Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC — March 2006

(2006/C 133/05)

1. Introduction

Based on Article 29(2) of Directive 2001/83/EC as amended [1] the scope of this guideline is to set out in more detail in which exceptional cases a Member State concerned in a mutual recognition procedure as referred to in Article 28(2) or in a decentralised procedure as referred to in Article 28(3) can refuse to recognise a marketing authorisation or a positive assessment on the basis of a potential serious risk to public health.

In the case that at least one of the Member States [2] concerned by the application cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of a potential serious risk to public health, as set out in Article 29(1) of Directive 2001/83/EC, when requested to mutually recognise a marketing authorisation granted by another Member State, it shall give a detailed explanation of the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant.

As the Community pharmaceutical legislation fully harmonises the standards for quality, safety and efficacy of a medicinal product, a marketing authorisation granted by one Member State should generally be recognizable by the other Member States.

In the mutual recognition procedure, according to Article 28(2) of Directive 2001/83/EC, the reference Member State will assess the data in the dossier and issue a national marketing authorisation, provided the risk-benefit balance of the product is considered to be favourable and the quality, safety and efficacy of the medicinal product is sufficiently guaranteed and no other or further reasons for the refusal of the marketing authorisation according to Article 26 of Directive 2001/83/EC is given. For the process of mutual recognition the reference Member States has to provide an assessment report that is sufficiently detailed to explain to the Member State concerned why this risk-benefit balance is considered to be favourable, together with the approved summary of product characteristics, labelling and package leaflet. In the decentralised procedure, according to Article 28(3) of Directive 2001/83/EC, no prior national procedure is intended and no existing marketing authorisation is in place at that time. After receipt of a valid application it is the duty of the reference Member State to prepare, within 120 days, a draft assessment report, a draft summary of products characteristics and a draft of the labelling and package leaflet.

Article 29(1) of Directive 2001/83/EC describes the procedure to be followed if a concerned Member State cannot approve the assessment report, summary of products characteristics, package leaflet and labelling as prepared by the reference Member State. In Article 29(1) reference is made to Article 28(4), which in turn refers to Article 28(2) and (3). These articles concern both the mutual recognition procedure and the decentralised procedure. Consequently, the grounds for refusal are the same irrespective of whether the concerned Member State evaluates an assessment report, summary of products characteristics, labelling and package leaflet from the reference Member State in a mutual recognition procedure, or a draft assessment report, draft summary of products characteristics and draft of the labelling and package leaflet and from the reference Member State in a decentralised procedure.

By defining in which exceptional cases the concerned Member State can refuse to recognise a marketing authorisation in a mutual recognition procedure, or a draft assessment report, a draft summary of products characteristics, and a draft of the labelling and package leaflet from the reference Member State in a decentralised procedure, on the basis of a potential serious risk to public health, this will also concurrently limit the variety and number of objections raised by Member States.

A concerned Member State that raises major objections based on a potential serious risk to public health shall give a detailed explanation of the reasons for its position.

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[1] Amended by Directive 2004/27/EC (OJ L 136, 30.4.2004, p. 34).

[2] Member States in this context refers to all countries of the European Economic Area.

In this context, it should be considered that a Member State plays a different role when it is called upon to approve the evaluation report, the summary of product characteristics, the labelling and package leaflet for a medicinal product submitted to it by the reference Member State and the role that it plays when it is the only one to issue a national marketing authorisation for a medicinal product that has not yet been the subject of an application for authorisation in another Member State of the Community, or when it is itself the reference Member State.

In the case of an authorisation not referring to another authorisation the Member State is fully competent to determine the content of the marketing authorisation for the medicinal product in accordance with Directive 2001/83/EC, while in recognising the first authorisation or evaluation, done by the reference Member State it is consequently for the Member States that are informed of authorisation or evaluation not to decide whether or not it can be improved on, but rather to establish clearly and in a well-argued fashion why the proposed authorisation (or refusal) presents a potential serious risk to public health.

