited exemption has been agreed).²

Where a new leaflet has been implemented with an amended listing of batch release sites, the expectation is that the updated package leaflet would be used in the next scheduled packaging run. However, in order to minimise supply issues which might result from this expectation, the HPRA can accept a longer period before which the leaflet is used, but would expect that the revised package leaflet be used in packaging runs no later than six months after the change to the site of batch release has taken place.

European Commission Permitted Flexibilities to Facilitate Supply of Medicines to the Irish Market

The [European Commission has published a Notice](#) on 'Application of the Union's pharmaceutical acquis in markets historically dependent on medicines supply from or through Great Britain after the end of the transition period (2021/C 27/08).'^{2'}

This notice outlines that, due to the historical dependence of Ireland, Malta, Cyprus and Northern Ireland (UK(NI)) on medicines supplied from Great Britain, in the exceptional cases where additional time is required to transfer certain functions to EU/EEA, and in the exceptional circumstance of a global pandemic, an additional period of up to one year (January 2021 to 31 December 2021) to comply with aspects of the Union's acquis, has been agreed. These exemptions, which are applicable for medicinal products and investigational medicinal products are as follows, and are subject to certain conditions:

1. Medicinal products or investigational medicinal products can be imported from Great Britain into one of the above markets by wholesalers/importers which do not hold the relevant manufacturer's/ importer's authorisation to act as the site of physical importation and/ or to act as the site of batch release for those markets. This means that medicines and investigational medicinal products can be imported from Great Britain into one of the above markets and placed on the market in accordance with Union law, having been subject to batch release by a qualified person in Great Britain applying equivalent quality standards to those laid down in Union law, thus ensuring an equivalent level of protection of human or animal health.
2. Medicines can be imported from Great Britain into one of the above markets and placed on the market in accordance with Union law having undergone quality control testing in Great Britain, in line with Article 20 (b) of Directive 2001/83/EC for human medicinal products or Art 24(b) of Directive 2001/82/EC for veterinary medicines.
3. Article 22 of the Commission Delegated Regulation (EU) 2016/161 on safety features obliges wholesalers to decommission

unique identifiers (UIs) on products they intend to distribute outside of the Union. The conditional exemptions include a provision that allows a 12-month exemption from decommissioning the UIs on joint EU/UK packs that are intended for export to Great Britain.

The presence of UIs on the medicinal products imported into Ireland, Northern Ireland, Cyprus and Malta through Great Britain is an essential requirement as regards ensuring a high level of public health protection. The presence of UIs can only be achieved at present, if wholesale distributors, located in the Union, do not decommission the UIs on medicinal products in joint packs.

In order for the MAH (**which must be established in the Union**) or EU based sponsor/legal representative for a clinical trial, to apply for this **time-limited conditional exemption**, [a request form must be submitted to the HPRA](#) for the evaluation of the request (*no later than 30 Jan 2021 where it relates to quality control (QC) testing*). Please use brexit@hpra.ie for human medicines and vetinfo@hpra.ie for veterinary medicines requests. Approval of this request will be primarily based on the information provided and the conditions agreed to by the applicant in this form, which should be carefully completed according to the instructions included in the form. The exemptions relating to batch release and QC testing are intended to allow these activities to continue for a short period of time at currently registered sites in Great Britain to facilitate continued supply of medicines while these functions are being transferred to sites in the Union or Northern Ireland. Please note that these exemptions may not generally be availed of where the specific functions have already been transferred to EU/ EEA sites.

As part of the exemption, there is a requirement to provide regular updates on progress towards compliance to HPRA.

Acceptance by the HPRA of any requests for exemptions applies only to medicinal products/ investigational medicinal products supplied to the Irish market/clinical trials being carried out in Ireland. The exemptions are limited in time and will expire no later than 31 December 2021.

There will be no fee for these exemption requests.

Use of Stock Sourced from Great Britain to Mitigate Medicine Shortages to the Irish Market Where the Product is Authorised in Both Markets

Medicine shortages may be alleviated by supplying medicines, which have been authorised for use in Great Britain, to the Irish market, under a formal batch specific request (BSR) process agreed with the HPRA. In order to avoid product shortages, the HPRA may permit an MAH to place on the Irish market a medicine, which has been previously certified and placed on the market in Great Britain.

To apply to the HPRA to place a product imported from Great Britain on the Irish market to prevent a medicines shortage, please use the BSR application form.⁵

All queries in relation to such BSRs should be directed to brexit@hpra.ie

MAHs are reminded that any potential shortages should also be reported to the HPRA's shortages unit (shortages@hpra.ie) and to the HSE as outlined in section 5.1 of the [Medicines Shortages Framework](#).

Parallel Product Authorisations

Parallel importation, as defined by the European Commission communication on *Parallel Imports of Proprietary Medicinal Products for which Marketing Authorisations have already been granted* (COM(2003)839), is a lawful form of trade within the internal market as per article 28 of the EC Treaty and subject to the derogations provided by article 30 of the EC Treaty.

Since the 31 December 2020, Great Britain is no longer part of the internal market, and has reverted to the status of a third country. However, the provisions of Union law apply to the United Kingdom in respect of Northern Ireland, under the conditions referred to in Annex 2 of the Protocol on Ireland/Northern Ireland after the 31 December 2020.

This means that PPA holders may no longer be based in Great Britain or UK (NI), and repackaging and batch certification may no longer take place in Great Britain.

