HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Implementation of Packaging Changes to Authorised Veterinary Medicinal Products

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

1 SCOPE

This guideline provides information on the framework and timelines under which changes to the product literature must be implemented.

2 INTRODUCTION

Product (marketing) authorisations are a means of ensuring public confidence in the quality, safety and efficacy of veterinary medicinal products. They are precise legal documents granted by regulatory Competent Authorities.

Companies marketing medicines are obliged to conform to the conditions attaching to the product authorisation. A key component of the conditions of the authorisation is the Summary of Product Characteristics (SPC). The SPC specifies the target species, the indications and contraindications for use, the warnings and precautions, storage conditions and shelf-life, the method of disposal, and, in the case of veterinary medicinal products intended for use in food-producing animals, the appropriate withdrawal period(s). Additionally, the method of supply is also specified on the authorisation document. Product labelling, packaging and package leaflets must comply with all of the conditions of the authorisation and with the relevant national legislation. In the case of veterinary medicinal products authorised nationally, the product literature must be approved by the Health Products Regulatory Authority (HPRA). By this means, authoritative instructions on the safe and effective use as well as instructions on the storage and disposal of a medicine are available to the user.

Once a product authorisation has been granted by the HPRA, it may change, subject to approval by the HPRA, for several reasons. These reasons include changes brought about by commercial considerations (e.g. a new indication for use or transfer of the authorisation to another company), by pharmacovigilance reports (e.g. a new warning being needed), by legislative or regulatory changes in requirements (e.g. statements on in-use shelf life or storage condition) or for administrative reasons (e.g. change to a company's address).

Once approved, product literature-related changes will affect the content of the product labelling, packaging, or package leaflet. In practice, there is a time lag between the approval of updated information and the incorporation of these data into the product literature. The length of this time lag can vary depending on the complexities of the technical and quality control procedures involved (printing and packaging) and other logistical considerations (manufacture and release of finished product). In addition, stocks of product already on the market, which may have shelf lives of up to 5 years, will not conform to the revised conditions of the product authorisation. However, the public health significance of the non-conformity must be evaluated in order to ensure that regulatory action is appropriate, to avoid problems of animal welfare which could result from the recall of essential medicines. In the interests of public and animal health and to facilitate the process of implementing product literature

changes, a tiered risk assessment approach is necessary. A framework and timeline within which decisions of the regulating Competent Authority are incorporated into the product literature is given hereunder.

3 CLASSIFICATION OF CHANGES

Amendments to product literature may be categorised into three groups according to the perceived risk for public health, animal health, or for the safety of the environment:

- Urgent safety restrictions,
- Other safety restrictions, and
- Neutral or less restrictive changes.

The judgement of which category best fits a particular situation follows a case-by-case assessment of the risk by the HPRA. It is helpful if the marketing authorisation holder addresses the risk assessment in their notification to the HPRA.

3.1 Urgent safety restrictions

This category includes those where the risk is judged to be unacceptable. Examples of such changes include but are not limited to the following:

- The identification of a significant new contraindication or warning in the authorised indications for use.
- The identification of a specific user warning judged immediately necessary for the continued safe use of the product.
- The increase of the withdrawal period where the extent of the increase is significant[1] and the risk assessment indicates a medium or high potential risk to public health.
- A new and important environmental warning judged immediately necessary for the continued safe use of the product.

Such changes require immediate incorporation into the product literature in the interests of prescribers, users and patients alike. Particular issues should be discussed on a case-by-case basis between the marketing authorisation holder and the Veterinary Sciences Department of the HPRA. In all cases, the marketing authorisation holder will be expected to:

[1] Significance is determined by the HPRA with regard to the toxicity or allergenicity of a substance, the therapeutic class of the substance, the pharmaceutical form, the duration of time by which the withdrawal period is increased compared to the original withdrawal period and the type of tissue to which the hazard relates (i.e. milk, eggs, honey, for which the existing withdrawal periods are short are likely to be more significant than would an increase of a few days to a product authorised with a withdrawal period for slaughter of 2 months). However, not all changes to a withdrawal period are classified as urgent; certain changes brought about by a company primarily for administrative reasons (e.g. harmonisation of withdrawal period with another EU Member State) may be classified as non-urgent.

