Guideline on the individual medication preparation (IMP)
Version October 2013

1. Introduction

- In this guideline, the FAMHP (Federal Agency for Medicines and Health Products) clarifies the application of the Royal Decree implementing the regulation regarding individual medication preparation (IMP) [1]. In the case of IMP, a pack is prepared containing one or several products, intended to be administered to a specific patient at a specific moment in time. The products may be medicinal products and/or food supplements. IMP can be performed automatically or manually.

- This guideline consists of two parts, namely.:
  - ✓ Recommendations for registered pharmacists performing IMP
  - ✓ Recommendations for marketing authorisation holders with the intention to market bulk containers to be used for IMP purposes.

- In function of IMP:
  - ✓ The marketing authorisation holder remains responsible for the quality of the product in the sealed original packaging (throughout the product's shelf life and provided the storage instructions are respected).
  - ✓ The registered pharmacist performing IMP is responsible for any changes to the licensed medicinal product that may affect the quality of that product throughout the IMP process (product not being stored in its original packaging, combining the product with other types of medication or food supplements, labelling of IMP packaging, etc.).

- This guideline will be amended in function of further developments in the application of IMP.

2. Recommendations for registered pharmacists performing IMP

2.1. Shall not be included in an IMP pack:

- Medicinal products not presented in solid oral dosage form, except when kept in their primary packaging and handled by manual IMP.

  E.g.: effervescent tablets, ampoules, etc.

- Medicinal products for the acute treatment of suddenly manifesting symptoms

  E.g.:
  - *Narcotic analgesics for the treatment of breakthrough pain*

- Medication where the posology must be adjusted on a regular basis in function of therapeutic monitoring, unless the frequency of the IMP can accommodate appropriate adjustments.

  E.g.:
  - *Coumarin anticoagulants*
  - *Some products used to treat diabetes, such as hypoglycaemic sulphonamides*

- Fragmented (e.g. ½ or ¼) tablets, unless there is no other alternative to obtain the correct dosage.

- Medication where the dosage must be titrated until the patient stabilises during the titration stage, unless the frequency of the IMP can accommodate appropriate adjustments.

  E.g.:
  - *Medication to treat epilepsy*
  - *Calcium antagonists*

- Products that are extremely sensitive to humidity, air and/or light (to be assessed on a product-by-product basis by the registered pharmacist performing IMP).

- Products where cross-contamination can result in serious risks, for instance by the product's genotoxic or highly allergenic nature (to be assessed on a product-by-product basis by the registered pharmacist preparing the IMP).

2.2. <u>Cannot be combined in one and the same IMP (pack for a specific patient to be administered at a specific moment in time)</u>

- Medication for which stringent administration rules apply.

  E.g.:
  - *Bisphosphonates*

- (Oral) forms with different administration instructions.

  E.g.:
  - *Tablets or capsules (to be swallowed) in combination with orodispersible tablets or sublingual tablets. Swallowing orodispersible tablets or sublingual tablets may reduce their therapeutic effect.*
  - *Medicines that have to be taken on an empty stomach in combination with those that have to be taken with food.*

- Medicines that interact pharmacologically (to be assessed by the registered pharmacist performing IMP on the basis of section 4.5 of the summaries of product characteristics - SPCs).

- Medicines between which incompatibilities exist (to be evaluated by the registered pharmacist performing IMP on the basis of section 6.2 of the summaries of product characteristics - SPCs), except when the medicinal product is kept in its primary packaging during IMP (e.g. a tablet in a blister).

2.3. <u>Specific information on IMP packaging</u>

- In article 7, the RD [1] lists the minimum details that must feature on all IMP packaging.

- The use of additional warnings is recommended, a. o. in case of:
  - ✓ Anaesthetics (e.g.: “careful: anaesthetic”)
  - ✓ Products that may be harmful to nursing staff if the capsule cap or tablet coating is damaged, such as anti-tumour products and highly allergenic medication (e.g.: “careful: do not crush: anti-tumorous product”)
  - ✓ Products whose effectiveness may be affected when crushed (e.g.: “careful: do not crush - gastric- resistant coating”)

- ✓ In cases where strict administration instructions apply (e.g. *bisphosphonates)*

2.4. Bulk products

- The annex to the RD (1.1) describes that bulk containers:
  - ✓ May be prepared by IMP staff by removing the medication from its original packaging and placing it in a sealed bulk container
  - ✓ May be supplied as such by the manufacturer of the medicinal product.