A medicinal product may be sourced for the purposes of parallel trade from Great Britain only when it can be demonstrated that the batch of the goods in question was placed on the market in Great Britain prior to 11 pm (GMT) 31 December 2020. Medicinal products may be newly sourced from UK (NI) for the purposes of parallel trade after 31 December 2020 where UK(NI) is registered as a new source country. This is without prejudice to the rules on intellectual property, in particular trademarks.

A list of Q&As for PPAs will be available shortly on the HPRA website.

Clinical Trials

Sponsors of clinical trials conducted in Ireland are reminded of the legal situation applicable after the end of the transition period as described in the Commission Notice *Withdrawal of the United Kingdom and EU rules in the field of Clinical trials*⁶. Sponsors of clinical trials or their legal representatives for clinical trials must now be established in the EU. Furthermore, import of investigational medicinal product into the EU is subject to the holding of a manufacturer's/importer's authorisation (MIA) and, in order to certify batch release, the qualified person has to be established in the EU/EEA/UK(NI), unless a time-limited exemption has been approved by the HPRA for a trial in Ireland (see section on EU Commission flexibilities² above). Since 31 December 2020, Great Britain is a third country with regards to implementation of clinical trials legislation Directive 2001/20/EC. Therefore, where authorised products are being used in clinical trials, they should be sourced from the EU/EEA/UK(NI). In order to mitigate difficulties arising with trial supplies from Great Britain, sponsors may consider sourcing sufficient stocks of batches which were released in UK before 31 Dec 2020 (see note on Article 41 above).

Sponsors who identify regulatory difficulties in relation to their trials in Ireland are advised to contact the HPRA at brexit@hpra.ie.

Useful Links

A list of useful links is provided below:

1. [European Commission Notice to Stakeholders: Withdrawal of the United Kingdom and EU rules for medicinal products for human use and veterinary medicinal products March 2020](#)
2. [European Commission Notice: 'Application of the Union's pharmaceutical acquis in markets historically dependent on medicines supply from or through Great Britain after the end of the transition period](#)
3. [HPRA Brexit Guidance for Stakeholders](#)
4. [HPRA information on multilingual packaging](#)
5. [Batch specific request application form](#)
6. [European Commission Notice to Stakeholders: Withdrawal of the United Kingdom and EU rules in the field of clinical trials May 2020](#)
7. [Practical guidance for procedures related to Brexit for medicinal products for human use approved via MRP/DCP December 2020 CMDh/373/2018 Rev 5 Corr 1](#)
8. [Practical guidance on the implementation of the Protocol on Ireland/Northern Ireland for medicinal products for human use approved via MRP/DCP December 2020 CMDh/426/2020](#)
9. [EMA Questions and Answers to stakeholders on the implementation of the Protocol on Ireland/Northern Ireland \(December 2020\). EMA/520875/2020](#)
10. [EMA Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure EMA/478309/2017 Rev 5](#)
11. [HPRA guide to transfers of marketing authorisations, parallel import licenses and dual pack import registrations for human medicines](#)

Worksharing Variations (with National and/or MR Products) for which Ireland is the Reference Authority

The designated mailbox (worksharing@hpra.ie) for work-sharing variation requests for the HPRA to act as a reference authority has been reinstated.

MAHs are requested to advise of upcoming work sharing procedures by email to this mailbox at least two weeks before the planned submission, using the HMA [template for the letter of intent](#) for the submission of a work sharing procedure.

Such pre-submission information – known as the ‘letter of intent’ – should contain the following information:

- List of the concerned marketing authorisations;
- Explanation as to why all concerned marketing authorisations are considered to belong to the same holder;
- Description of the variation;
- List of the proposed reference authorities in preferred order;
- In case the preferred reference authority has not granted a marketing authorisation for all concerned marketing authorisations, the MAH should explain the choice of the preferred reference authority;
- Explanation as to why the holder believes that a work sharing procedure is suitable;
- Planned submission date.

Product Information Update (PIU)

The HPRA has updated the guidance on Product Information Updates (PIUs) and the mailbox address (info@hpra.ie). PIUs can now be searched on the Safety Notices page of our website as a 3rd party publication. For more information, please see the [Product Information Update](#) page on our website.

Registered Product Information

The following approach is requested in relation to the registration of product information for Ireland:

Marketing authorisation applications

Product information provided by the applicant at the end of a marketing authorisation application should be submitted as the ‘national text’ (i.e. in the form of QRD template texts for the SmPC, leaflet and labels including national elements such as agreed name and PA number), along with colour mock-ups if the product is being marketed in Ireland.

Where the product is not being immediately marketed, it is acceptable to only submit the national text. The mock-ups can be registered using an Article 61(3) notification at a later date prior to marketing.

For MR/DCP procedures where the product is not being immediately marketed, while the HPRA would prefer to receive the national text, the EU common text can be accepted in the national phase at the end of the authorisation procedure. Where the EU common text has been submitted, the subsequent Article 61(3) must also include the national text for reference. However, where additional national warnings are required on the labelling, the national text must be provided in the national phase at the time of authorisation.

The HPRA considers the national text version of the product information to be the registered product information.

The HPRA reviews colour mock-ups to ensure user-friendly designs, readability and to avoid the arrangement of information in a format that could lead to confusion for the healthcare professional or patient. The HPRA does not review the text in the label and package leaflet mock-ups, and it is the responsibility of the marketing authorisation holder to ensure that the text in the labelling and leaflet mock-up and on the marketed product are in line with the registered product information text templates.

