Brexit Update

Current Position

The UK House of Commons has passed a Bill which approves the Withdrawal Agreement and commits to leaving the EU on 31 January 2020 and to conclude a trade deal with the EU by 31 December 2020.

What does this mean?

According to the EU Commission:

“The Withdrawal Agreement ensures a smooth winding-down of current EU-UK arrangements during a transition period that lasts until 31 December 2020. The EU will treat the UK as if it were a Member State during the transition.”

It further states:

“During the transition, all EU legislation, rules and court decisions will continue to apply to and in the UK as if it were a Member State. This means the UK will continue to participate in the EU Customs Union and the Single Market (with all four freedoms) and all Union policies. Any changes to EU legislation or rules will automatically apply to the UK.”

Implications for Medicine and Medical Device Companies

The HPRA has developed guidance in respect of the implications of the transition period for the pharmaceutical and medical devices industries. We will publish this update on the Brexit section of our website as soon as possible subject to clarification on certain matters from the Commission which is expected shortly. This information will be disseminated via our website alerting service once published.
Human Marketing Authorisation Holder Regulatory Contact

To ensure consistent and reliable communication, the HPRA would like to ensure our contact details for your entity are accurate and current.

If you are concerned contact details may not be up to date or have recently changed please submit the below details for your entity to regaffairs@hpра.ie:

- Marketing Authorisation Holder Name & Address
- Marketing Authorisation Holder Number
- Email address (generic regulatory contact)

The HPRA will accept a generic mailbox/address contact for this purpose.

We in turn will ensure to update our records accordingly.

For any Brexit queries relating to human medicines, please e-mail brexit@hpра.ie

Multilingual Packaging

The HPRA views the management of medicines availability as a key priority in the protection of public health and therefore is actively working with companies to ensure that the impact of Brexit on medicine availability is minimised.

To this end, the HPRA has worked with the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh) to draw up the CMDh Best Practice Guide on Multilingual Packaging. This contains useful principles for companies to follow when developing multilingual packaging. Following on from this, the HPRA Guide to Labels and Leaflets of Human Medicines has been further updated in December 2019 to highlight areas where the HPRA will be flexible in order to facilitate multilingual packaging, recognising the difficulties in developing such packaging with two or more languages. The updated guide is available on the HPRA website.

As multiple member states are likely to be involved in the assessment of the multilingual mock-ups, the HPRA can be flexible where sufficient justification is provided. Applicants can facilitate this by coordinating assessments across the relevant member states and by sharing their comments. If necessary, the HPRA can also assist in directly liaising with the other member states on behalf of the Marketing Authorisation Holder (MAH) if the other member states are agreeable to this.

The HPRA would also like to remind MAHs that dual labelling for human products, whereby a single approved label includes both the Irish and UK particulars will continue to be acceptable for the Irish Market.

For further advice on the design of multilingual labelling, including those authorised via the centralised procedure, please contact the HPRA’s Customer Services section at info@hpра.ie. See also the Multilingual Packaging section of our website.

Considerations for Submission of Type 1A/1AIN Variations

Type IA variations should require minimal review and, according to the CMDh Best Practice Guide (CMD(h)/293/2013/Rev.22), there should be no request by the RMS for clarification, information or documentation from the MAH and there is no clock-stop or suspension of the process. The European Medicines Agency (EMA) also advises that Type IA variations are intended to provide for a simple, rapid and efficient procedure for minor changes. The MAH should be aware that the submission of redundant information or a confusing dossier presentation will not facilitate such procedures. Similarly, deficient and missing documentation can lead to rejection of the variation (EMEA-H-19984/03 Rev. 84).

However, the HPRA regularly identifies errors in IA submissions and frequently has to correspond with applicants requesting, for example, additional information or a corrected version of the relevant page of the classification guideline. In order to address these issues, and to ensure timely processing of Type IA variations, applicants are reminded of the following minimum requirements. Non-adherence to these requirements in future may lead to rejection of the variation:

- Provide a “precise scope and background for change” in the application form.
- Provide a “present versus proposed” to clarify all changes. This can be in the application form or with reference to a document in the annex where appropriate.

