EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems and products
Medicinal products

Revision 4

NOTICE TO APPLICANTS

VOLUME 2C
Regulatory Guidelines

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

July 2019

This guideline will be included in The Rules governing Medicinal Products in the European Union
The Notice to Applicants - Volume 2C – Regulatory Guidelines

Revision 4 – July 2019

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

Introduction

Commission Regulation (EC) No 1234/2008 as amended by Commission Regulation (EU) No 712/2012 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products defines the scope of what can be considered a variation to the terms of a marketing authorisation within the meaning of Article 1(26a), 23b 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[1]. The corresponding provisions in Regulation (EC) No 726/2004 are found in Articles 5 and 16a for medicinal products for human use and in Articles 30 and 39[2] for veterinary medicinal products, respectively.

Article 2(4) of Commission Regulation (EC) No 1234/2008, states that an extension of marketing authorisation means a variation which is listed in Annex I and fulfils the conditions laid down therein. Annex I 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; change or addition of target species.

For the changes listed in Annex I any application will follow the same procedure as for the granting of the initial marketing authorisation to which it relates. The extension can either be granted as a new marketing authorisation or will be included in the initial marketing authorisation to which it relates.

A typical extension application that could be included is Annex I 1(d) modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different.
Exceptions that are not extension applications even though there is a change in active substance are: changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza, replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue, replacement of a strain for a veterinary vaccine against equine influenza. Although they concern a change in the active substance only a Type II variation is necessary.

As experience has shown problems in the classification of extension applications (covered by Annex I) versus variations particularly regarding the items **pharmaceutical form and strength**, it is necessary to establish a common understanding of these terms.

Based on the European Pharmacopoeia document "STANDARD TERMS – Introduction and Guidance for Use"[3] this Guideline proposes a harmonised and agreed interpretation of the above mentioned terms, with the aim of facilitating the application of the Regulation on variations throughout the EU.

[1] The new Regulation (EU) 2019/6 on veterinary medicinal products will apply from 28 January 2022 and it will repeal Directive 2001/82/EC.
[2] Until these provisions will be repealed by the Regulation (EU) 2019/6.
[3] https://www.edqm.eu/sites/default/files/standard_terms_introduction_and_guidance_for_use.pdf

This guideline relates only to the procedure regarding the application of the Commission Regulation (EC) No 1234/2008 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 SmPC, labelling and package leaflet. 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, SmPC, labelling and package leaflet) 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**

According to the European Pharmacopoeia document 'STANDARD TERMS Introduction and Guidance for use', the terms dosage form and pharmaceutical form are defined as follows:

Dosage form
Pharmaceutical dose form. (Note: 'Dosage form' and 'Pharmaceutical dose form' are synonymous.)

Pharmaceutical dose form
Physical manifestation or a product that contains the active ingredient(s) and/or inactive ingredient(s) that are intended to be delivered to the patient. (Note 1: 'Pharmaceutical dose form' and 'Dosage form' are synonyms. Note 2: 'Pharmaceutical dose form' can refer to the administrable dose form or the manufactured dose form, depending on the product that it is describing').

Pharmaceutical form
A pharmaceutical dose form, a combined pharmaceutical dose form or a combined term. (Note: In the assessment of marketing authorisations applications in Europe, pharmaceutical forms that only differ with respect to the container/administration device may not always be considered as different pharmaceutical forms).
A pharmaceutical dose form is used to describe the manufactured product (i.e. the item as presented in the packaging by the manufacturer) or the pharmaceutical product (i.e. the item as intended to be administered to the patient, after any necessary transformation has been carried out). When used to describe the manufactured item, it may be referred to as the manufactured dose form; when describing the pharmaceutical product, it may be referred to as the administrable dose form.
The Standard Terms database[4] does not explicitly distinguish between manufactured dose forms and administrable dose forms. However, for a term representing a manufactured dose form such as 'Powder for solution for injection', the words 'for solution for injection' indicate that a reconstitution is required, and that the resulting administrable dose form is 'Solution for injection'.

According to § 6.2 / xii of the European Pharmacopoeia document "STANDARD TERMS – Introduction of standard terms" of the European Directorate for the Quality of Medicines and Healthcare (EDQM), combined terms are sometimes necessary where a special container, closure or administration device is required for the correct administration of the medicinal product; the closure or administration device may be an integral part of the immediate container. This applies for example to pre-filled syringes, pre-filled pens, pressurised preparations for inhalation and single-dose eye preparations . Therefore, these specific containers are generally regarded as different pharmaceutical forms and a change, a replacement or an

[4] Available at https://standardterms.edqm.eu/

addition of such a container would result in an extension application of the marketing authorisation[5].