Renewals

It is no longer necessary to submit product information at the end of the renewal procedure unless minor editorial changes are being introduced. In these cases, revised product information should be submitted as the national text and mock-ups (if marketed).

Where more significant changes to the product information are identified as being required during the renewal procedure, these changes will need to be introduced by variation or Article 61(3) notification post-renewal.

Post-authorisation changes to product information

Where a variation or an Article 61(3) submission relates to a change to the wording in the labelling/leaflet text and hence also on the mock up, then both the national text and the mock up should be submitted. Where there are no wording changes, then text versions are not required to be submitted with the Article 61(3). Refer to the HPRA Guide to Labels and Leaflets of Human Medicines, as not all changes require a submission and these situations are outlined in the guide.

All submissions in which there have been changes to the leaflet text should be accompanied by a clean national text version of the leaflet, as this is the version that will be made available on the HPRA website.

Shortened Renewal Procedure – CMDh Best Practice Guide on the Processing of Renewals in the Mutual Recognition and Decentralised Procedures

The HPRA would like to remind marketing authorisation holders that products authorised under Directive 2001/83/EC may follow a shortened renewal procedure, i.e. a 30-day timetable under certain circumstances (see relevant sections of the best practice guide). The application should comprise a cover letter and an application form (without annexes) and a declaration that full documentation will be available for submission upon request. Changes to MA particulars, or an updated RMP, will not be accepted during a shortened renewal

procedure. Please see the [CMDh Best Practice Guide on the processing of renewals in the Mutual Recognition and Decentralised Procedures](#) for further information.

Examples

- A product authorised under Article 10(1) of Directive 2001/83/EC in all Member States concerned, i.e. 'generics' may follow a shortened procedure if there are no proposed changes to the MA.

- A renewal application in line with Covid-19 flexibilities: consider a shortened procedure if there are no proposed changes to the MA.
- Mutual Recognition Procedures where unlimited validity has already been agreed in the RMS (Including Repeat Use Procedures): a shortened renewal procedure may be applied in certain situations.

Please note that a shortened renewal can also be applied to nationally authorised products.

Article 57 Database: Updates to Qualified Person Responsible for Pharmacovigilance (QPPV) and the Pharmacovigilance System Master File (PSMF)

Marketing Authorisation Holders are reminded that any changes to the QPPV, including their contact details, or to the location of the PSMF, must be updated in the Article 57 database immediately. This is particularly important if there have been any recent changes arising from Brexit. Such changes are not subject to a type 1AIN variation.

Compliance with the QRD Template

The EMA working group on Quality Review of Documents (QRD) develops, reviews and updates templates for product information for use by marketing authorisation holders (MAHs) for human medicines on an ongoing basis. The HPRA wishes to remind MAHs that their product information should comply with current QRD requirements.

The QRD template was updated in June 2019 to QRD template v10.1. At that time, contact details for reporting suspected adverse reactions to the HPRA were amended in Appendix V in line with the preferred method for submission of reports (online). Therefore, the wording in section 4.8 of the Summary of Product Characteristics (SmPC) and section 4 of the Package Leaflet (PL) for authorised products in relation to the submission of ADR reports, should reflect the wording in Appendix V of the template and if not already updated, this should be undertaken at the next regulatory opportunity.

In addition, Direct Healthcare Professional Communications (DHPCs) or any other documents providing contact details for reporting of suspected adverse reactions to the HPRA should also include the wording specified in Appendix V of the template.

Version 10.2 of the QRD template (updated as of 01/01/2021) is available on the EMA [website](#).



Brexit Implications for Veterinary Medicinal Products

The UK departed the EU as of 31 January 2020 and the transition period ended on 31 December 2020. Marketing Authorisation Holders (MAHs) will be aware that this necessitates several changes to products for which key regulatory activities are located in the UK. In relation to quality control (QC) testing

and batch release in the UK, MAHs should refer to the separate article (below) relating to time-limited exemptions for veterinary medicinal products in Ireland. In relation to transfer of MAH from a UK to an EU legal entity, MAHs are reminded that these transfers should be conducted as soon as possible and that location of

an MAH in the UK is not compliant with the EU *acquis*. In addition, there is a requirement that the QPPV responsible for pharmacovigilance is resident in the EU and any changes to product authorisations to ensure compliance with this requirement should also be made without delay.



Time-limited Conditional Exemptions to Facilitate Supply of Medicines to the Irish Market after Brexit

The European Commission has [published a Notice](#) on 'Application of the Union's pharmaceutical *acquis* in markets historically dependent on medicines supply from or through Great Britain after the end of the transition period'.

This notice outlines that due to the historical dependence of Ireland (IE), Malta, Cyprus and Northern Ireland (UK (NI)) on medicines supplied from Great Britain, in the exceptional cases where additional time is required to transfer certain functions to EU/EEA, and in the exceptional circumstance of a global pandemic, an additional period of up to one year (January 2021 to 31 December 2021) to comply with aspects of the Union's *acquis*, has been agreed. These exemptions, which are applicable for medicinal products and investigational medicinal products are as follows, and are subject to certain conditions:

1. Medicinal products or investigational medicinal products can be imported from Great Britain into one of the above markets by wholesalers/importers which do not hold the relevant Manufacturer's/Importer's Authorisation to act as the site of physical importation and/ or to act as the site of batch release for those markets. This means that medicines and investigational medicinal products can be imported from Great Britain (GB) into one of the above markets and placed on the market in accordance with Union law, having been subject to batch release by a Qualified Person (QP) in Great Britain applying equivalent quality standards to those

laid down in Union law, thus ensuring an equivalent level of protection of human and animal health.