2. **Definition of potential serious risk to public health**

Directive 2001/83/EC does not provide for a definition of a 'potential serious risk to public health'. However, the following definitions are given in that Directive:

— The term 'risk related to the use of the medicinal product' is defined in point 28 of Article 1, first indent of Directive 2001/83/EC as *'any risk relating to the quality, safety or efficacy of the medicinal product as regards to patients' health or public health' (or any risk of undesirable effects on the environment).*

— The term 'risk-benefit balance' is defined in point 28a of Article 1of that Directive as 'an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28, first indent'

For the application of this guideline, the following definitions shall apply:

— A '**risk**' is defined as the probability that an event will occur

— A '**potential serious risk to public health**' is defined as a situation where there is a significant probability that a serious hazard resulting from a human medicinal product in the context of its proposed use will affect public health.

— 'Serious' in this context means a hazard that could result in death, could be life-threatening, could result in patient hospitalisation or prolongation of existing hospitalisation, could result in persistent or significant disability or incapacity, or could be a congenital anomaly/birth defect or permanent or prolonged signs in exposed humans.

The assessment of a 'potential serious risk to public health' cannot be made in isolation but has to take into account the positive therapeutic effects of the medicinal product in question. Consequently, the term 'potential serious risk to public health' as used in Article 29(1) of Directive 2001/83/EC has to be understood as relating to the overall risk-benefit assessment of the medicinal product, taking into account the positive therapeutic effects of the medicinal product in relation to the risks.

Therefore, a potential serious risk to public health in relation to a particular medicinal product can mainly be considered to exist under the following circumstances:

— Efficacy: the data submitted to support therapeutic efficacy in the proposed indication(s), target population(s), and proposed dosing regimen (as defined by the proposed labelling), do not provide sound scientific justification for the claims for efficacy; adequate proof for bioequivalence demonstrated by generic medicinal products to the reference medicinal product is lacking.

— Safety: the evaluation of the preclinical toxicity/safety pharmacology, clinical safety data and post-marketing data does not provide adequate support for the conclusion that all potential safety issues for the target population have been appropriately and adequately addressed in the proposed labelling or the absolute level of risk from the medicinal product, in the context of its proposed use, is considered unacceptable.

— Quality: the proposed production and quality control methods cannot guarantee that a major deficiency in the quality of the product will not occur.

— Overall risk-benefit: the risk-benefit-balance for the product is not considered to be favourable, taking into account the nature of the identified risk(s) and the potential benefit in the proposed indication(s) and target patient population(s).

— Product Information: the information is misleading or incorrect for either the prescribers or the patients to ensure the safe use of the medicinal product.

Any major objection must be scientifically justified taking into account the nature and degree of any hazards, the magnitude of the risks involved, the benefits associated with the use of the product and the feasibility and practicality of the implementation of any measures to mitigate the risks. The Member State intending to refuse the application for marketing authorisation for the medicinal product should be prepared to substantiate its grounds for refusal in the coordination group procedure and if that procedure fails in a referral to the Committee of Human Medicinal Products. This would also cover any existing knowledge of the substance and specific risks in the Member State concerned which are not outlined in the dossier of the medicinal product or the assessment report of the reference Member State and which are not included in the summary of products characteristics during the mutual recognition procedure or decentralised procedure.

Member States have accepted common rules and guidelines relating to manufacturing, quality control, evaluation of medicinal product efficacy, evaluation of medicinal product safety and quality assurance and labelling. These scientific guidelines give guidance for the evaluation of an application in general, but different interpretations cannot be excluded on a specific set of data. It has to be recognised that in these circumstances a lack of compliance with the scientific guidelines may not automatically result in a serious risk to public health unless they fulfil the conditions as described under section 2 of this guideline.

Any objection on the ground of a potential serious risk to public health cannot be justified by differences in national administrative or national scientific requirements, or internal national policies, unless the conditions or Article 29(1) of Directive 2001/83/EC are fulfilled.

DG Enterprise and Industry will publish a list of examples related to the above definitions of issues which normally would not be considered as grounds for a 'Potential Serious Risk to Public Health'. This list will be updated based on experience gained with the decentralised and mutual recognition procedure.