- Cease supplying the market with existing stock with immediate effect. This means that no packs leaving the custody of the marketing authorisation holder, including the manufacturer and/or wholesalers, should be released to the market in the existing livery.
- Initiate a product recall. Depending on the nature of the product and the restriction, the recall may be targeted to specific groups such as wholesalers, distributors, retailers, veterinary practitioners, and pharmacists.
- Inform the users by means of a 'Dear Veterinary Practitioner / Pharmacist' letter; by mailing veterinary practices or pharmacies and other outlets; and by placing advertisements in the relevant press or journals.
- In the case of products supplied by licensed merchants, or other licensed suppliers, notify those involved by letter or public notice.

Product should not be returned to the market until the product labels, packaging and package leaflets are in compliance with the varied/amended authorisation. In exceptional cases where no alternative veterinary medicine is available and the recall would result in animal suffering, a marketing authorisation holder may seek the agreement of the Department of Agriculture, Food and the Marine for the continued supply of limited amounts of product pending the availability of compliant stock, and inform the HPRA's Compliance Department accordingly.

The marketing authorisation holder should fully discuss the appropriate actions to be taken to effect the recall and notification of the changes to the users with the HPRA's Compliance Department. These actions include the agreement of the HPRA on the content of any press release, advertisement or 'Dear Veterinary Practitioner / Pharmacist' letter.

Where the agreement of the HPRA has been obtained, as an exceptional measure, it is permitted to over-label any returned product with an amended label provided (i) the adhesive is sufficiently strong as to obliterate the existing label, and (ii) the process is conducted by a licensed manufacturer of veterinary medicinal products. In order to effect any such change to the label, leaflet or packaging, the authorisation holder must submit a batch-specific request application to the HPRA. The application should include details of the batch numbers of affected products, the number of products involved, the details of the changes requested and the date for compliance.

The Department of Agriculture, Food and the Marine and the HPRA's Compliance Department should be informed of any such agreed changes.

3.2 Other safety restrictions

This category includes those changes where the risk is judged to be such as not to require an immediate recall of the existing stock. Examples of such changes include the following:

- Necessary change(s) to the text of existing warnings or contraindications not arising from a pharmacovigilance alert.

- The withdrawal by an applicant of an authorised indication for use where the change was not related to a pharmacovigilance alert.
- Changes to the in-use shelf-life or storage conditions brought about by compliance with EMA guidance notes.
- The introduction of new warnings or precautions which are deemed prudent and good regulatory practice but for which the risk assessment indicates a low potential for risk.
- The increase of the withdrawal period where the extent of the increase is not significant (see footnote on page 3) and the risk assessment indicates a low potential risk to public health.

This category also includes those changes which provide important information for the user but which would not normally require a 'Dear Veterinary Practitioner / Pharmacist' letter. Particular issues should be discussed on a case-by-case basis between the marketing authorisation holder and the HPRA's Veterinary Sciences Department. In all cases, the marketing authorisation holder will be expected to:

- Co-ordinate the supply/importation of stock to ensure the introduction of the amended product labelling and literature as soon as possible and, in any case, within six months of the approval of the amendment. Products in old livery should not be released from the manufacturing site after six months from the date of approval.
- Where considerable amounts of product exist in the marketplace, to place notices in the farming press and/or professional journals as appropriate, alerting users to the changes.
- Inform retailers of the changes.

In exceptional cases where no alternative medicine is available and updated stock will not be available within six months and where the deprivation of the supply chain would result in animal suffering, a marketing authorisation holder may seek the agreement of the Department of Agriculture, Food and the Marine for the continued supply of limited amounts of product pending the availability of compliant stock, and inform the HPRA's Compliance Department accordingly.

3.3 Neutral or less restrictive changes

A neutral or less restrictive amendment is one which will have no adverse impact on product safety. Such changes might include:

- the granting of a new indication
- the removal of a contraindication or warning
- the shortening of a withdrawal period
- the lengthening of shelf-life
- any administrative change to the address of the marketing authorisation holder

Nevertheless, while there is no safety implication associated with the change, there are legal considerations especially when the authorisation holder has changed. Therefore, it will be expected that within a twenty-four month period from the date of approval of the amendment application all supplies leaving the companies' distribution point (company warehouse or agent) should comply with the amended packaging.

4 MONITORING OF COMPLIANCE

In respect of all amendments or restrictions to the product labels and literature, the HPRA will liaise closely with the Department of Agriculture, Food and the Marine to monitor compliance. Noncompliance with the conditions of the Veterinary Product Authorisation within the agreed timeframe will jeopardise the authorisation and may result in the product being removed from the market.