2. Medicines can be imported from Great Britain into one of the above markets and placed on the market in accordance with Union law having undergone quality control testing in Great Britain, in line with Article 20 (b) of Directive 2001/83/EC for human medicinal products or Art 24(b) of Directive 2001/82/EC for veterinary medicines.
3. Article 22 of the Commission Delegated Regulation (EU) 2016/161 on safety features obliges wholesalers to decommission unique identifiers (UIs) on products they intend to distribute outside of the Union. The conditional exemptions include a provision that allows a 12-month exemption from decommissioning the UIs on joint EU/UK packs that are intended for export to Great Britain.

The presence of UIs on the medicinal products imported into Ireland, Northern Ireland Cyprus and Malta through Great Britain is an essential requirement as regards ensuring a high level of public health protection. The presence of UIs can only be achieved at present, if wholesale distributors, located in the Union, do not decommission the UIs on medicinal products in joint packs.

In order for the MAH (which must be established in the Union) or EU-based sponsor/legal representative for a clinical trial, **to apply for this time-limited conditional exemption**, a

request form must be submitted to HPRAs for the evaluation of your request (*no later than 30 January 2021 where it relates to quality control (QC) testing*). The form is available to [download from the HPRAs website](#).

Please send to brexit@hpra.ie for human medicines and vetinfo@hpra.ie for veterinary medicines requests. Approval of this request will be primarily based on the information provided and the conditions agreed to by the applicant in this form, which should be carefully completed according to the instructions provided within. The exemptions relating to batch release and QC testing are intended to allow these activities to continue for a short period of time at currently registered sites in Great Britain to facilitate continued supply of medicines while these functions are being transferred to sites in the Union or Northern Ireland. Please note that these exemptions may not generally be availed of where the specific functions have already been transferred to EU/EEA sites. As part of the exemption, there is a requirement to provide regular updates on progress towards compliance to the HPRAs.

Acceptance, by the HPRAs, of any requests for exemptions, applies only to medicinal products/ investigational medicinal products supplied to the Irish market/clinical trials being carried out in Ireland. The exemptions are limited in time and will expire no later than 31 December 2021.

There will be no fee for these exemption requests.

Communicating with the Veterinary Sciences Department on General Matters

For general queries, i.e. those not related to on-going applications, the most efficient means to contact us is by email at the following email address: vetinfo@hpra.ie. This email address is

managed on a daily basis by colleagues within our department. Use of other email addresses may mean a delay in the HPRAs response, as the enquiry will need to be relayed onward. We expect

to revert to all queries submitted within three working days of them being received by our department.

Compliance of Veterinary Medicines for Exotic Pets with New Regulatory Requirements

Article 5.6 of Regulation 2019/6 has significant implications for the regulation and availability of those medicines for exotic pets (aquarium and pond animals, cage birds, homing pigeons, terrarium animals, small rodents, ferrets and pet rabbits) which previously were exempted under national legislation (e.g. SI. No. 786 of 2007 and prior statutory instruments). The Regulation states that the medicines concerned must either be authorised as veterinary medicinal products or, where specific provision is made under new national legislation, be registered in accordance with specific new requirements. The HPRAs is in discussion with the Department of Agriculture, Food and the Marine

about the elaboration of new national legislation and whether provision will be made for a new registration system, which must meet certain standards and criteria, including:

- a. They must not contain substances that are controlled under veterinary prescription (e.g. antiparasitic substances);
- b. They must be manufactured in accordance with Good Manufacturing Practice, by a licensed veterinary medicines manufacturer;
- c. The product labelling and package leaflet information must be approved in the Member State so that it can be uploaded to a new EU central

database of veterinary medicinal products (known as the Union Product Database [UPD]);

- d. They are subject to controls, including inspections, advertising controls and pharmacovigilance obligations.

In order to address the current situation and to assist industry in meeting the new requirements, the HPRAs is organising a virtual meeting with stakeholders in the coming months. Participation to this event is by invitation only. To request an invitation, please contact vetinfo@hpra.ie in the first instance.

HPRAs has Commenced Implementation of Regulation 2019/6 — How to Keep Track of Developments

Regulation 2019/6 may appear to the general public to represent only an incremental change in the regulatory framework for veterinary medicinal products. However, for those involved in the business of manufacturing, importation, supplying or distribution of veterinary medicinal products in Ireland, this is a generational change. It will have significant ramifications for both those already involved in the animal health business in Ireland, as well as others who up to now were legally entitled to supply certain veterinary medicinal products that had been exempt from the requirements of a marketing authorisation.

