EU MAH on FMD Related Responsibilities

In relation to medicinal products for human use, where applicable, the MAH has a number of responsibilities related to the Falsified Medicines Directive (FMD) 2011/62/EU and the related Delegated Regulations (including the Safety Features Regulation 2016/161). One of those responsibilities, as discussed in Section 5.2 of this Reflection Paper (Audits & Qualification Activities), relates to the need to confirm the GMP status of the active substance manufacturer by means of GMP audits. This responsibility is stated in Article 8(ha) of Directive 2001/83/EC, which originated in the FMD Directive.

Safety Features

Other FMD-related responsibilities concern safety features on product packaging:

- Commission Delegated Regulation (EU) 2016/161 sets out what is expected of the MAH in relation to the upload to the repositories system of pack serialisation data, as well as responsibilities in relation to the decommissioning of pack serialisation codes.
- Article 33 of this Regulation requires the MAH to ensure that the information of unique identifier and various additional defined data about the medicinal product and its distribution are "uploaded to the repositories system before the medicinal product is released for sale or distribution by the manufacturer, and that it is kept up to date thereafter." (Note that the Q&A Document on the Commission's Website provides additional guidance in this area – see Q&A 4.5)

It is considered that the QP who certifies batches prior to their release to the market should be satisfied with the arrangements that have been put in place by the MAH for the upload of the safety features data to the repositories system. (In relation to QP responsibilities in this general area, it is useful to note that Annex 16 to the GMP Guide places a responsibility on the QP to ensure that the following point is secured, that:

> "In the case of medicinal products for human use intended to be placed on the market in the Union, the safety features referred to in Article 54(o) of Directive 2001/83/EC, as amended, have been affixed to the packaging, where appropriate." (Ref. Annex 16, Paragraph 1.7.21).
>
> Annex 16 indicates that this task may be delegated to "appropriately trained personnel or third parties", and in this regard, the Annex recognises that the QP will "need to rely on the pharmaceutical quality system" that is in place and it requires the QP to have "on-going assurance that this reliance is well founded". (Ref. Annex 16, Paragraph 1.7)

It is considered that the transfer of the unique identifier (UI) data from the location where they were generated until their upload to the European Hub is performed in a secure manner and in such as a way that the integrity of data is not compromised.

The Repositories System & MAH Responsibilities

The repositories system is expected to be established and managed by the MAHs (Ref. Paragraph 28 of the preamble text of Delegated Regulation (EU) 2016/161). Article 32 of the Delegated Regulation sets out the required structure of the repositories system – there should be a central information and data router (known as the European Hub) and repositories which serve the territory of one or multiple

Member States. Those repositories are required to be connected to the EU-Hub. The European Medicines Verification Organisation (EMVO) is the organisation representing stakeholders who have taken responsibility for the formation of the European Medicines Verification System (EMVS/EU-Hub).

Each EU Member State is expected to implement a National Medicines Verification System (NMVS) which will be set up and managed by a National Medicines Verification Organisation (NMVO). The MAHs are expected to liaise with both the EMVO and the relevant NMVOs for the concerned products.

Various items of information are required to be uploaded to the repositories system, including:

- The data elements of the unique identifier
- The coding scheme of the product code
- The name and the common name of the medicinal product, the pharmaceutical form, the strength, the pack type and the pack size
- The Member State or Member States where the medicinal product is intended to be placed on the market
- The name and address of the manufacturer placing the safety features
- A list of wholesalers who are designated by the MAH, by means of a written contract, to store and distribute the products covered by the marketing authorisation on his behalf MAH

This and other information is intended to be stored in all of the national or supranational repositories serving the territory of the Member State, or Member States, where the medicinal product bearing the UI is intended to be placed on the market for at least one year after the expiry date of the medicinal product, or five years after the product has been released for sale or distribution, whichever is longer. The same responsibility applies to persons responsible for placing parallel imported or parallel distributed medicinal products onto the market.

Serialisation Data - Uploading Responsibilities

The MAH may delegate the uploading of the information laid down in Article 33(2) to a third party; such delegation is expected to be documented in a written agreement between both parties. It is important to note that the MAH may subcontract, or delegate, data uploading only to parties which perform the data upload by means of infrastructure, hardware and software, which is physically located within the EEA. Importantly, the MAH remains legally responsible for such tasks, as stated in the document titled 'Safety Features For Medicinal Products For Human Use; Questions And Answers', available on the European Commission's website.

Unique Identifier Decommissioning Responsibilities

In relation to decommissioning, which is a term that relates to various pack statuses within the repositories, including the pack status called 'supplied', it is an MAH responsibility according to Article 40 of the Delegated Regulation to ensure the decommissioning of pack codes in the case of a product recall or withdrawal. Article 40 states that "the marketing authorisation holder shall promptly take all the following measures:

(a) ensure the decommissioning of the unique identifier of a medicinal product which is to be recalled or withdrawn, in every national or supranational repository serving the territory of the Member State or Member States in which the recall or the withdrawal is to take place
(b) ensure the decommissioning of the unique identifier, where known, of a medicinal product which

has been stolen, in every national or supranational repository in which information on that product is stored

(c) indicate in the repositories referred to in points (a) and (b) that that product has been recalled or withdrawn or stolen, where applicable.

The same responsibility applies to persons responsible for placing parallel imported or parallel distributed medicinal products onto the market.

It is worth noting that "decommissioned" as such is not a status in the system; multiple statuses that are different from "active" have been developed in the EMVS by EMVO, such as "RECALLED", "DESTROYED" or "STOLEN". All of these are considered as "decommissioned".

For the above responsibilities to be met by the MAH, it is considered that there should be robust communication systems in place between the MAH and the manufacturer (or other third party) to whom such tasks have been delegated. This is because the various data elements that must be uploaded to the repositories system may be held by the different entities – the manufacturer will likely hold the actual pack serialisation codes per batch, while the MAH may hold the information about the wholesalers which have been designated by it to store and distribute the product, as well as information about the distribution of free medical samples and about product recall actions.

Reference

Reflection paper on GMP and MAH (Jan 2022) EMA/INS/3094/2022