Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required (Text with EEA relevance)

COMMISSION DELEGATED REGULATION (EU) No 357/2014

of 3 February 2014

supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[(1)], and in particular Article 22b thereof,

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[(2)], and in particular Article 10b thereof,

Whereas:

(1) Authorisation decisions for medicinal products should be made on the basis of the objective criteria of quality, safety and efficacy of the medicinal product concerned, to ensure that only high quality medicinal products are placed on the market and administered to patients. As a consequence, new medicinal products have to undergo extensive studies, including clinical efficacy trials, before they are authorised.

(2) According to Article 21a(f) of Directive 2001/83/EC and to Article 9(4)(cc) of Regulation (EC) No 726/2004 it may be necessary in specific situations to complement the data available at the time of authorisation with additional information concerning the efficacy of a medicinal product, to address concerns that could not be resolved prior to the granting of the marketing authorisation. Moreover, according to Article 22a(1)(b) of Directive 2001/83/EC and to Article 10a(1)(b) of Regulation (EC) No 726/2004 post-authorisation information may require significant revision of previous efficacy evaluations and call for additional, confirmatory efficacy data, while the marketing authorisation is maintained. In both situations, the national competent authorities, the European Medicines Agency and the Commission (hereinafter ‘the competent authorities’) may oblige the marketing authorisation holder to conduct a post-authorisation efficacy study.

(3) The obligation to conduct a post-authorisation efficacy study should address certain well-reasoned scientific concerns, which could have a direct impact on the maintenance of the marketing authorisation. It should not be used as a justification for the premature granting of a marketing authorisation. According to Article 22a(1) of Directive 2001/83/EC and to Article 10a(1) of Regulation (EC) No 726/2004 the obligation to conduct such a study should be justified on a case-by-case basis, taking into account the properties of a medicinal product and the available data. The study should provide the competent authorities and the marketing authorisation holder with necessary information, in order to either complement initial evidence or to verify whether the marketing authorisation should be maintained as granted, varied, suspended or revoked on the basis of new data resulting from the study.

(4) Article 22b of Directive 2001/83/EC and Article 10b of Regulation (EC) No 726/2004 empowers the Commission to specify the situations in which post-authorisation efficacy studies may be required. In the interests of transparency and legal certainty, and in the light of developments in scientific knowledge, it is appropriate to draw up a list of specific situations and the circumstances that might be considered.

(5) In various therapeutic areas, surrogate endpoints, such as biomarkers or tumour shrinkage in oncology, have been used as a tool to define the efficacy of medicinal products in exploratory or confirmatory clinical studies. To substantiate the assessment based on those endpoints, it may be relevant to generate further efficacy data in the post-authorisation phase to verify the impact of the intervention on clinical outcome or disease progression. It may also be necessary to verify whether the overall survival data in the post-authorisation phase is discordant with or confirmative of the outcome of the surrogate endpoint.

(6) Some medicinal products may be used regularly in combination with other medicinal products. While the applicant for marketing authorisation is expected to address the effects of such combinations in clinical studies, it is often neither required nor appropriate to study exhaustively all possible combinations covered by the marketing authorisation in general terms pre-authorisation. Instead, the scientific assessment may be based partly on extrapolation of existing data. In certain cases it may be relevant to gain further clinical evidence post-authorisation for some specific combinations if such studies could clarify an uncertainty that has not already been addressed. This applies particularly if such combinations are used or are expected to be used in everyday medical practice.

(7) In the pivotal clinical studies conducted prior to granting marketing authorisation, it may be difficult to gather robust representation of all the different sub-populations to which the medicinal product is administered. This may not necessarily preclude an overall positive benefit-risk balance at the time of authorisation. However, for some specific sub-populations for which uncertainties with respect to benefits have been raised, further substantiation of evidence of efficacy may be necessary, with specifically targeted clinical studies in the post-authorisation phase.

(8) Under normal circumstances, there is no mandatory requirement for long-term follow-up of efficacy of medicinal products as part of post-authorisation surveillance, even

for medicinal products authorised for chronic conditions. In many instances, the effects of a medicinal product wane over time, requiring a redefinition of therapy. However, this does not necessarily compromise the benefit-risk balance of the medicinal product and the appraisal of the beneficial effect exerted up to that point in time. In exceptional cases, post-authorisation studies should be imposed where a potential lack of efficacy in the long term could raise concerns with respect to the maintenance of a positive benefit-risk balance of the intervention. This could be the case for innovative therapies in which interventions are supposed to modify the course of the disease.

(9) In exceptional situations, studies in everyday medical practice could be requested where there is clear evidence that the benefits of a medicinal product demonstrated in randomised controlled clinical trials is significantly affected by the real-life conditions of use or where the specific scientific concern is best studied by having access to data collected in everyday medical practice. Furthermore, protective efficacy studies of vaccines are not always feasible. Alternatively, estimates of effectiveness from prospective studies conducted during vaccination campaigns after authorisation could be used in order to gain further knowledge on the ability of the vaccine to confer protection in the short or long term.