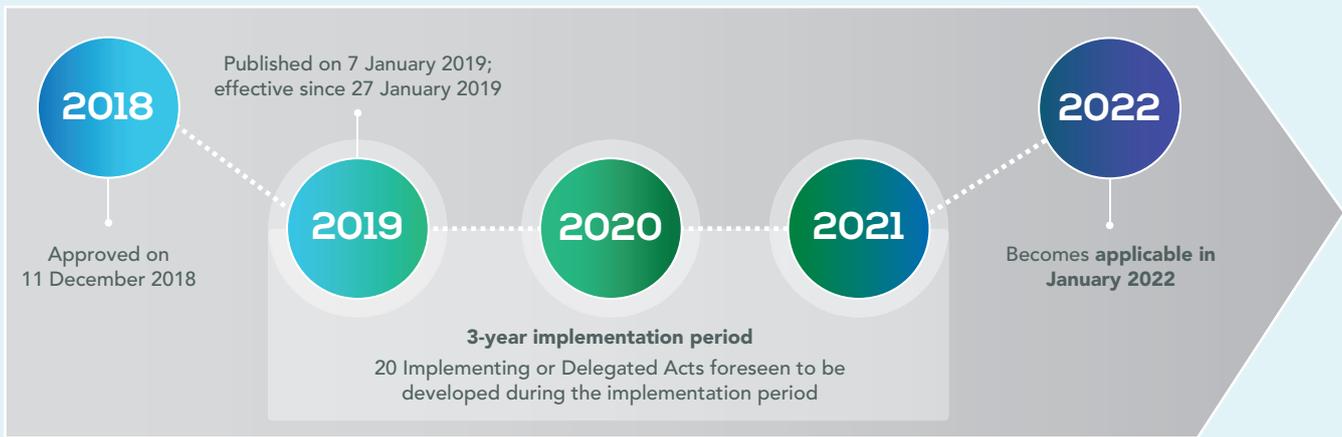
To assist stakeholders to make the necessary changes to their businesses to comply with the new legislation, which takes effect from 28 January 2022, the HPRAs has developed a dedicated section on our website hpra.ie/NewVetReg where you can follow developments. This website is being updated on a regular basis to provide stakeholders with the latest information. The website also contains links to both the EU Commission's and the EMA's website of latest developments in relation to the implementation of the Regulation.

The HPRAs has commenced an internal project to ensure that any work processes, forms and guides that

must be changed to facilitate the new legislation are completed expediently. The HPRAs aims to ensure that the relevant forms and guides are available on our website by 30 November 2021 (2 months ahead of go-live of the new system), or as soon as new national legislation is available and the final requirements are known to us.

If you have suggestions for content for our webpage, or for the provision of workshops or webinars to assist in meeting the new requirements, please contact the HPRAs (vetinfo@hpra.ie).

New Veterinary Regulation: Timeline



Update on Irish Language Case

In respect of proceedings relating to the provision of bilingual packaging of veterinary medicines in the Irish and English languages brought against the Department of Agriculture Food and the Marine (DAFM), the European Court of Justice (ECJ) gave its preliminary judgement on 14 January 2021. The issue being decided is whether the court of a Member State has the discretion in judicial review cases to refuse relief where the rights in question come from EU law. This question arises due to differences in the legal systems between 'Common Law' countries,

such as Ireland, and those of mainland European 'Civil Law' countries. In the former case, judges have broad discretionary powers in deciding cases but in the latter case, judges do not.

The EU Court said that the national court in Member States have certain discretion to find a case-appropriate and proportionate outcome, even if rights based on EU law are at stake. Therefore, it will be up to the Irish Court to decide whether to grant the applicant's request to see dual-language labelling for veterinary medicines authorised in Ireland.

Once the matter has been finalised by the ECJ, the decision is expected to be returned to the High Court in Dublin to decide on what to do next, in the knowledge that Regulation 2019/6 provides that Member States can choose the language of the text to be used in the package leaflet and labelling. Regulation 2019/6 applies from 28 January 2022.

The HPRA will continue to monitor developments in this case.

Update on Stakeholder Survey in September 2020

The purpose of the survey was to enquire of animal health companies regarding their planning for 2021, including planning for the effects of Brexit and preparations for the new veterinary regulation (Regulation 2019/6). The HPRA hopes that by being aware of industry plans we will be better placed to position the HPRA to serve the needs of animal health.

There was a 20% response rate to the survey. This means that the results must be interpreted with caution as they may not reflect the views of the industry overall. Concerning the expectations of industry, some 52% of responders advised that they expected to increase the number of veterinary medicines in Ireland over the next two years, with a further 33% advising that they expect

to maintain current portfolios. Some 95% of responders expect to maintain joint-labelled packs with the UK notwithstanding the effects of Brexit, while 5% expect to introduce multi-lingual packs with EU Member States in response to Brexit. No companies plan to introduce medicines with specific labelling uniquely for the Irish market. Some 39% opined that if a common UK/Ireland label is no longer feasible, medicines will be withdrawn from the market in this country. Some considered that the market for vaccines was especially vulnerable and that a national initiative to identify alternative routes of supply should be undertaken. A few companies considered that the reduced labelling requirements under Regulation 2019/6 will facilitate multi-lingual packs from 2022.

Regarding the drivers for selection of Reference Member State (RMS) in decentralised procedures, the biggest factors cited were the openness to meet / good communications between the RMS and the applicant (> 90%) and the range of technical expertise / advice available (> 80%). Cost was an important factor in 75% of cases, while the ability to book procedures at short notice was cited as important by 88% of responders. Thirteen responders advised that they expect to use the HPRA as RMS during 2021 with the majority of them advising that they expected to conduct one or two procedures during the year. Regarding the expected impact of opening up the centralised procedure to all new products from 2022, 44% of responders advised that they did not expect this

to impact on their demands for HPRA services, with a further 44% advising that they expect to make greater use of the centralised procedure rather than the decentralised procedure.

