EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, implementation and legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
F2/AW D(2002)

Final – Revision 3

NOTICE TO APPLICANTS

GUIDELINE ON THE CATEGORISATION OF EXTENSION APPLICATIONS (EA) versus VARIATIONS APPLICATIONS (V)

OCTOBER 2003

This guideline will be included in:
The Rules governing Medicinal Products in the European Union
The Notice to Applicants - Volume 6C - Regulatory Guidelines

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GUIDELINE ON THE CATEGORISATION OF EXTENSON APPLICATIONS (EA) versus VARIATIONS APPLICATIONS (V) Medicinal products for human and veterinary use

A Guideline on the categorisation of EXTENSION APPLICATIONS (EA) VERSUS VARIATIONS APPLICATIONS (V) has been prepared in order to facilitate the operation of the procedures for variations through the mutual recognition procedure or the centralised procedure.

Introduction

Commission Regulation (EC) No 1084/2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products granted by a competent authority of a Member State and Commission Regulation (EC) No 1085/2003 concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council Regulation (EEC) No 2309/93, defines the scope of what can be considered a variation to the terms of a marketing authorisation within the meaning of Article 35 of Directive 2001/83/EC relating to medicinal products for human use and Article 39 of Directive 2001/82/EC relating to veterinary medicinal products. The corresponding provisions in Regulation (EEC) No 2309/93 are found in Article 15 paragraph 4 and Article 37 paragraph 4 for medicinal products for human use and veterinary medicinal products, respectively.

In Article 2 of the Regulations, it is stated that extensions of marketing authorisations as defined in Annex II are not considered to fall within the scope of the Regulations on variations. Annex II lists three main categories:

1. Changes to the active substance(s)
2. Changes to strength, pharmaceutical form and route of administration
3. Other changes specific to veterinary medicinal products to be administered to food-producing animals.

For the changes listed in Annex II any application will follow the procedure as for the granting of a marketing authorisation. An extension to or a modification of the existing marketing authorisation will have to be granted by the competent authorities or by the Community, as the case may be, subject to a favourable outcome of the evaluation.

One exception is the annual renewal procedure for human influenza vaccines, and possibly other human diseases for which a pandemic situation occurs. Although it concerns a change in the active substance, only a Type II variation is necessary.
As experience has shown problems in the classification of extensions (covered by Annex II) versus variations particularly regarding the items **pharmaceutical form and strength**, it is necessary to establish a common understanding of these terms.

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Based on the European Pharmacopoeia document "STANDARD TERMS - Pharmaceutical dosage forms - Routes of administration - Containers - December 2002" this Guideline proposes a harmonised and agreed interpretation of the above mentioned terms, with the aim of facilitating the application of the Regulations on variations throughout the EU, both within the centralised procedure and the mutual recognition procedure.

The proposed interpretation applies only to the procedure regarding the application of the Regulations on variations and **does not automatically affect other regulatory decisions**, such as the granting of a marketing authorisation or modification of an existing marketing authorisation, policies of competent authorities regarding the system of issuing authorisation numbers (sub- numbers) or on the fees calculation, changes to the name of a medicinal product or to the product information. In particular, the definition of strength in this Guideline has no implication for the strength which is included in the name of the medicinal product in the SPC, labelling and package leaflet/package insert. The appropriate expression of the strength depends on the medicinal product concerned and must allow a correct use of the medicinal product. The product information (name, SPC, labelling and package leaflet/package insert) must carry the adequate expression of the strength. It is however at the discretion of each competent authority to apply (parts of) the definitions below to other regulatory decisions, where appropriate (e.g. fees).

A) Definitions and principles

1) Pharmaceutical form

Regarding the terminology: dosage form and pharmaceutical form have exactly the same meaning. The title of the European Pharmacopoeia document "STANDARD TERMS Pharmaceutical dosage forms - Routes of administration – Containers - December 2002" includes both terms. The pharmaceutical form is defined as in this document.

The pharmaceutical form is the combination of the form in which a pharmaceutical product is presented by the manufacturer (form of presentation) and the form in which it is administered including the physical form (form of administration). If the physical form in which the product is supplied by the manufacturer is different from that in which it is to be administered to/used by the patient, that is, if transformation of the product is required before it can be administered/used, both these elements of information need to be conveyed within the term. If the product has certain special characteristics that are relevant to its use, these need to be included in the term.

In some cases the pharmaceutical form needs to be further qualified: "effervescent powder", "modified-release tablet" or "prolonged-release tablet", "gastro-resistant capsule" should be used and are considered as different pharmaceutical forms.