A change or addition of a pharmaceutical form results in an extension application except in case of a deletion of the solvent, which results in a variation. A deletion of a pharmaceutical form results in a variation. However, in cases where a given pharmaceutical form has received a marketing authorisation which is separate to the marketing authorisation for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the marketing authorisation.

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 (e.g. 250 mg/g) or per unit of volume (e.g. 2 mg/ml) or in percentage (e.g. 5%) for products for which the strength has traditionally been expressed in such way. 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 actuation, per drop, per kg, per m^2, or 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 actuation, 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 multi-dose or single-dose partial use preparations, or defined by the total amount in the container if single dose, total use [6];
- for concentrates for solutions (single dose, partial use or multidose) for injection or for infusion, the strength is defined as the concentration of the concentrate before dilution;
- for concentrates (single dose, total use), the strength is defined as the total amount in the container;
- for transdermal preparations for systemic use for single dose (e.g. transdermal patches), the strength is defined as the amount of active substance released from the transdermal preparation per unit time;
- for preparations for cutaneous use (e.g. cutaneous patches, medicated plaster), single dose, the strength is defined as the total amount of active substance in the preparation.

[5] In light of the note in the EDQM definition for the pharmaceutical form *'In the assessment of marketing authorisation applications in Europe, pharmaceutical forms that differ only with respect to the container/administration device may not always be considered as different pharmaceutical forms'*, for the purpose of the centralised procedure as the marketing authorisation covers different pharmaceutical forms and strengths, introduction of pharmaceutical forms that differ only with respect to the container/administration device or addition/deletion of a solvent may be handled as a variation. Applicants are advised to confirm with the Agency before submission.

[6] The key principles in relation to single-dose total and partial use as well as multidose should be followed.

A different strength (as defined above), or any other changes to the active substance(s) as defined in Annex I of Commission Regulations (EC) No 1234/2008, results in an extension application. A deletion of a strength results in a variation. In cases where a given strength has received a marketing authorisation which is separate to the marketing authorisation for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the marketing authorisation.

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 generally results in an extension application (both for addition and replacement)[7].

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.

A different pack size (including parenterals) results in a variation, for which the classification depends on whether the change is within or outside the range of currently approved pack sizes. The deletion of a pack-size is a variation.

A change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products is a variation. A change in the fill volume/ fill weight of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products, is a variation.

4)**Route of administration**

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

[7] For the purpose of the centralised procedure as the marketing authorisation covers different pharmaceutical forms and strengths, introduction of pharmaceutical forms that differ only with respect to the container/administration device or addition/deletion of a solvent may be handled as a variation. Applicants are advised to confirm with the Agency before submission.

According to Annex I of Commission Regulation (EC) No 1234/2008, a change or addition of route of administration results in an extension application, where the following clarification is also included:
'*For parenteral administration, it is necessary to distinguish between intra-arterial, intravenous, intramuscular, subcutaneous and other routes. For administration to poultry, respiratory, oral and ocular (nebulisation) routes used for vaccination are considered to be equivalent routes of administration.*'

5)**Inclusion of medical devices**

The addition or replacement of a measuring or administration device which is not an integrated part of the primary packaging is a variation, for instance the addition or replacement of spacer devices for metered dose inhalers or the deletion of measuring or administration devices not being an integrated part of the primary packaging unless this change should be accompanied with a change of the expression of the strength. This includes for example the addition or replacement of needles, plasters, alcohol-swabs. The addition or replacement of a device which is an integrated part of the primary packaging is a variation unless the modification 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 an extension of an existing MA or be granted a new marketing authorisation).
- The examples take into account the *Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2013/C 223/01).*

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 above.
- The third column gives the procedural route to be followed for the 500 mg tablet.

