HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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Guide to
Combining Multiple Presentations of a Parenteral Product in One Product Authorisation

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

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1 SCOPE

The guidance in this document applies to Product Authorisations (PAs) issued by the HPRA for parenteral medicinal products for human use, authorised nationally, through mutual-recognition or through the decentralised procedure. The guidance does not apply to medicinal products authorised through the centralised procedure. The guidance is applied by the HPRA as part of new applications and variation applications for parenteral medicinal products.

2 LEGAL BASIS

Applications to market new medicinal products are assessed in line with the requirements of Directive 2001/83/EC (as amended) and if appropriate a Product Authorisation (PA) is granted by the HPRA under the Medicinal Products (control of placing on the market) Regulations 2007.

This guidance has been developed taking into account other relevant existing guidance including the ~~Notice to Applicants Guideline on the Categorisation of Extension Applications (EA) versus Variations Applications (V) October 2003.~~
Notice to Applicants Guideline on the Categorisation of Extension Applications (EA) versus Variations Applications (V) October 2003.

3 INTRODUCTION

The purpose of this document is to provide guidance for applicants on the factors that are considered by the HPRA when determining whether it is appropriate to combine different presentations of a parenteral medicinal product in one PA.

In developing this guidance, the HPRA has considered current legislative requirements as well as existing guidance in this area. The HPRA has also taken into account the established practice associated with the use of parenteral medicinal products on the Irish market and the need to ensure that the approved product information (SmPC, labels and package leaflet) is clear and facilitates the correct and safe use of such products.

The HPRA has also carefully considered the definition of the strength of a medicinal product as defined in relevant European guidance and the need to ensure consistency in the expression of the strength of medicinal products on the Irish market. In addition, the HPRA is mindful that, for well-established medicinal products on the Irish market, healthcare professionals and patients may be very familiar with the existing expression of strength and that significantly changing the expression of strength of such products solely to allow the merging of PAs may not be appropriate.

The criteria described in this guideline are applied for all new marketing authorisation applications and variation applications for medicinal products. However, it is recognised that for certain parenteral medicinal products there may be specific safety-related factors that are not foreseen in this guideline which may necessitate listing different presentations of that product on separate PAs. Therefore, the HPRA reserves the right to issue separate PAs for different presentations of a parenteral product if deemed necessary for safety reasons in order to ensure that the product information is clear and facilitates the correct and safe use of such products.

4 CRITERIA FOR INCLUDING DIFFERENT PRESENTATIONS ON ONE PA

The following criteria are applied when considering whether it is appropriate to include different presentations of a parenteral product on the same product authorisation:

4.1 Same active substance in the same formulation

Each presentation must contain the same formulation in terms of quantitative and qualitative composition of the active substance(s) and excipients per unit volume or per unit weight.

4.2 Single-dose and multi-dose preparations

Single-dose and multi-dose preparations of any parenteral medicinal product must always be listed on separate PAs.

Single-dose preparations
A single-dose container holds a quantity of the medicine intended for total or partial use as a single administration. This definition encompasses:

(i) *Single dose, total use*
Medicinal products designed in such a way that the amount of active substance in the individual container is given **in total** ('total use') as a single administration based on a fixed dose as stated in section 4.2 of the SmPC which is independent of factors such as patient weight or body surface area

(ii) *Single dose, partial use*
Medicinal products which hold a certain quantity intended for use by a single administration. The dose to be administered is usually calculated on an individual patient basis (in mg/kg bodyweight, in mg/m^2) and any unused portion of the preparation is to be discarded ('partial use').

Multi-dose preparations
A multi-dose preparation is a presentation supplied in a single container which contains more than one dose of the medicinal product. Multi-dose preparations often have a different composition regarding excipients than an equivalent single-dose preparation.

The above definitions should also be taken into account when considering the strength of a liquid parenteral medicinal product as defined below.