- Provide the “ticked classification guideline(s)”. This is in itself a declaration that the conditions for the change are met and that all documentation are provided. Note: The type IA “z” category is only a valid classification when specifically listed in the CMD(h) Article 5 recommendations.

- If any documentation is not provided, this may be acceptable in exceptional circumstances. A short explanation stating the reason is required, which should be included either in the application form or the guideline page.

- Provide the implementation date for each change, i.e. ≤ 14 days for Type IAIN and ≤ 12 months for Type IA.
Type IA Annual Reporting of Variations

The HPRA would like to remind MAHs that Type IA variations are considered minor variations that have no or minimal impact on the quality, safety or efficacy of the medicinal product. Type IA variations do not require approval prior to implementation, therefore, should be submitted to the HPRA within 12 months following implementation (“do and tell”).

For further information, please see the CMDh Best Practice Guides (BPGs) for the Submission and Processing of Variations in the Mutual Recognition Procedure for information.

To ensure successful and efficient processing, please reference specific HPRA guidance within our previous article entitled ‘Considerations for Submission of Type 1A/1AIN variations’.

- The use of an annual report may be used for submission of type IA variations. The usual requirements for groupings apply.
- Updated label mock-ups and/or leaflet text must be included with the submission, there is no national phase for texts. Design changes should be submitted by Article 61(3) and not by Type IA variation.
- Editorial changes are only allowed if the changes apply to the same part of the dossier that is updated by the variation. They should be clearly identified in the present versus proposed section and appropriately justified as editorial.

For further guidance, the EMA has published a Pre-notification check for type IA/IAIN Variations aimed at facilitating submissions of complete and correct Type IA variations (EMA/746161/2014). The EMA has also published guidance on how to complete the scope for a large number of variation categories, (EMA/220707/2017). The principles can be applied to national and MR Type IA variations.

A notification is considered acceptable on the basis of the Marketing Authorisation Holder undertaking that:

i. The notification of change complies with all conditions specified in the Commission guideline on the classification of variations.

ii. all supporting documentation as listed in the Commission guideline on the classification of variations have been provided e.g. an updated section 3.2.P.3.1 for changes to manufacturing sites.

iii. the application has been submitted simultaneously to all Concerned Member States and the relevant fees have been paid as required by national competent authorities.

Failure to comply with any of the above may subsequently deem the notification unacceptable.

With respect to grouped type IA variations, including those submitted with type IB/II variations, applicants are reminded that the present versus proposed should clearly identify the relevant eCTD sections in support of each variation.

Veterinary Medicines

Update on Irish Language Case

In respect of proceedings relating to the provision of bilingual packaging of veterinary medicines in Irish and English languages brought against the Department of Agriculture Food and the Marine (DAFM) by Mr. Peadar MacFhannchadha, Galway, in July 2018, on 24 October 2019 Judge Ní Raifeartaigh decided to refer to the European Court of Justice (ECJ) the question of 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.

Judge Ní Raifeartaigh had previously indicated that she accepted that Directive 2001/82/EC was not properly transposed into Irish law. The applicant had argued that as both Irish and English are official languages of the State, packaging text should be in both languages. The DAFM had argued that this would cause practical consequences for the animal health industry and would adversely affect medicines availability in this country.

The question to be decided by the ECJ arises because Regulation 2019/6 provides that Member States can choose the language of the text to be used in the package leaflet and labelling. The Regulation comes into effect on 28 January 2022, making Irish language labelling optional from then on. The question facing the High Court and the ECJ is what to do in the meantime.

The HPRA will continue to monitor developments in this case.
Progress update on Report of the Task Force on the Method of Supply of Antiparasitic Veterinary Medicinal Products intended for Food-Producing Animals

The report of the task force, that was established by the HPRA’s Advisory Committee for Veterinary Medicines (ACVM) to review the method of supply of antiparasitic veterinary medicinal products that are intended for food-producing animals against the criteria set out in Directive 2006/130/EC and Regulation 2019/6, was adopted by the Authority of the HPRA at its meeting of 5 December 2019.