Examples			**"Strength", only for classification as EA / Variation**	**Classification as EA / Variation**
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*	1g 2 g	1 g 2 g	EA
Solid – Multi-dose				
3. Granules (bottle)	*from*	100 mg/ 5g (spoon)	20 mg/g	

	to	500 mg/ 5g	100 mg/g	EA
	from	500 g bottle	100 mg/g	Variation
	to	1000 g bottle (of 100 mg/g)	100 mg/g	
Solid – Fixed combinations				
4. Tablets (Fixed combination)	*from*	5 mg X / 10 mg Y 10 mg X / 20 mg Y	5 mg / 10 mg 10 mg / 20 mg	EA
	to	5 mg X / 10 mg Y 5 mg X / 20 mg Y	5 mg / 10 mg 5 mg / 20 mg	EA
5.Tablets (Oral contraceptives)	*from*	12 tablets X + 12 tablets Y + 4 tablets Placebo		EA
	to	16 tablets X + 12 tablets Y or vice versa		
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	
	to	30 g jar (of 100 mg/g)	100 mg/g	Variation
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	
	to	20 g (to 400 ml)	50 mg/ml	Variation
Liquid ready-to-use – Single-dose, total use				
9. Oral solution (sachet)	*from*	100 mg/5 ml	100 mg	EA
	to	200 mg/5 ml	200 mg	
	from	100 mg/5 ml	100 mg	EA
	to	200 mg/10 ml	200 mg	
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	
	to	1000 mg/100 ml	10 mg/ml	Variation
B. PARENTERAL PREPARATIONS				
Liquid ready-to-use – Single-dose, total use				

11. Solution for injection (pre-filled syringe)	*from* *to* *from* *to* *from* *to*	100 mg/1 ml 200 mg/1 ml 100 mg/1 ml 200 mg/2 ml 100 mg/1 ml 100 mg/0.5 ml	100 mg 200 mg 100 mg 200 mg 100 mg 100 mg	EA EA Variation
Liquid ready-to-use – Multi-dose or Single-dose, partial use				
12. Solution for injection (vial)	*from* *to* *from* *to*	500 mg/50 ml 1000 mg/50 ml 500 mg/10 ml 1000 mg/20 ml	10 mg/ml 20 mg/ml 50 mg/ml 50 mg/ml	EA Variation
	from *to*	50 mg/5 ml 100 mg/10 ml	10 mg/ml 10 mg/ml	Variation
Liquid ready-to-use – From Single-dose, total use to Single dose, partial Use				
13. Solution for injection (pre-filled vial)	*from* *to*	40 mg/0.8 ml *(single dose, total use)* 40 mg/0.8 ml *(single dose, partial use)*	40 mg 50mg/ml	 **EA**
Parenterals – change of container only				
14. Solution for injection	*from* *to* *from* *to* *from* *to*	vial pre-filled syringe *(same concentration)* vial pre-filled pen *(same concentration)* pre-filled syringe pre-filled pen *(same concentration)*		**EA**[8] **EA**[9] **EA**[10]
15. Solution for injection	*from* *to*	vial ampoule *(same concentration)*		Variation

[8, 9, 10] For the purpose of the centralised procedure as the marketing authorisation covers different pharmaceutical forms and strengths, introduction of pharmaceutical forms that differ only with respect to the container/administration device or addition/deletion of a solvent may be handled as a variation. Applicants are advised to confirm with the Agency before submission.

	from *to*	ampoule-plastic ampoule-glass *(same concentration)*		Variation
16. Solution for injection	*from* *to* *from* *to* *from* *to* *from* *to*	vial cartridge *(same concentration)* cartridge cartridge in disposable pen *(same conc. & cartridge)* cartridge cartridge in reusable pen (the pen is provided in the MA) *(same conc. & cartridge)* cartridge prefilled pen		Variation Variation Variation EA[11]
17. Powder + Solvent	*from* *to*	solvent vial solvent pre-filled syringe *(same concentration)*		Variation
Powder for reconstitution – Single-dose, total use				
18. Powder for solution for injection	*from* *to* *from* *to* *from* *to* *from* *to*	100 mg (to 2 ml) 200 mg (to 2 ml) 250 IU (to 5 ml) 500 IU (to 5 ml) 100 mg (to 2 ml) 200 mg (to 4 ml) 3 g (to 5 ml) 3 g (to 10 ml)	100 mg 200 mg 250 IU 500 IU 100 mg 200 mg 3 g 3 g	EA EA EA Variation
Powder for reconstitution – Multi-dose or single-dose partial use				
19. Powder for solution for infusion or powder for concentrate for solution for infusion	*from* *to* *from* *to* *from* *to*	500 mg (to 50 ml) 1000 mg (to 50 ml) 200 IU (to 100 ml) 600 IU (to 200 ml) 500 mg (to 50 ml) 1000 mg (to 100ml)	10 mg/ml 20 mg/ml 2 IU/ml 3 IU/ml 10 mg/ml 10 mg/ml	EA EA Variation
Concentrate for solution for infusion- Multi-dose or single dose partial Use			**BEFORE DILUTION**	

[11] For the purpose of the centralised procedure as the marketing authorisation covers different pharmaceutical forms and strengths, introduction of pharmaceutical forms that differ only with respect to the container/administration device or addition/deletion of a solvent may be handled as a variation. Applicants are advised to confirm with the Agency before submission.