4.3 Same strength

Each presentation must contain the same strength of the active substance which is defined as follows:

4.3.1 Definition of 'strength' for parenteral medicinal products presented as liquids

The following definitions of 'strength' ~~will be~~are applied by the HPRA to parenteral medicinal products presented as liquids:

Type of Use (see section 4.2 above)	Definition of Strength*	Comment on merging of PAs
Single dose, total use	Total amount of the active substance in each container	Different fill volumes will require separate PAs
Single dose, partial use	Amount per unit volume	Different fill volumes may not require separate PAs if other criteria are met
Multi-dose	Amount per unit volume	Different fill volumes may not require separate PAs if other criteria are met

* For concentrates the strength before dilution should be considered

4.3.2 Definition of 'strength' for parenteral medicinal products presented as powders

The strength in the product name of the parenteral medicinal products presented as powders on the Irish market has historically been expressed as the total quantity of the active substance in each container. It is appropriate to avoid any unnecessary confusion on the market that could arise from the introduction of a significantly different expression of strength in the product name for well-established medicinal products. Therefore, for parenteral powders, the strength in the product name is defined as the total quantity of the active substance in each container. ~~-~~Separate PAs are required for different fill weights unless a different expression of strength has been previously approved in the product name for a similar medicinal product authorised for use in Ireland (for example via the centralised procedure).

4.4 Same pharmaceutical form

The pharmaceutical form must also be the same and in some cases a complete characterisation of the pharmaceutical form must also take into account the nature of the container.

Vials and ampoules may be eligible to be listed on the same PA even if there are differences in the materials from which the containers are constructed ~~and similarly~~. Similarly bags made from different types of plastics may be listed on the same PA provided that other criteria are also met.

Pre-filled syringes are considered to represent a different pharmaceutical form to other presentations such as vials or ampoules and must be listed on a separate PA.

Different administration devices supplied with or as an integrated part of a parenteral medicinal product may also be considered to be separate pharmaceutical forms requiring a separate PA, where there are considered to be significant differences associated with the use of the different administration devices.

Containers which are overwrapped in an outer packaging material can be included on the same PA as containers which do not contain this overwrap. Containers which are overwrapped in different materials may be included on the one PA.

4.5 Same clinical and pharmacological particulars in the SmPC

The information in sections 4 and 5 of the SPC must be the same for all containers listed on one PA.

In relation to the clinical particulars, PAs may only be merged where the dose to be given in a single administration is calculated on an individual patient basis (in mg/kg bodyweight, or in mg/m^2 body surface area). For parenteral products where the dose is fixed (e.g. 400mg three times daily) and independent of factors such as patient weight or body surface area (e.g. some antibiotics), the total content of a container represents a single dose to be administered to the patient comparable with a single dose on a tablet or capsule. Each fill volume or fill weight therefore represents a separate unit dose or strength of the product and must be listed on separate PAs.

The approved dosage regimen for some products may contain fixed dosages for some of the approved indications and patient-variable dosing for other indications. In these cases, different fill volumes or fill weights will generally not be combined on one PA, particularly where the products are long-established. For new products, the decision as to whether or not they can be combined on one PA is taken on a case-by-case basis.

The HPRA advises applicants if they are in doubt as to whether or not their product would meet the criteria for including several presentations on one PA.

5 MERGING OF EXISTING SEPARATE PAs FOR DIFFERENT PRESENTATIONS OF THE SAME PARENTERAL MEDICINAL PRODUCT

Appropriate PAs which meet all of the criteria outlined above may be merged ~~either~~ as part of a Type IB or II quality variation~~ or at time of renewal.~~. If, following ~~reviewing~~review, the HPRA agrees that the presentations can be merged into a single PA, the PAs will be combined to the first PA number in the series, e.g. PA 125/67/10-12~~ would be~~ combined to PA 125/67/10. The redundant PA numbers will not be re-assigned to a new product.

The covering letter for such applications should clearly request that the PAs be merged and indicate the PAs involved, their names, strengths and container types. Unless specifically requested to do so by MAHs, the HPRA will not merge PAs and MAHs may choose to retain separate PAs if they wish to do so.

6 APPLICATIONS TO ADD A NEW PRESENTATION TO AN EXISTING PA OR RANGE OF PAs FOR A PARENTERAL PRODUCT

If only one PA exists, a new presentation should be applied for by variation if it meets the criteria for inclusion on the same PA.

If there is a range of PAs which meet all of the criteria outlined in section 5 above and are suitable for merging, the ~~preferred route is that the~~ new presentation should be applied for as a variation to the first PA in the range~~, and that the~~. The company ~~would~~should also request that the remaining PAs be merged at the same time.

A new presentation for an existing range of PAs may also be granted a new PA number if the company wishes to maintain separate PAs. In this case, a new application should be submitted for the new PA.