The report, which has been communicated to the Department of Agriculture, Food and the Marine (DAFM) and Marketing Authorisation Holders (MAHs), has been published on the HPRA website.

The report concluded that antiparasitic veterinary medicinal products that are authorised without veterinary prescription for food-producing species in accordance with previous advice from the DAFM, are not considered to comply with all the criteria set out in Article 34 of Regulation 2019/6. This means that in the future, the supply of such products should be in accordance with a veterinary prescription. Under current national legislation, Licensed Merchants are already entitled to dispense antiparasitic veterinary medicinal products that are supplied under prescription and this framework should facilitate their continued involvement in the supply of the products concerned. However, the labelling and packaging for antiparasitic veterinary medicinal products that are not currently supplied under veterinary prescription will have to change. The HPRA invites MAHs and interested parties to respond to a consultation regarding the timeline needed for implementation and transition to the revised classification status (prescription only). Details of the consultation are also available from the HPRA website. The consultation is open until 28 February 2020. MAHs are advised that applications for variations to give effect to any needed labelling or packaging changes will be required.

All new and pending applications for antiparasitic veterinary medicinal products that contain established substances can benefit from the status quo method of supply in the interim, pending the finalisation of the deadline for compliance with the prescription requirement but will have to change to prescription only supply before January 2022.

Shortages of Veterinary Medicinal Products in Ireland

The HPRA has been working with the Department of Agriculture, Food and the Marine (DAFM) in recent times to help put in place strategies to help mitigate against the risk of shortages of veterinary medicinal products. The DAFM has overall responsibility in this area, and is the competent authority for the licensing of veterinary medicinal products under the exceptional authorisation procedures (so-called ‘AR 16’ and ‘AR 18’ licences).

An early warning system to flag potential product shortages has been identified as a useful tool to assist in planning for shortages. In this regard, the HPRA wishes to draw the attention of MAHs to the requirements of Directive 2001/82/EC. Article 27a requires MAHs to notify the HPRA if a veterinary medicinal product ceases to be placed on the market in Ireland, either temporarily or permanently. Such notification shall, other than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product. Given this requirement, MAHs should continuously monitor the supply and demand for their products on the national market and ideally develop a shortages prevention plan to avoid interruption in supply.

The HPRA wishes to draw the MAHs’ attention to a template for the notification of shortages of veterinary medicinal products that has been developed by jointly the Heads of Medicines Agencies (HMA) and the EMA and which should be used to notify the HPRA’s Veterinary Sciences Department of anticipated shortages by forwarding the completed notification to vetinfo@hpra.ie. The HPRA expects that on receipt of such information, it will engage with the DAFM to highlight the issue in the first instance and explore possible solutions. If necessary, the HPRA will communicate information on shortages to stakeholders, in accordance with EMA-HMA guidance on communication of medicines’ availability issues.
Compliance

Attainment of Qualified Person Status in Ireland

The legal bases for qualified persons (QPs) are described in EU Directives 2001/20/EC, 2001/82/EC and 2001/83/EC. These Directives, which have been transposed into Irish law, apply, inter alia, to manufacturers of investigational medicinal products, medicinal products for veterinary use and medicinal products for human use, respectively. The educational and experience requirements for a QP are also defined in this legislation.

A ‘QP’, is defined within Irish law applicable to human medicinal products* as ‘a person with the qualifications and experience specified in Schedule 5 and named in the manufacturer’s authorisation as being responsible at the manufacturer’s premises for the functions set out in Regulation 13(3).’ A similar definition is provided for in Irish law relevant to veterinary medicinal products**.

The primary legal responsibility of the QP is to certify batches of medicinal products prior to use in a clinical trial or prior to release for sale and placing on the market. Persons performing certification of batches must be named in Annex 5 to the Manufacturer’s / Importer’s Authorisation (MIA)/ Manufacturer’s Licence. This applies equally to QPs who are performing QP confirmation at a manufacturing site, in accordance with Annex 16 of the EU GMP Guide, in relation to intermediate steps in the manufacture of a medicinal product.

