# Workshop on drug policy, new pharmaceutical procedures in EC

## Sofia
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EU Marketing Authorisation (MRP+DCP+CMD(h)

→ Presentation and discussion of the Guideline 'Potential serious risk to public health' concerning medicinal products

# Directive 2001/83/EC (codified)

*Article 29*

1. If, within the period laid down in Article 28(4), a Member State cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of potential serious risk to public health, it shall give a detailed exposition of the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant. The points of disagreement shall be forthwith referred to the coordination group.

2. Guidelines to be adopted by the Commission shall define a potential serious risk to public health.

*(Член 29*
1. Ако в рамките на срока, посочен в член 28,параграф 4, дадена държава-членка не може да одобри оценъчния доклад, обобщението на характеристиките на продукта и тикетирането и листовката с упътвания за опаковката по причини, свързани с потенциален сериозен риск за общественото здраве, тя представя подробно изложение на причините за позицията си пред референтната държава-членка, пред останалите засегнати държави-членки и пред заявителя. Въпросите, по които съществуват несъгласия, незабавно се отнасят до координационната група.
2. Комисията трябва да приема ръководства за определяне потенциалния сериозен риск за общественото здраве.)

# 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)
*(Official Journal C 133, 8/6/2006 p. 5 – 7)*

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

## ANNEX

Examples of issues which normally would not be considered as grounds for a ‘Potential Serious Risk to Public Health’1 in accordance with specific requirements according to Directive 2001/83/EC as amended.

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm

Content:

1. Introduction

2. Definition of potential serious risk to public health

Final sentence:

*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.*

Link to the Annex

## Content:

## 1. Introduction

- 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.

⇨Strenghten the position of the Reference Member State

Content:

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

- 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.

Cont.:

- 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 prod taking into account the positive therapeutic effects of the medicinal pro in relation to the risks.

Cont.:

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

- **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 product 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 suppo 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.

Cont.:

- **Quality**: the proposed production and quality control methods cannot guarant major deficiency in the quality of the product will not occur.

- **Overall risk-benefit**: the risk-benefit-balance for the product is not considere 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.

Cont.:

Member States have accepted common rules and guidelines relating to manufac
quality control, evaluation of medicinal product efficacy, evaluation of medicinal
safety and quality assurance and labelling. These scientific guidelines give guida
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.

# Annex

Examples of issues which normally would not be considered as grounds for a 'Potential Serious Risk to Public Health' in accordance with specific requirements according to Directive 2001/83/EC as amended.

**Efficacy**:

- The absence of an active comparator study versus a specific medicinal product
- The absence of clinical trials in non-target populations, e.g. the elderly, children
- An absence of evidence demonstrating added therapeutic value of the new medicinal products under assessment in comparison to existing medicinal products
- The length of the treatment varies according to national medical practices in the various Member States

**Safety**:

- The targeted population is too narrow, and should include patients who are allergic or intolerant to medicinal products approved for the same indications
- A Member State requires a special interaction study with a medicinal product that is not usually prescribed or used together with the new medicinal product

# Annex

Cont.

**Quality**:

- A requirement to use alternative analytical methods if the methods proposed in the documentation have demonstrated their suitability
- A requirement to use complementary analytical tests if these tests do not provide any additional results in terms of product safety
- A request for physico-chemical parameters testing for in-use stability data which are not relevant to the pharmaceutical form of the product
- A request to tighten the limits of the active ingredient for the shelf-life specification of the finished product
- The request to tighten the limits of the specification for the active ingredient

# Annex

Cont.

**Overall risk-benefit:**

- For products with **well-established medicinal use authorised** according to Article 10a of Directive 2001/83/EC as amended, the absence of data from new pre-clinical tests or clinical studies if posology is based on "systematic and documented use" and the safety is based on pharmacovigilance data.

- For **homeopathic medicinal products** registered according to Articles 14 and 15 of Directive 2001/83/EC, the absence of a therapeutic indications, the lack of documentation on pre-clinical tests and clinical trials.

- For **traditional herbal medicinal products** registered according to Article 16a of Directive 2001/83/EC with indications exclusively appropriate to traditional herbal medicinal products, the lack of documentation on pre-clinical tests and clinical trials.

- The isolated fact that the product has a **different legal status** (prescription only/non-prescription) in another Member State.

# Annex

Cont.

**Product Information**:

- The claimed indication cannot be granted because this would trigger the need to harmonise Summary of Products Characteristics of other products approved at a national level

- The absence of a contra-indication for a non-target population (e.g. children, the elderly, patients with renal or hepatic insufficiency)

- The absence of contra-indications relevant to other medicinal products of the same class, if the scientific data provided in the documentation justify that the same contraindications do not apply to the medicine under assessment