Regarding the impact of COVID-19 on the supply of veterinary medicinal products in Ireland, 67% of responders advised that there was no significant

impact, with 27% advising that they have experienced issues with supply chain management/sourcing of raw materials. Some 7% advised that they had delayed the development of new products as a result of COVID-19.

The HPRA wishes to thank all those who responded to the survey. We are available to discuss our availability

to act as RMS or to provide scientific advice during 2021. For further information, contact Ms Elaine Hynes, Planning and Authorisation Manager (elaine.hynes@hpra.ie).

HPRA Veterinary Information Day 2021

The HPRA is planning to host a Veterinary Information Day in late 2021. The principal focus of the information day is to update marketing authorisation holders and other stakeholders with respect to changes to our work processes and activities as a result of the implementation of Regulation 2019/6. The meeting will also be of interest to those involved in the manufacture or import of veterinary medicinal products, as personnel

from both the HPRA's Compliance Department and the Veterinary Science Department will be involved.

If progress on new national legislation to replace SI No. 786 of 2007 is advanced sufficiently, the HPRA would also hope to provide information on its impact on the regulation of veterinary medicinal products in Ireland. If you have ideas for topics you would like to see covered, please make your

suggestions to vetinfo@hpra.ie, quoting Vet Info Day 2021 in the subject heading.

At present, the HPRA is not in a position to confirm whether this meeting will take place physically or virtually. A final decision on the date of the meeting will be made early in 2021 and details will be available on the [HPRA website](#).

Compliance

Annex 2 of the Wholesale Distribution Authorisation (WDA) — Contract Storage Site(s) in the United Kingdom

The UK departed the European Union on 31 January 2020 and the associated transition period ended on 31 December 2020. At the end of the transition period, the UK reverted to the status of third country.

The scope of the WDA normally applies to wholesaling activities carried out directly by the WDA holder or, indirectly, through contracted storage sites located in the EEA. This means that, since the end of 2020, **wholesalers in Ireland are no longer able to store medicines in contract storage sites in Great Britain (GB)**. However, in accordance with the Northern Ireland protocol, wholesalers will continue to be able to store medicines in contract storage sites in Northern Ireland.

The above change applied from 31 December 2020; however, in order to provide adequate time for companies to vary their WDA(s) to remove contract storage site(s) located in GB the necessary **variation(s) can be submitted up to 31 March 2021**.

- If the WDA lists only a contract storage site(s) in GB, a technical variation to Annex 2 will need to be submitted to add an alternate contract storage site located in the EEA and to remove the contract storage site(s) located in GB. A fee will be applied to the technical variation, but no fee will be applied to the administrative variation (i.e. the removal of GB storage sites).

- If the WDA lists contract storage sites within the EEA and contract storage sites in GB, an administrative variation to Annex 2 will need to be submitted to remove those site(s) located in GB. No fee will be applied to the administrative variation.

If WDA holders become aware of an issue that could potentially affect supply of a medicine to patients in Ireland because of the above changes, we request that you engage with the HPRA immediately at compliance@hpra.ie.

Mutual Recognition Agreements with Third-country Authorities – Supporting Documentation Required for Addition of Sites Located in these Territories to Annex 3 and Annex 4 of Manufacturing Importation Authorisations (MIAs)

The EU has mutual recognition agreements (MRAs) or an agreement on conformity assessment and acceptance of industrial goods (ACAA) with third-country authorities concerning the conformity assessment of regulated products. Such agreements contain a sectoral annex on the mutual recognition of good manufacturing practice (GMP) inspections and batch certification of human and veterinary medicines.

MRAs/ACAAs allow EU authorities and their counterparts to:

- rely on each other’s GMP inspection system;
- share information on inspections and quality defects;
- waive batch testing of products on import into their territories.

Each agreement has a different scope. A detailed list of product types not covered under the terms of the MRA/ACAA between the EU and partner countries is summarised below:

Country	Products Excluded
Australia	<ul style="list-style-type: none"> - Advanced Therapy Medicinal Products (ATMPs). - Investigational Medicinal Products (IMPs) used in phase I clinical trials. - Active Pharmaceutical Ingredients (APIs), other than those for human medicinal products.
Canada	<ul style="list-style-type: none"> - Stable medicinal products derived from human blood or blood plasma. - ATMPs. - APIs. - Veterinary biologicals. - IMPs manufactured by manufacturers which do not hold a manufacturing authorisation or establishment licence.
Israel	<ul style="list-style-type: none"> - Medicinal gases. - Homeopathic medicines. - IMPs. - Medicinal products derived from human blood or human plasma. - Veterinary immunologicals. - ATMPs.
Japan	<ul style="list-style-type: none"> - Veterinary medicines. - Stable medicines derived from human blood or blood plasma. - ATMPs - Medicinal gases. - IMPs. - Homeopathic products not classified as medicinal products in Japan.
New Zealand	<ul style="list-style-type: none"> - ATMPs. - APIs.
United States	<ul style="list-style-type: none"> - Human blood and plasma. - Human tissues and organs. - Veterinary immunologicals. - ATMPs. - IMPs. - Veterinary medicines.* - Vaccines for human use and plasma-derived medicines.*

* Transitional provisions apply for veterinary medicines, vaccines for human use and plasma-derived medicines. The assessment of the GMP inspectorates for veterinary medicines for the veterinary scope is ongoing.

