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Orphan drugs assessment in the centralised procedure

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Summary. On the basis of the author's experience as member of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and in order to facilitate the access of new orphan drugs to the patients, some suggestions were given. Among these the following should be taken into account by the regulatory bodies: 1) conditional approval or approval under exceptional circumstances should be granted more frequently; 2) the opinion of international societies for rare diseases should be taken into greater account by the EMA Committees; 3) the guidelines requirements should be interpreted more flexibly; 4) in comparison to the fulfilment of primary and secondary endpoints, the improvement of the quality of life should justify the approval of a new orphan drug; 5) the rigidity of guideline requirements should not prevail over the unmet medical need for severe and lethal rare disorders; 6) the statistical values of clinical data to the limit of significance should not prevail over the opinion of patients' associations and international scientific societies; 7) the current legislation should be amended.

Key words: orphan drugs, European Medicines Agency, national regulatory agencies, guidelines.

Riassunto *(Valutazione dei farmaci orfani nella procedura centralizzata: una breve nota)*. Sulla base dell'esperienza acquisita quale membro del Committee for Medicinal Products for Human Use (CHMP) dell'European Medicines Agency (EMA), e allo scopo di facilitare l'accesso dei pazienti ai nuovi farmaci orfani, vengono forniti in questa breve nota alcuni utili suggerimenti. Tra questi, le agenzie regolatorie dovrebbero tenere in considerazione in particolare: 1) l'approvazione condizionata o l'approvazione in caso di circostanze eccezionali dovrebbe essere concessa più frequentemente; 2) il parere delle società internazionali per le malattie rare dovrebbe essere tenuto in maggiore considerazione dai Comitati dell'EMA; 3) i requisiti delle linee guida dovrebbero essere interpretati in modo più flessibile; 4) rispetto al raggiungimento degli obiettivi primari e secondari, il miglioramento della qualità della vita dovrebbe giustificare l'approvazione di nuovi farmaci orfani; 5) la rigidità dei requisiti delle linee guida non dovrebbe prevalere sulle necessità di carattere medico relative a patologie causate da malattie rare gravi e letali; 6) i limiti di significatività statistica dei dati clinici non dovrebbero prevalere sulle opinioni delle associazioni dei pazienti e delle società scientifiche internazionali; 7) la legislazione corrente dovrebbe essere aggiornata.

Key words: farmaci orfani, European Medicines Agency, agenzie regolatorie nazionali, linee guida.

INTRODUCTION

The Reg. (EC) No 141/2000 defines that medicines intended for the treatment, prevention or diagnosis of rare diseases (*i.e.* those conditions affecting less than 5:10 000 individuals in the European Union) can be designated as orphan drugs (ODs). The designation confers additional incentives including:

- *market exclusivity* of 10 years after the grant of a market authorisation (MA) within the Community. During this period, directly competitive similar products cannot be normally placed on the market;
- *protocol assistance* (PA), which constitutes a scientific advice for ODs provided by EMA in order to optimise development;
- direct access to the *centralised procedure* for the application of the MA;
- *fee reductions* for all types of centralised activities, including applications for MA, inspections, variations and PA will be granted by EMA;
- EU-funded research through special grants provided by the Community (*i.e.* Community framework programmes) and Member State programmes are available for organisations intending to conduct research for the development of orphan medicinal products.

THE ORPHAN DRUG REGULATION

So far the Regulation (EC) No 141/2000 has been a great success for the promotion of activities in orphan drug

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Table 1 | *Overview of orphan drug applications in the timeframe 2000-2009*

Year	Application submitted	Positive COMP opinions	Application withdrawn	Final negative COMP opinions	Designation granted by Commission
2009	61	48	6	-	47
2008	119	86	31	1	73
2007	125	97	19	1	98
2006	104	81	20	2	80
2005	118	88	30	0	88
2004	108	75	22	4	72
2003	87	54	41	1	55
2002	80	43	30	3	49
2001	83	64	27	1	64
2000	72	26	6	0	14

development (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:EN:PDF).

In addition, the Regulation has the merit of:
- having increased public awareness of rare diseases;
- carrying on groundbreaking work with patients' representatives;
- allowing increased transparency;
- implementing the protocol assistance procedure for better drug development.

This has led to a constant increase in number of application submitted and, later, granted *(Table 1)*.

However, to date the Regulation presents some limitations as well:
- the Regulation does not include the obligation to market the products in all Member States;
- there is a lack of public funding of clinical trials for rare diseases;
- issues exist on differences in approval of added therapeutic value of orphan drugs;
- there is the need to increase fee reduction and protocol assistance.

CONDITIONAL APPROVAL

When the Committee has based its positive opinion on data which, while not yet comprehensive, indicate that the medicine's *benefit outweigh its risk*, the CHMP recommends that a medicine is granted "conditional approval". The company is given obligations to fulfil and the approval is renewed on yearly basis. When all obligations have been fulfilled, the conditional approval is converted into normal approval.

Conditional approval can only be granted to medicines that satisfy an *unmet medical need*, meaning a medicine intended to be used for a disease or condition for which no treatment is readily available, and therefore it is important that patients have early access to such medicine.

EXCEPTIONAL CIRCUMSTANCES

When the applicant can show that it is not possible to provide comprehensive data on efficacy and safety of a medicine due to the *rarity of the condition* it is intended for, or *limited knowledge* in the therapeutic area or *ethical considerations* involved in the collection of such data, the CHMP may recommend that a medicine is approved under "exceptional circumstances". Also in such cases, the applicant is given obligations to fulfil, particularly relating to the safety. These are re-assessed every year until the approval can be converted into a normal one.

FINAL CONSIDERATIONS

Some general considerations are subject of discus sions and question whether:
- the extent of incentives is sufficient to promote development;
- conditional approval or approval under exceptional circumstances should be granted more frequently;
- the opinion of international societies for rare diseases should be taken into greater account by the EMA Committees;
- the guidelines requirements should be interpreted more flexibly;
- in comparison to the fulfilment of primary and secondary endpoints, the improvement of the quality of life should justify the approval of a new orphan drug;
- the rigidity of guidance requirements should not prevail over the unmet medical need for severe and lethal rare disorders;
- the statistical values of clinical data to the limit of significance should not prevail over the opinion of patients' associations and international scientific societies;
- the current legislation should be amended.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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