(10) During the life cycle of an authorised medicinal product, a significant change may occur in the standard of care for the diagnosis, treatment or prevention of a disease, leading to the need to re-open discussions on the established benefit-risk balance of the medicinal product. The European Court of Justice has ruled that a modified consensus within the medical community regarding the appropriate assessment criteria of the therapeutic efficacy of a medicinal product may constitute concrete and objective factors capable of acting as a basis for the finding of a negative benefit-risk assessment of that product[(3)]. It may therefore be necessary to provide new evidence on the efficacy of the medicinal product to maintain a positive benefit-risk assessment. Likewise, if an improved understanding of the disease or the pharmacology of a medicinal product has brought into question the criteria used to establish the efficacy of the medicinal product at the time the marketing authorisation was granted, additional studies may be considered.

(11) To obtain meaningful data, it is necessary to ensure that the design of a post-authorisation efficacy study is appropriate to answer the scientific question that it intends to address.

(12) Competent authorities may impose obligations to ensure or confirm efficacy of a human medicinal product in the context of a conditional marketing authorisation and/or a marketing authorisation that has been granted subject to exceptional circumstances, or as a result of a referral procedure initiated under Articles 31 and 107i of Directive 2001/83/EC or Article 20 of Regulation (EC) No 726/2004. Additionally, holders of a marketing authorisation for an advanced therapy medicinal product or a medicinal product for paediatric use may have to comply with certain measures to ensure the follow-up of efficacy. As a consequence, it is necessary to conduct a post-authorisation efficacy study. The need for such a study should be assessed in the context of those

procedures and independently of the specific situations and circumstances specified in this Regulation,

HAS ADOPTED THIS REGULATION:

Article 1

1 The national competent authorities, the European Medicines Agency or the Commission may require a post-authorisation efficacy study to be carried out by the holder of a marketing authorisation in accordance with Articles 21a(f) and 22a(1)(b) of Directive 2001/83/EC and Articles 9(4)(cc) and 10a(1)(b) of Regulation (EC) No 726/2004:

a where concerns relating to some aspects of efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed;

b where the understanding of the disease, the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly.

2 The national competent authorities, the European Medicines Agency or the Commission shall only apply paragraph 1 if one or more of the following cases arise:

a an initial efficacy assessment that is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions;

b in case of medicinal products that are used in combination with other medicinal products, the need for further efficacy data to clarify uncertainties that had not been addressed when the medicinal product was authorised;

c uncertainties with respect to the efficacy of a medicinal product in certain sub-populations that could not be resolved prior to marketing authorisation and require further clinical evidence;

d the potential lack of efficacy in the long term that raises concerns with respect to the maintenance of a positive benefit-risk balance of the medicinal product;

e benefits of a medicinal product demonstrated in clinical trials are significantly affected by the use of the medicinal product under real-life conditions, or, in the case of vaccines, protective efficacy studies have not been feasible;

f a change in the understanding of the standard of care for a disease or the pharmacology of a medicinal product that requires additional evidence on its efficacy;

g new concrete and objective scientific factors that may constitute a basis for finding that previous efficacy evaluations might have to be revised significantly.

3 The situations set out in paragraph 1 and 2 are without prejudice to the imposition of the obligation on the holder of a marketing authorisation to conduct a post-authorisation efficacy study in the context of any of the following situations:

a a conditional marketing authorisation granted in accordance with Article 14(7) of Regulation (EC) No 726/2004;

b a marketing authorisation granted in exceptional circumstances and subject to certain conditions in accordance with Article 14(8) of Regulation (EC) No 726/2004 or Article 22 of Directive 2001/83/EC;

c a marketing authorisation granted to an advanced therapy medicinal product in accordance with Article 14 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council[(4)];

d the paediatric use of a medicinal product in accordance with Article 34(2) of Regulation (EC) No 1901/2006 of the European Parliament and of the Council[(5)];

e a referral procedure initiated in accordance with Articles 31 or 107i of Directive 2001/83/EC or Article 20 of Regulation (EC) No 726/2004.

Article 2

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 3 February 2014.

For the Commission

The President

José Manuel BARROSO

(**1**) OJ L 311, 28.11.2001, p. 67.

(**2**) OJ L 136, 30.4.2004, p. 1.

(**3**) Case C-221/10P *Artegodan* v *Commission*, not yet published, paragraphs 100-103.

(**4**) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

(**5**) Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1).

Changes to legislation:
There are outstanding changes not yet made to Commission Delegated Regulation (EU) No 357/2014. Any changes that have already been made to the legislation appear in the content and are referenced with annotations.
View outstanding changes

Changes and effects yet to be applied to :

– Regulation revoked in part by S.I. 2019/775 Sch. 9 para. 1(cc)