There are four different scenarios when a contract site located in an MRA/ACAA partner country is required to be included in an MIA:

- Addition of a contract site to a commercial MIA where the product concerned is covered by the scope of the MRA: The MIA holder is required to provide the documentation listed in the table below to support the application.

- Addition of a contract site to a commercial MIA where the product concerned is not covered by the scope of the MRA: The MIA holder is required to provide a GMP Certificate issued by an EU regulatory authority that covers the dosage form.
- Addition of a contract site to an IMP MIA where the product concerned is covered by the scope of the MRA: The MIA holder is required to provide the documentation listed in the table below to support the application.

- Addition of a contract site to an IMP MIA where the product concerned is not covered by the scope of the MRA: The MIA holder is required to provide a Qualified Person (QP) declaration to support the activities to be included in Annex 3 or Annex 4 of the MIA.

In certain circumstances, it may be necessary for the HPRA to request further information from the relevant MRA/ACAA partner prior to approval of the variation to add the contract facility to the MIA.

Country	Supporting Documents
Australia	- GMP certificate issued by the Therapeutic Goods Administration (TGA), Australia.
Canada	- Evidence of compliant status of the Canadian site with regard to the relevant category of manufacturing activity, or - Inspection exit notice issued by Health Canada.
Israel	- GMP certificate issued on EudraGMP by the Institute for Standardization and Control of Pharmaceuticals, Israel
Japan	- GMP certificate issued by the Ministry of Health, Labour and Welfare (MHLW), Japan.
New Zealand	- GMP certificate issued by Medsafe.
Switzerland	- GMP certificate issued by Swissmedic.
United States	- FDA Establishment Identifier (FEI) number for the site.

Updated Details for Reporting of Quality Defects

The HPRA Quality Defects and Recall (QDR) group is responsible for receipt and investigation of quality defect issues for human and veterinary medicines on the Irish market, as well as medicines manufactured in Ireland for other markets.

Suspected quality defects may be reported to the HPRA through the following means:

1. The HPRA [online reporting system](#) for healthcare professionals, pharmacists and the public.

2. By email to: qualitydefects@hpra.ie,
Manufacturers, marketing authorisation holders and wholesalers wishing to report a quality defect are requested to consult the following guidance document: [Guide to Reporting and Initial Investigation of Quality Defects in Medicinal Products for Human and Veterinary Use](#), and to complete a [Quality Defect Report Form](#). The completed form should be submitted via email to qualitydefects@hpra.ie.

3. By telephone (urgent issues) to the following numbers:

Please note some changes have been made to the HPRA's contact details for urgent Quality Defects and Recalls.

Contact Name	Telephone (Office hours)	Mobile No. (Out of hours)	Email Address
Dr Michelle Cuffe Quality Defects and Recall Manager	+353 1 676 4971	+353 86 008 3221	michelle.cuffe@hpra.ie
Ms Breda Gleeson Market Compliance Inspector	+353 1 676 4971	+353 87 970 3559	breda.gleeson@hpra.ie
Dr Kevin O'Donnell Market Compliance Manager	+353 1 676 4971	+353 87 956 2818	kevin.odonnell@hpra.ie
Mr John Lynch Director of Compliance	+353 1 676 4971	+353 87 234 7294	john.lynch@hpra.ie

A Review of Deficiencies Cited during Good Distribution Practice (GDP) Inspections in 2018 and 2019

A review was carried out on the deficiencies cited during GDP inspections for medicinal products in 2018 and 2019. This review examined the classification of the deficiencies and the GDP chapters of the EU Guidelines on GDP of Medicinal Products for Human Use against which the deficiencies were cited.

Findings

In total, 286 GDP inspections of distributors of medicinal products were included in the review. Of these, 1% had a citation of at least one critical deficiency, 77% had a citation of at least one major deficiency, and 98% had a citation of at least one "other" deficiency. All inspections had a minimum of one deficiency cited. The different combinations of deficiencies cited were analysed. As seen in Graph 1, the most common combination was the citation of both a major and "other" deficiency and the least common was the citation of both a critical and major deficiency.

Critical deficiencies

Critical deficiencies were most commonly cited (66%) against EU GDP Chapter 6: *Complaints, returns, suspected falsified medicinal products and medicinal product recalls*. The inadequate management of complaints, recalls and training and the failure to apply the principles of quality risk management to the management

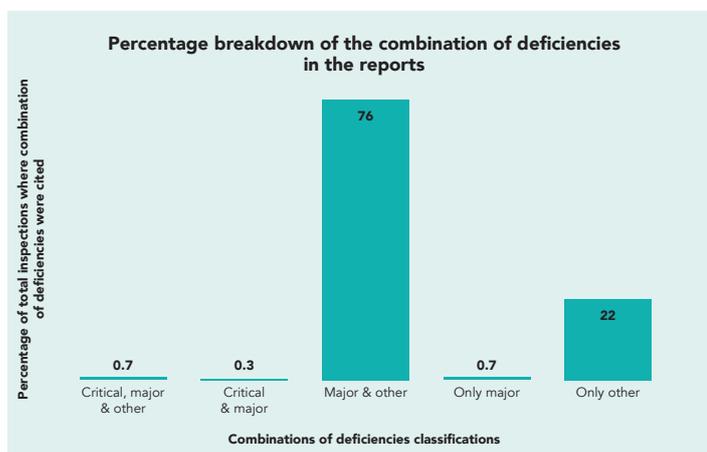
of a falsified product accounted for half of the critical deficiencies cited. Examples of critical deficiencies cited in relation to the mismanagement of a recall included failure to quarantine all affected batches of the product and the supply of a recalled batch. Examples of critical deficiencies cited in relation to the mismanagement of complaints included not thoroughly investigating the complaint to identify the root cause.