Candidates must have acquired practical experience over at least two years, in one or more undertakings which are authorised to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products. The duration of practical experience may be reduced where additional specific educational requirements are met. Further guidance regarding the qualification and experience required in order to be eligible to act as a QP are detailed in the ‘HPRA Guide to Attainment of Qualified Person Status in Ireland: Educational Requirements, Training and Licensing’. This guidance is available on the HPRA website.

Prior to submitting an application requesting that a candidate be named as a QP on an MIA, it is the responsibility of the MIA holder to ensure that the person proposed is eligible. Queries related to QP eligibility can be submitted to compliance@hpра.ie by the holder, or proposed holder, of an MIA in advance of making a formal application.

An application to name a QP in Annex 5 of the MIA should include the following:

- A copy of relevant qualifications as issued by a relevant third level institution to support educational requirements for a QP.
- A copy of the proposed QP’s CV. This should include evidence of QP status where the applicant has acted as a QP in another EU jurisdiction.
- The current email address for each proposed QP.
- Summary of training, relevant to the role of QP, performed at the manufacturing site concerned. This should be in the form of a training programme for the role of QP at the site rather than simply a printout of training in various standard operating procedures (SOPs), for example as might be obtained from a learning management system. This should be signed by the proposed QP and, if applicable, their relevant superior.
- Details of product specific training should also be included in cases when the product types are new to a site.

Where all relevant training has not been completed at the time of application, then a statement should be included in the training summary or in the application stating that the required minimum training will be completed prior to commencement of batch certification activity by the proposed QP. See also the HPRA Guide to Attainment of Qualified Person Status in Ireland.

* Medicinal Products (Control of Manufacture) Regulations 2007
** European Communities (Animal Remedies) (No. 2) Regulations 2007
In line with continued improvements to the submission process for applications for certificates of free sale, it has been decided that it will no longer be necessary to provide a notarised document when applying for certificates of free sale for medical devices.

This means that, while all other requirements for the provision of correct documentation will remain, the requirement for a notary public stamp on either a declaration of conformity or manufacturer’s statement will not now be required.

The HPRA Guide to Applications for Certificates of Free Sale for Medical Devices, which is available from the HPRA website, outlines the information and documentation required when making an application for certificates of free sale.

Queries should be sent to exportcerts@hpra.ie

Cosmetic product responsible persons and manufacturers should be aware of the importance of the Technical Document on Cosmetic Claims that was published, in July 2017, on the website of the European Commission. While the views expressed in the document are not legally binding, the purpose is to provide guidance for the application of Commission Regulation (EU) No 655/2013, which established the common criteria for the justification of claims used in relation to cosmetic products.

There are four Annexes in the document, as described below:

I. Annex I provides a detailed description of the common criteria established by Commission Regulation (EU) No 655/2013, including illustrative and non-exhaustive examples of claims that may or may not be appropriate.

II. Annex II provides guidance on best practices, specifically relating to the type of evidential support used for the substantiation of cosmetic claims.

III. Annex III provides guidance on the application of the common criteria to ‘free from’ claims, including illustrative and non-exhaustive examples in relation to restrictions on ‘free from’ claims. For example, claims such as ‘free from parabens’, ‘free from preservatives’, and ‘free from alcohol’ are discussed within this section of the document.

IV. Annex IV provides guidance on the application of the common criteria to ‘hypoallergenic’ claims.

Guidance on this topic was originally published in July 2013 but included only Annexes I and II above. Annex III and IV were added on 3 July 2017, and were deemed to be applicable as of 1 July 2019.

Therefore, all new batches of a cosmetic product placed on the market are expected to be in line with the revised document, as well as meeting the legal requirements of Commission Regulation (EU) No 655/2013.

Companies should review the technical document on cosmetic claims to ensure that the claims on their cosmetic products are acceptable.

For further information on cosmetic claims, please contact cosmetics@hpra.ie