As stated in the "Standard Terms" document, in certain cases a complete characterisation of the pharmaceutical form requires additional information about the container. This applies in any case to pre-filled syringes, pressurised preparations and single-dose preparations which are considered as specific pharmaceutical forms. The same applies also where the administration of the same physical form differs due to a different design of the container/administration device. A pressurised container and a spray pump are considered as specific pharmaceutical forms ("cutaneous spray, solution, pressurised container" and "cutaneous spray, solution, spray pump" are two pharmaceutical forms).

A change or addition of pharmaceutical form results in an Extension Application except in case of a deletion of the solvent, which results in a Type II Variation.

a) Single-dose preparations

Single-dose preparations are supplied in an individual container (sachet, vial, pre-filled syringe, ampoule, small bottle).

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

i) 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;
ii) 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"). The presentation could be provided with a suitable measuring device.

b) Multi-dose preparations

Preparations that are supplied in a multi-dose container (bottle, tube, large vial, cartridge for pen) which hold two or more doses and which are usually administered by a suitable measuring device (spoon, graduated empty syringe, dosing cup).

These preparations will often have a different composition regarding excipients (e.g. preservatives) than an equivalent single-dose preparation.

A change from multi-dose to single-dose or vice-versa always results in an Extension Application (both for addition or replacement).

2) Strength

The quantitative composition in terms of active substance represents the strength. The concept of strength and the concept of concentration are inherently linked. The strength represents the amount of active substance in the pharmaceutical form, which can be defined per unit dose or as a concentration. The concentration can be stated per unit of mass (250mg/g) or per unit of volume (2mg/ml) or in percentage (5%). For the purpose of this Guideline:

- for single-dose preparations, total use, the strength is defined as the amount of active substance per unit dose;
- for single-dose preparations, partial use, the strength is defined as the concentration expressed as the amount of active substance per ml, per puff, per drop, per kg, per m^2, in percentage as appropriate;
- for multi-dose preparations, the strength is defined as the concentration expressed as the amount of active substance per ml, per puff, per drop, per kg, per m^2 as appropriate;

- for powder for reconstitution (powder for oral solution or suspension, powder for solution for injection, etc.) the strength is defined as the concentration after dissolution or suspension (reconstitution) to the volume and liquid recommended;
- for concentrates for solutions (for injection or for infusion) the strength is defined as the concentration of the concentrate before dilution;
- for transdermal patches the strength is defined as the amount of active substance released from the patch in 24h.

A different strength (as defined above), or any other changes to the active substance(s) as defined in Annex II of Commission Regulations (EC) No 1084/2003 and 1085/2003, results in an Extension Application.

3) Presentation

The presentation includes the size of the container (fill-volume/fill-weight) and/or the pack size. The pack size equals number of tablets, number of sachets, number of ampoules, etc. per outer packaging.

The provisions are detailed in variation no. 41 in Annex I. A different pack size (including parenterals) results in a Type IA or IB variation, depending if the change is within or outside the range of currently approved pack sizes. A change in the fill-weight/ fill-volume of non-parenteral multi-dose products is a variation Type IB. Any other change in pack-size, fill-volume or fill-weight, which does not involve a change in strength, is a Type II variation.

4) Route of administration

The route of administration is defined in the Standard Terms.
A medicinal product may be intended for more than one route of administration.

A change or addition of route of administration results in an Extension Application.

5) Inclusion of medical devices

The addition, replacement or deletion of measuring or administration devices not being an integrated part of the primary packaging are Type IA or Type IB (No 43) for medicinal products for human use and Type IB for veterinary medicinal products. This includes the addition or replacement of needles, plasters, alcohol-swabs etc. The addition or replacement of spacer devices for metered dose inhalers is a Type II variation, unless the device is an integral part of the medicinal product and the change results in a change to the strength, pharmaceutical form or route of administration for which an Extension Application should be submitted.

B) Examples

Notes:

- The examples below are applicable to both replacements and additions of a strength or pharmaceutical form.
- EA = Extension Application (which may result in a modification or an extension of an existing MA).
- The examples take into account the updated "Guideline on dossier requirements for Type IA and Type IB Notifications".

How to read the table:

Example 1:

- The first column describes the situation: existing authorisation for a 100 mg tablet ("*from*"); MAH applies for an additional 500 mg tablet ("*to*").
- The second column indicates the "strengths" to be compared for the classification as an Extension Application or Variation, applying the definitions given in the document above (*Guideline on the categorisation of extension applications versus variation applications*).
- The third column gives the procedural route to be followed for the 500 mg tablet.

