Regulation (EC) No 141/2000				
Art.	**Par.**	**Original text**	**Amendments**	**Comments**
3	1	A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than **five** in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;	A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than ***one*** in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;	The deletion of the profitability criterion is not acceptable.

ESIP aisbl
Maison Européenne de la Protection Sociale
Rue d'Arlon 50 • 1000 Bruxelles • +32 2 282 05 60 • +32 2 282 05 98
esip@esip.eu • www.esip.eu • @ESIP_EU • VAT: BE 0808.072.950

		and (b) that **there exists** no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.	***and*** ***b) that an overall prevalence threshold of 5 in 10 thousand persons in the Community for all authorised indications is not exceeded when the application is made*** and ***c)*** that ~~***there exists***~~ no satisfactory method of diagnosis, prevention or treatment of the condition in question has been authorised in the Community or, if such a method exists, the medicinal product will be of significant benefit to those affected by that condition.	
5	12	A designated orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products: (c) at the end of the period of market exclusivity as laid down in Article 8.	A designated orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products: (c) at the end of the period of market exclusivity as laid down in Article 8-***a***.	
7	3	The marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3. This is without prejudice to the possibility of applying for a separate marketing	The marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3. ~~***This is without prejudice to the possibility of applying for a separate marketing authorisation for other***~~	This provision results in different marketing authorisations with unclear effects. For the purpose of distributing OMPs under different tradenames, the provisions of Art. 82 of

		authorisation for other indications outside the scope of this Regulation.	~~***indications outside the scope of this Regulation.***~~	Regulation (EC) 2004/726 should be sufficient.
8	2	This period may however be reduced to **six years** if, at the end of the **fifth** year, it is established, in respect of the medicinal product concerned, that **the criteria laid down in Article 3 are no longer met, inter alia, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met** and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose.	This period may however be reduced ***to a minimum of two years*** ~~***six years***~~ if, at the end of the ***second*** year, it is established, in respect of the medicinal product concerned, that the criteria laid down in ~~***Article 3 are no longer met, inter alia, where it is shown on the basis of available evidence that the product is sufficiently profitable not to***~~ ***Article 8-a no longer*** justify maintenance of market exclusivity. To that end, ~~***a Member State shall inform***~~ the Agency ***shall review whether the criteria as laid down in Article 8-a of this Regulation*** ~~***on the basis of which market exclusivity was granted***~~ ***are still*** met and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose. ***If market exclusivity has been maintained, the Agency shall review on an annual basis, starting at the end of the second year, whether these criteria for market exclusivity are still met to justify maintenance of it.***	

8	***3 new***		***Market exclusivity criteria as laid down in Article 8-a shall also be reviewed when the sponsor/marketing authorisation holder applies for a new indication of the medicinal product, regardless whether this new indication has an orphan designation or not.***	
8-a	**new**		***Criteria for market exclusivity*** ***Market exclusivity is maintained only for orphan medicinal products if the sponsor can establish:*** ***(a) that it is intended for the diagnosis, prevention or treatment of a condition affecting not more than one in 10 thousand persons in the Community AND that in sum not more than five in 10 thousand persons are affected if the medicinal product is authorised for more than one condition;*** ***and*** ***(b) that the marketing of the medicinal product in the Community does not exceed a set threshold of volume of sales, defined as above 1 billion EUR per year;***	

			and ***(c) that a clinically meaningful benefit has been demonstrated;*** ***and*** ***(d) that the medicinal product has been placed on the Union market and a pricing and reimbursement application has been submitted, if applicable, in all EU Member States within two years after marketing authorisation and prior to the first review by the Agency.***	
Regulation (EC) No 847/2000				
2	1(a)	the documentation shall include appended authoritative references which demonstrate that the disease or conditions for which the medicinal product would be administered, affects not more than **five** in 10 000 persons in the Community at the time at which the application for designation is submitted, where these are available;	the documentation shall include appended authoritative references which demonstrate that the disease or conditions for which the medicinal product would be administered, affects not more than ***~~five~~ one*** in 10 000 persons in the Community at the time at which the application for designation is submitted, where these are available. ***This documentation shall include information on all medicinal products with this active pharmaceutical ingredient;***	
2	3(b)	either a justification as to why the methods referred to in paragraph (a) are not considered satisfactory;	either a justification as to why the methods referred to in paragraph (a) are not considered satisfactory ***and the new method***	Proposal corresponding to amendment of Article 3 (1) of Regulation (EC) 141/2000

			is expected to have the potential of addressing the need in a satisfactory way;	
3	2	'significant benefit' means a **clinically relevant advantage or a major contribution to patient care**.	'significant benefit' means a clinically ***~~relevant~~ meaningful*** advantage ***~~or a major contribution to patient care~~***.	
3	3(d)	'clinically superior' means that a medicinal product is shown to provide a **significant therapeutic or diagnostic advantage** over and above that provided by an authorised orphan medicinal product in one or more of the following ways: (1) greater efficacy than an authorised orphan medicinal product (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative efficacy claim for two different medicinal products. Direct comparative clinical trials are generally necessary, however comparisons based on other endpoints, including surrogate endpoints may be used. In	'clinically superior' means that a medicinal product is shown to provide a ***statistically*** significant ***and clinically meaningful*** therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways: (1) greater efficacy than an authorised orphan medicinal product (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative efficacy claim for two different medicinal products. Direct comparative clinical trials are generally necessary, however comparisons based on other endpoints, including surrogate endpoints may be used. In any case,	

		any case, the methodological approach should be justified; (2) greater safety in a substantial portion of the target population(s). In some cases, direct comparative clinical trials will be necessary; or **(3) in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care.**	the methodological approach should be justified; ***or*** (2) greater safety in a substantial portion of the target population(s). In some cases, direct comparative clinical trials will be necessary***. ~~Or~~*** (3) ***~~in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care.~~***	