20. Concentrate for solution for infusion	*from* *to* *from* *to*	1 g/10 ml 2g/10ml 1g /10 ml 2g/20ml	100 mg/ml 200 mg/ml 100 mg/ml 100 mg/ml	EA Variation
Concentrate for solution for infusion- single-dose, total use				
21. Concentrate for solution for infusion	*from* *to* *from* *to* *from* *to*	100mg/1ml 200mg/1ml 100mg/1ml 100mg/0.5ml 1200mg/20ml 900mg/15ml	100mg 200mg 100mg 100mg 1200mg 900mg	EA Variation EA
C. LOCAL PREPARATIONS				
Cutaneous Semi-solid – Multi-dose or Single-dose, partial use				
22. Cream	*from* *to* *from* *to* *from* *to*	20 mg/g 100 mg/g (sachet) 20mg/g 40 mg/2g (sachet) 20g tube (100 mg/g) 30 g tube (100 mg/g)	20 mg/g 100 mg/g 20 mg/g 20 mg/g 100 mg/g 100 mg/g	EA Variation Variation
Topical, spot-ons – Single-dose, total use				
23. Spot-on solution	*from* *to*	20 mg/pipette (30 mg/ml) large dog 30 mg/pipette (30 mg/ml) X-large dog	20 mg 30 mg	EA
24. Cutaneous patch for local use	*from* *to* *from* *to*	100mg in patch 10cm x 10cm 200mg in patch 10cm x 10cm 100mg in patch 10cm x 10cm100 mg in patch 5 x	100mg 200mg 100 mg 100mg	EA Variation
25. Transdermal patch for systemic use	*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 Variation
Eye preparations, liquid ready-to-use – Multi-dose or Single-dose, partial use				
26. Eye drops, Solution	 *from* *to* *from* *to* *from* *to*	- Multi-dose: 50 mg/5 ml 100 mg/5 ml 50 mg/5 ml 100 mg/10 ml -Single dose 10 mg/0.5 ml 20 mg/0.5 ml	 10 mg/ml 20 mg/ml 10 mg/ml 10 mg/ml 20 mg/ml 40 mg/ml	 EA Variation EA

Local preparations –change of the container only				
27. Cutaneous spray	*from* *to*	spray pump pressurised container		EA[12]
28. Cream	*from* *to*	jar tube		Variation
D. PREPARATIONS FOR INHALATION				
Liquid ready-to-use – Multi-dose				
29. Pressurised inhalation solution	*from* *to* *from* *to*	5 mg/actuation 10 mg/actuation 60 actuations 100 actuations per container (of 5 mg/actuation)	5 mg/actuation 10 mg/actuation 5 mg/actuation 5 mg/actuation	EA Variation
Powder – Single-dose, total use				
30. Inhalation powder, hard capsule	*from* *to*	1 mg 2 mg	1 mg/actuation 2 mg/actuation	EA
Powder – Multi dose				
31. Inhalation powder	*from* *to* *from* *to*	6 mg/actuation 12 mg/actuation 60 actuations 100 actuations per container (of 6 mg/actuation)	6 mg/actuation 12mg/actuation 6 mg/actuation 6 mg/actuation	EA Variation
Inhalation preparations– change of the container only				
32. Inhalation powder	*from* *to*	hard capsule disc		EA[13]
Change of propellant				
33. 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
34. New propellant, same active substance(s) and excipients and same				Variation

[12, 13] For the purpose of the centralised procedure as the marketing authorisation covers different pharmaceutical forms and strengths, introduction of pharmaceutical forms that differ only with respect to the container/administration device or addition/deletion of a solvent may be handled as a variation. Applicants are advised to confirm with the Agency before submission.

pharmaceutical form				
E. PREPARATIONS FOR RECTAL or VAGINAL USE				
(Semi)-solid, liquid ready-to-use – Single-dose, total use				
35. Suppository	*from* *to*	100 mg 200 mg	100 mg 200 mg	EA
(Semi)-solid, liquid ready-to-use – Multi dose				
36. Vaginal cream	*from* *to* *from* *to*	20 mg/g 100 mg/g 20 g tube 30 g tube (of 100 mg/g)	20 mg/g 100 mg/g 100 mg/g 100 mg/g	EA Variation