Examples			**"Strength", only for classification as EA / Type II / Type IA/IB**	**Classification as EA / Type II / Type IA/IB**
A. ORAL PREPARATIONS				
Solid – Single-dose, total use				
1. Tablets	*from* *to*	100 mg 500 mg	100 mg 500 mg	EA
2. Granules (sachet)	*from* *to*	1 g 2 g	1 g 2 g	EA
Solid – Multi-dose				
3. Granules (bottle)	*from* *to* *from* *to*	100 mg/5 g (spoon) 500 mg/5 g 500 g bottle 1000 g bottle (of 100 mg/g)	20 mg/g 100 mg/g 100 mg/g 100 mg/g	EA Type IB (no 41(b))
Solid – Fixed combinations / combination packs				
4. Tablets (Fixed combination)	*from* *to* 	5 mg X + 10 mg Y 10 mg X + 20 mg Y 5 mg X + 10 mg Y 5 mg X + 20 mg Y	5 mg + 10 mg 10 mg + 20 mg 5 mg + 10 mg 5 mg + 20 mg	EA EA

Examples			"Strength", only for classification as EA / Type II / Type IA/IB	Classification as EA / Type II / Type IA/IB
5. Tablets (Oral contraceptives)	*from*	12 tablets X + 12 tablets Y + 4 tablets Placebo		
	to	16 tablets X + 12 tablets Y		EA
Semi-solid – Multi-dose				
6. Gel	*from*	20 mg/g	20 mg/g	
	to	100mg/g	100 mg/g	EA
	from	20 g jar	100 mg/g	Type IB
	to	30 g jar (of 100 mg/g)	100 mg/g	(no 41(b))
Powder for oral solution / suspension – Single-dose, total use				
7. Powder for oral solution (sachet)	*from*	100 mg (to 2 ml)	100 mg	
	to	200 mg (to 2 ml)	200 mg	EA
	from	100 mg (to 2 ml)	100 mg	
	to	200 mg (to 4 ml)	200 mg	EA
Powder for oral solution / suspension – Multi-dose				
8. Powder for oral suspension (bottle)	*from*	10 g (to 200 ml)	50 mg/ml	
	to	20 g (to 200 ml)	100 mg/ml	EA
	from	10 g (to 200 ml)	50 mg/ml	Type IB
	to	20 g (to 400 ml)	50 mg/ml	(no 41(b))
Liquid ready-to-use – Single-dose, total use				
9. Oral solution (sachet)	*from*	100 mg/5 ml	100 mg	
	to	200 mg/5 ml	200 mg	EA
	from	100 mg/5 ml	100 mg	
	to	200 mg/10 ml	200 mg	EA
Liquid ready-to-use – Multi-dose				
10. Oral solution (bottle)	*from*	500 mg/50 ml	10 mg/ml	
	to	1000 mg/50 ml	20 mg/ml	EA
	from	500 mg/50 ml	10 mg/ml	Type IB
	to	1000 mg/100 ml	10 mg/ml	(no 41 (b))
B. PARENTERAL PREPARATIONS				
Liquid ready-to-use – Single-dose, total use				
11. Solution for injection	*from*	100 mg/1 ml	100 mg	

Examples			"Strength", only for classification as EA / Type II / Type IA/IB	Classification as EA / Type II / Type IA/IB
(pre-filled syringe)	*to*	200 mg/1 ml	200 mg	EA
	from	100 mg/1 ml	100 mg	
	to	200 mg/2 ml	200 mg	EA
	from	100 mg/1 ml	100 mg	
	to	100 mg/0.5 ml	100 mg	Type II
Liquid ready-to-use – Multi-dose or Single-dose, partial use				
12. Solution for injection (vial)	*from*	500 mg/50 ml	10 mg/ml	
	to	1000 mg/50 ml	20 mg/ml	EA
	from	500 mg/10 ml	50 mg/ml	
	to	1000 mg/20 ml	50 mg/ml	Type II
	from	50 mg/5 ml	10 mg/ml	
	to	100 mg/10 ml	10 mg/ml	Type II
Parenterals – different containers				
13. Solution for injection	*from*	vial		
	to	pre-filled syringe *(same concentration)*		EA
14. Solution for injection	*from*	vial		
	to	ampoule *(same concentration)*		Type II
	from	ampoule-plastic		
	to	ampoule-glass *(same concentration)*		Type II
15. Solution for injection (insulins)	*from*	vial		
	to	cartridge *(same concentration)*		Type II
	from	cartridge		
	to	cartridge in disposable pen *(same conc. & cartridge)*		Type II
16. Powder + Solvent		<u>solvent</u>		
	from	vial		
	to	pre-filled syringe *(same concentration)*		EA
Powder for reconstitution – Single-dose, total use				
17. Powder for solution	*from*	100 mg (to 2 ml)	100 mg	