Major deficiencies

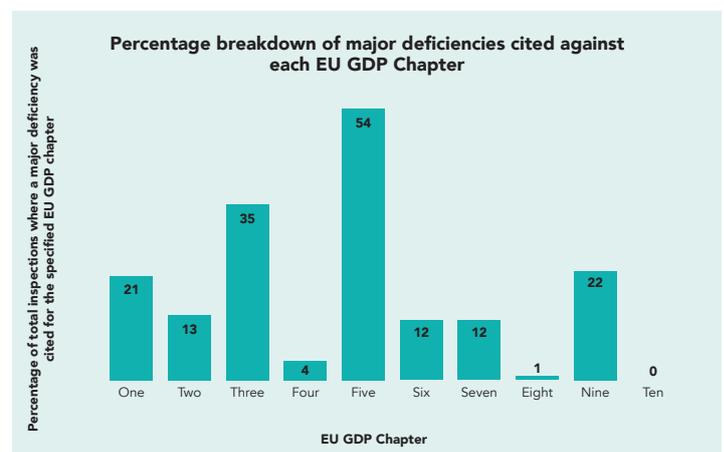
As evident from Graph 2, EU GDP Chapter 5: *Operations*, was that against which major deficiencies (54%) were most commonly cited. The majority of these were in relation to the qualification of customers and suppliers. Of this group of deficiencies, the most common (52%) was that the wholesaler did not ensure that customers and/or suppliers complied with the principles of the EU GDPs. This included not obtaining copies of the customer/supplier's GDP certificate or obtaining a GDP certificate for the wrong site. Other major deficiencies cited against Chapter 5 included inadequate traceability or records for the receipt, storage, picking or supply of a medicinal product. This accounted for 26% of major deficiencies and examples included inconsistent recording of a batch number throughout the documentation and incorrectly documented goods in checks.

"Other" deficiencies

EU GDP Chapters 1: *Quality Management* and 6: *Complaints, returns, suspected falsified medicinal products and medicinal product recalls* were those against which the highest percentage (64%) of "other" deficiencies were cited. The majority of "other" deficiencies (30%) cited against Chapter 1 were in relation to deviations not handled correctly or not raised. Examples included no documented investigation into the deviation and no documented justification for the Responsible Person's decision. The majority of "other" deficiencies (41%) cited against Chapter 6 were in relation to the inadequate management of mock recalls or no mock recall being performed. Deficiencies in relation to inadequate management of mock recalls included the company not completing the product recall form or no reconciliation records being available for review. The mismanagement of complaints accounted for approximately a quarter of the "other" deficiencies cited and included a failure to trend complaints or record distribution-related complaints.



Graph 1: Depicts the percentage of total inspections where each combination of deficiencies was cited.



Graph 2: Depicts the percentage of total inspections in which each EU GDP Chapter had a major deficiency cited.

Requirements in Relation to Third Country Qualifications of Safety Assessors of Cosmetic Products

Article 10 of the European Cosmetics Regulation (EC) No. 1223/2009 requires the completion of a safety assessment to be carried out by a suitably qualified Safety Assessor for each cosmetic product placed on the market in the European Union (EU)/European Economic Area (EEA).

The Responsible Person (RP) for the cosmetic product must ensure that the Safety Assessor is suitably qualified and this should be appropriately justified and demonstrated in Part B of the Cosmetic Product Safety Report (CPSR).

For cosmetic products where the RP is located in Ireland, the HPRA assesses the suitability of the qualifications of safety assessors on a case-by-case basis, for example during the CPSR review, considering both the formal qualification and the relevant experience of the safety assessor.

For safety assessors who have received their university qualification(s) from a country outside the EU/EEA, please note that QQI (Quality and Qualifications Ireland) is an independent State agency responsible for promoting quality and accountability in education and training services in Ireland. Hosted by QQI, NARIC (National Academic Recognition Information Centre) Ireland provides advice on the recognition of foreign qualifications in Ireland. Safety assessors should utilise the QQI website, for example the [Qualifications Database tool](#), to obtain a comparability statement for their formal university qualification. It should be ensured the qualification is considered comparable to a university course in Ireland of theoretical and practical study in pharmacy, toxicology, medicine or a similar discipline. This statement should be included in Part B of the CPSR, along with evidence of the formal qualification received from the university outside the EU/EEA. It should be noted, the HPRA may review this and the relevant experience of the safety assessor during a CPSR review at a later date.

If a safety assessor who has received their university qualification from a country outside the EU/EEA, having consulted NARIC Ireland, ascertains their university course is not considered comparable to that of an equivalent course in Ireland, and they are currently acting as a safety assessor for a cosmetic product where the RP is established in Ireland, they should contact the HPRA without delay at cosmetics@hpra.ie.

Safety assessors of cosmetic products where the RP is established in another EU member state should refer to the competent authority in that member state for guidance on this topic. The contact details of the authorities are available on the [European Commission website](#).

Further information is available on this topic on the HPRA website: www.hpra.ie/cosmetics.