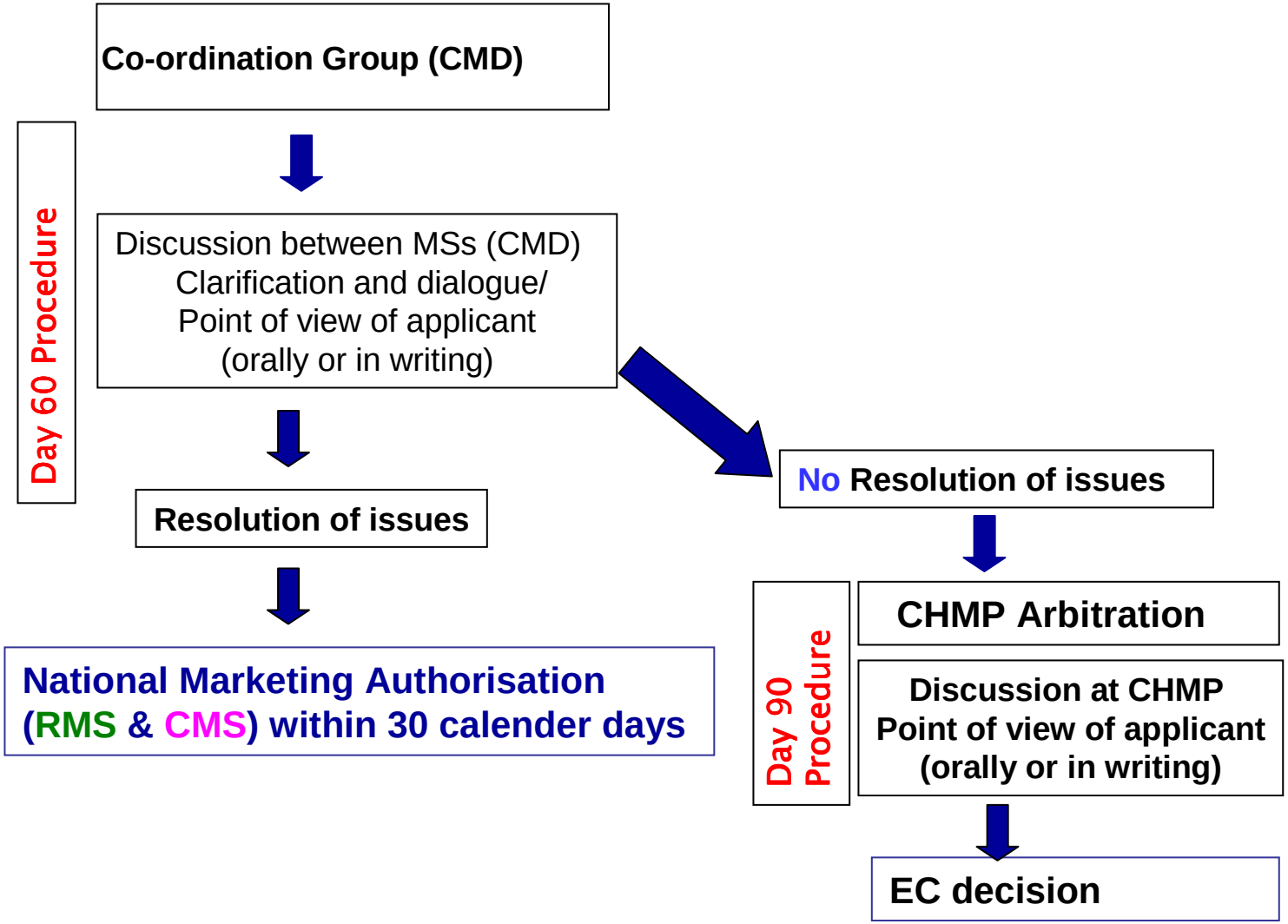
| | Reasons for withdrawals 2001 | Referrals to CMD(h) 2006 |
|---|---|---|
| **DOSSIER** | **38%** | **68%** |
| *Safety/Efficacy* | *23%* | *27%* |
| *Quality* | *10%* | *15%* |
| *Bioequivalence* | *5%* | *26%* |
| **SPC** | **57%** | **27%** |
| **Miscellaneous** | **5%** | **3%** |
| **Package Leaflet** | | **2%** |

| | Application finalised in 2006 | Referrals to CMD(h) 2006 |
|---|---|---|
| Generic | 379 | 80 |
| Generic Extension | 29 | 3 |
| Full Dossier | 55 | 12 |
| Bibliographic | 41 | 8 |
| Fixed Combination | 8 | 2 |
| | 535 | 105 (19%) |

# Decentralised Procedure or Mutual Recognition Procedure failed → Coordination Group Procedure!

Reference Member State (RMS)

Concerend Member States (CMS)



## Decentralised Procedure or Mutual Recognition Procedure and Coordination Group Procedure  failed!

Referrals to CMD(h) in 2006

MRP: 104

DCP: 1

- Agreement reached: 53
- CHMP Arbitration in 2006: 22
- Withdrawals: 5

# Directive 2001/83/EC

## Referral procedure → Articles 29

- Article 29 → Mutual recognition referral – Automatic referral in case of disagreement ("potential serious risk to public health")

  → Possibility for MS to grant MA without waiting for the outcome of the referral – Art. 29(6) Directive 2001/83/EC

CHMP Opinion
European Commission Decision
Member State comply

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Thank you for your attention