Examples			"Strength", only for classification as EA / Type II / Type IA/IB	Classification as EA / Type II / Type IA/IB
for injection	*to*	200 mg (to 2 ml)	200 mg	EA
	from	250 IU (to 5 ml)	250 IU	
	to	500 IU (to 5 ml)	500 IU	EA
	from	100 mg (to 2 ml)	100 mg	
	to	200 mg (to 4 ml)	200 mg	EA
	from	3 g (to 5 ml)	3 g	
	to	3 g (to 10 ml)	3 g	Type II
Powder for reconstitution – Multi-dose or Single-dose, partial use				
18. Powder for concentrate for infusion	*from*	500 mg (to 50 ml)	10 mg/ml	
	to	1000 mg (to 50 ml)	20 mg/ml	EA
	from	200 IU (to 100 ml)	20 IU/ml	
	to	600 IU (to 200 ml)	30 IU/ml	EA
	from	500 mg (to 50 ml)	10 mg/ml	
	to	1000 mg(to 100ml)	10 mg/ml	Type II
Concentrate for solution				
19. Concentrate for solution for infusion			**BEFORE DILUTION**	
	from	1 g/10 ml	100 mg/ml	
	to	2 g/10 ml	200 mg/ml	EA
	from	1 g/10 ml	100 mg/ml	
	to	2 g/20 ml	100 mg/m	Type II
C. LOCAL PREPARATIONS				
Cutaneous Semi-solid – Multi-dose or Single-dose, partial use				
20. Cream		20 mg/g	20 mg/g	
		100 mg/g (sachet)	100 mg/g	EA
		20mg/g	20 mg/g	Type IB
		40 mg/2 g (sachet)	20 mg/g	(no 41(b))
		20g tube	100 mg/g	Type IB
		30 g tube (of 100 mg/g)	100 mg/g	(no 41 (b))

Examples			"Strength", only for classification as EA / Type II / Type IA/IB	Classification as EA / Type II / Type IA/IB
Eye preparations, liquid ready-to-use – Single-dose, total use				
21. Eye drops, Solution	*from* *to*	10 mg/0.5 ml 20 mg/0.5 ml	10 mg 20 mg	EA
Transdermal patch				
22. Transdermal patch	*from* *to* *from* *to*	2 mg 3 mg 2 mg 2.5 mg	25 µg/24 h 30 µg/24 h 25 µg/24 h 25 µg/24 h	EA Type II
Eye preparations, liquid ready-to-use – Multi-dose or Single-dose, partial use				
23. Eye drops, Solution	*from* *to* *from* *to*	50 mg/5 ml 100 mg/5 ml 50 mg/5 ml 100 mg/10 ml	10 mg/ml 20 mg/ml 10 mg/ml 10 mg/ml	EA Type IB (no 41 (b))
Local preparations – different containers				
24. Cutaneous spray	*From* *to*	spray pump pressurised container		EA
25. Cream	*from* *to*	jar tube		Type II
D. PREPARATIONS FOR INHALATION				
Liquid ready-to-use – Multi-dose				
26. Pressurised inhalation solution	*from* *to* *from* *to*	5 mg/puff 10 mg/puff 60 puffs 100 puffs per container (of 5 mg/puff)	5 mg/puff 10 mg/puff 5 mg/puff 5 mg/puff	EA Type IB (no 41(b))
Powder – Single-dose, total use				
27. Inhalation powder, hard capsule	*from* *to*	1 mg 2 mg	1 mg/puff 2 mg/puff	EA

Examples			"Strength", only for classification as EA / Type II / Type IA/IB	Classification as EA / Type II / Type IA/IB
Powder – Multi dose				
28. Inhalation powder	*from* *to*	6 mg/puff 12 mg/puff	6 mg/puff 12 mg/puff	EA
	from *to*	60 puffs 100 puffs per container (of 6 mg/puff)	6 mg/puff 6 mg/puff	Type IB (no 41(b))
Inhalation preparations – different containers				
29. Inhalation powder	*from* *to*	hard capsule disc		EA
Change of propellant				
30. New propellant, quantitative change in active substance(s) or change in bioavailability, or different dosing schedule or content per actuation, or different pharmaceutical form				EA
31. New propellant, same active substance(s) and excipients and same pharmaceutical form				Type II
E. PREPARATIONS FOR RECTAL or VAGINAL USE				
(Semi)-solid, liquid ready-to-use – Single-dose, total use				
32. Suppository	*from* *to*	100 mg 200 mg	100 mg 200 mg	EA
(Semi)-solid, liquid ready-to-use – Multi dose				
33. Vaginal cream	*from* *to*	20 mg/g 100 mg/g	20 mg/g 100 mg/g	EA
	from *to*	20 g tube 30 g tube (of 100 mg/g)	100 mg/g 100 mg/g	Type IB (no 41(b))