- The annex to the RD (3.5.1.5) stipulates that the registered pharmacist determines the shelf life of bulk products on the basis of the physico-chemical characteristics of the product.

  In practice, pharmacists often lack the information that is needed to determine the shelf life of a product. A product's shelf life will depend on the nature of the active substance, the specific finished product containing the substance and the packaging used.

  To accurately determine a product's shelf life, specific stability studies under standardised conditions and with validated test conditions are needed.

  For that reason, preference should be given to bulk products the manufacturers supply as such, which come with recommendations from the manufacturer regarding the bulk product's shelf life in its sealed packaging and after opening. These recommendations are based on stability studies which are assessed by the FAMHP when a marketing authorisation is applied for or when a variation application is filed to add the bulk container to the marketing authorisation.

3. Recommendations for holders of a marketing authorisation who wish to market a bulk containers that can be used for IMP purposes

3.1. Types of applications

- An application for authorisation of a bulk container may be part of the original marketing authorisation application or may be filed afterwards in the form of a variation application.

- The applicant is in all cases advised to clearly state that the specific container is intended to be used for IMP purposes. This will allow the application to be assessed more efficiently and will prevent comments on discrepancies between posology and packaging size. IMP containers can only be proposed for solid oral drug products.

- Variation applications shall be filed in line with the provisions of the current EU guideline. This means that in cases where a particular medicinal product is not supplied in container form (e.g. in blister packs only) an IB-type variation will be needed to add the container. The same applies in cases where a container is available but where the packaging material of the proposed container is less protective. For any additional container with similar or more protective packaging, a type IA variation can be filed.

3.2. Chemico-pharmaceutical documentation

- The chemico-pharmaceutical documentation in the application dossier shall meet the general quality guidelines, as published on the EMA website.

A particular point of interest for bulk containers is the testing of their in-use stability, in respect of which reference can be made to the relevant guideline on the EMA website [2]. On the basis of the results, in-use shelf life and storage conditions may be proposed or the lack of specific in-use shelf life and storage conditions may be justified.

- When filing a variation application, due regard shall be paid to the standard documentation requirements of the current EU guideline.
  Aside from the items explicitly listed in the EU directive, applicants filing an application for an IMP bulk container are also expected to provide documentation on in-use stability tests. This may be regarded as a relevant part of the amended sections of the dossier, imposed by the EU guideline

3.3. Delivery mode

- The delivery mode of bulk containers is determined with respect to the existing FAMHP strategy and guidelines, as published on the FAMHP website [3, 4, 5].

- The general rule [3] is that no distinction in delivery status is made between different pack sizes or different package forms containing one and the same medicinal product. Bulk containers will therefore obtain the same delivery status as the other packs.

- For some therapeutic classes however, specific FAMHP guidelines have been put in place with regard to pack size or pack form. Currently, the FAMHP has issued guidelines regarding the mode of delivery of anaesthetics used for pain relief [4] and the mode of delivery of antidepressants, antipsychotics, hypnotics, sedatives, anxiolytics and antiepileptics [5]. The application of these guidelines means that bulk containers for drugs in these classes are reserved for hospital use only and cannot be used by public pharmacies for IMP purposes.

3.4. Labelling

- Bulk containers must be labelled in accordance with the provisions of the RD of 14/12/2006.

- Where applicable, the in-use shelf life and/or specific in-use storage conditions shall be listed on the primary packaging. Therefore, a space where the opening date can be recorded shall be provided.

References:

[1]. Royal Decree of 24 September 2012 implementing the regulation concerning the preparation of individual medication packs

http://www.fagg-afmps.be/en/items-HOME/laws_decrees/

[2]. CHMP Note for guidance on in-use stability testing of human medicinal products

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003475.pdf

[3]. FAMHP "mode of delivery" strategy

http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/procedures_vhb/procedures/

[4]. Anaesthetics as pain-relief medication - Strategy to limit the pack sizes that can be dispensed in public pharmacies.

http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/procedures_vhb/procedures/

[5]. FAMHP guideline on the mode of delivery of antidepressants, antipsychotics, hypnotics, sedatives, anxiolytics and antiepileptics. (Restriction of delivery in public pharmacies)

http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/procedures_vhb/procedures/