HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Guide to
Managing Changes to Registrations of Active Substance Manufacturers, Importers and Distributors

1 INTRODUCTION

The Falsified Medicines Directive (FMD) (2011/62/EU), which amends Directive 2001/83/EC, is the key legal instrument governing medicinal products for human and veterinary use, and requires that manufacturers, importers and distributors of active substances 'maintain' their registration with the local competent authority.

Changes can occur at facilities (e.g. the introduction of the manufacture of new active substances) which can potentially have a quality and safety impact. Therefore, it is important that such changes are managed through the formal application of change control and risk management, where appropriate.

The information below is designed to provide guidance to companies who hold registrations and the mechanisms for managing changes to these registrations.

The requirements of the FMD do not apply to active substances used for manufacture of investigational medicinal products for human and veterinary use, to medical devices or to veterinary medicines.

2 GENERAL GUIDANCE

Active substance registration means the registration of importers, manufacturers and distributors of active substances maintained by the Health Products Regulatory Authority.

Directive 2011/62/EU, which amends Directive 2001/83/EC, includes a number of provisions for manufacturers, importers and distributors of active substances used in finished product manufacture.

Article 52a of Directive 2001/83/EC as amended states that:

1. *'Importers, manufacturers and distributors of active substances who are established in the Union shall register their activity with the competent authority of the Member State in which they are established.'*

...

5. *'The persons referred to in paragraph 1 shall communicate annually to the competent authority an inventory of the changes which have taken place as regards the information provided in the registration form. Any changes that may have an impact on the quality or safety of the active*

substances that are manufactured, imported or distributed must be notified immediately.' [HPRA emphasis]

3 IMMEDIATE NOTIFICATIONS

3.1 Changes that must be notified to the HPRA immediately

Changes affecting the name of the company and the legally registered company name and/or address (on page one of the registration document) are required to be notified immediately.

The introduction of significant new active substance manufacturing activities also requires immediate notification. Examples of these changes include the following:

- Introduction of highly potent, sensitising active substances to the site
- Introduction of new technology to the site, e.g. hydrogenation; use of enzymes in processing; significant process changes, e.g. reduction in the number of synthetic steps, introduction of PAT applications for control or analysis, and preparative chromatography. This list is not exhaustive. Other technology changes should be evaluated through change control and risk management to evaluate when communication to the regulatory authority is warranted.
- Introduction of biological active substances to the site
- Introduction of low bioburden active substances to the site
- Introduction of recycled/recovered solvents, into manufacturing processes
- Introduction of new milling technology for specific particle size control (e.g. construction of a central milling area)

In cases where active substances manufacturers are unsure if the notification should be communicated immediately, they should contact the HPRA at compliance@hpra.ie.

3.2 Documentation required as part of an immediate notification to support the introduction of manufacture of an active substance

Registrants must provide the following information:

- Completed application form
- An overview of the chemistry of the new active substance
- Details of changes to the facility/equipment required to introduce the active substance
- Details of additional containment measures required to introduce the active substance
- Details of process validation studies performed or planned
- Details of cleaning verification/validation studies performed or planned

3.3 Requirement for GMP inspection

A GMP inspection may be required prior to approval of the changes. Each application will be considered on a case by case basis. The significance of the changes and the active substance will determine if an inspection is required to support the approval of the change to the registration.

3.4 Changes to API GMP certificate (manufacturers only)

Where a manufacturer holds both an API GMP certificate and an active substance registration, both documents will be updated simultaneously as a consequential change. There is no fee for

this change to an API GMP certificate. To ensure this change is made, complete section 1B of the registration application form.

4 ANNUAL COMMUNICATIONS

4.1 Changes required to be communicated annually to the competent authority

The following minor changes are examples of changes that would constitute an annual communication for **manufacturers** of active substances:

- Removal of an active substance from the registration
- Demolition or decommissioning of a production facility on site
- Outsourcing of stages of manufacture
- Introduction of the manufacture of an active substance to the site which meets the following criteria; similar synthetic processes, similar processing equipment, similar cleaning and containment measures

The following minor changes are examples of changes that would constitute an annual communication for **importers** of active substances:

- Removal of an active substance from the registration
- Addition of an active substance to the registration

The following minor changes are examples of changes that would constitute an annual communication for **distributors** of active substances:

- Removal of an active substance from the registration
- Addition of an active substance to the registration

4.2 When to submit an annual communication to the HPRA

Annual communication is only necessary if the scope of the registration requires updating as outlined under 4.1 above. Responses outlining any changes must be received one month in advance of the issued date on the registration. Companies will need to submit an immediate notification application instead of an annual update if a response is not received by the date specified.

If no communication is received, the HPRA understands the registration remains the same as previously registered.

Note: The annual communication month will remain the same for each additional year there is no communication submitted to the HPRA for no changes.

4.3 Documentation to provide with the annual communication

- List of changes
- Manufacturers are requested to submit a site master file (SMF)
- Signed application form

4.4 Inspections

The annual communication will be reviewed to assess the significance of the changes presented by the registrant and their compliance with the registration. Should the changes be considered significant, the HPRA will contact the registrant to discuss the changes. In general, the changes will be reviewed during the next inspection; however, a focussed inspection may be scheduled in some exceptional circumstances.

5 FEES FOR CHANGE MANAGEMENT

Codes **359** and **356** relate to notification of changes to the active substances register.

- Code **359** relates to immediate notification of a change which may have an impact on the quality or safety of the active substance.

- Code **356** relates to the notification of administrative changes.

These fee codes are listed in the 'Guide to Fees' and the fee application form (available on the 'Publications and Forms' section of www.hpra.ie). The fee application form should be completed and submitted with all applications.

Please note that there are no fees for annual updates/notifications.

If you have any queries relating to the above, please contact the Compliance Department on 01 6764971 or by email at compliance@hpra.ie.

HPRA
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