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 (Text with EEA relevance)

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

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee[(1)],

Having consulted the Committee of the Regions,

Acting in accordance with the procedure referred to in Article 251 of the Treaty[(2)],

Whereas:

(1) Before a medicinal product for human use is placed on the market in one or more Member States, it generally has to have undergone extensive studies, including pre-clinical tests and clinical trials, to ensure that it is safe, of high quality and effective for use in the target population.

(2) Such studies may not have been undertaken for use in the paediatric population and many of the medicinal products currently used to treat the paediatric population have not been studied or authorised for such use. Market forces alone have proven insufficient to stimulate adequate research into, and the development and authorisation of, medicinal products for the paediatric population.

(3) Problems resulting from the absence of suitably adapted medicinal products for the paediatric population include inadequate dosage information which leads to increased risks of adverse reactions including death, ineffective treatment through under-dosage, non-availability to the paediatric population of therapeutic advances, suitable formulations and routes of administration, as well as use of magistral or officinal formulations to treat the paediatric population which may be of poor quality.

(4) This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used

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to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations.

(5) While taking into account the fact that the regulation of medicinal products must be fundamentally aimed at safeguarding public health, this aim must be achieved by means that do not impede the free movement of safe medicinal products within the Community. The differences between the national legislative, regulatory and administrative provisions on medicinal products tend to hinder intra-Community trade and therefore directly affect the operation of the internal market. Any action to promote the development and authorisation of medicinal products for paediatric use is therefore justified with a view to preventing or eliminating these obstacles. Article 95 of the Treaty is therefore the proper legal basis.

(6) The establishment of a system of both obligations and rewards and incentives has proved necessary to achieve these objectives. The precise nature of these obligations and rewards and incentives should take account of the status of the particular medicinal product concerned. This Regulation should apply to all the medicinal products required for paediatric use and therefore its scope should cover products under development and yet-to-be authorised, authorised products covered by intellectual property rights and authorised products no longer covered by intellectual property rights.

(7) Any concerns about conducting trials in the paediatric population should be balanced by the ethical concerns about giving medicinal products to a population in which they have not been appropriately tested. Public health threats from the use of untested medicinal products in the paediatric population can be safely addressed through the study of medicinal products for the paediatric population, which should be carefully controlled and monitored through the specific requirements for the protection of the paediatric population who take part in clinical trials in the Community laid down in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use[(3)].

(8) It is appropriate to create a scientific committee, the Paediatric Committee, within the European Medicines Agency, hereinafter ‘the Agency’, with expertise and competence in the development and assessment of all aspects of medicinal products to treat paediatric populations. The rules on scientific committees of the Agency, as laid down in Regulation (EC) No 726/2004[(4)], should apply to the Paediatric Committee. Members of the Paediatric Committee should therefore not have financial or other interests in the pharmaceutical industry which could affect their impartiality, should undertake to act in the public interest and in an independent manner, and should make an annual declaration of their financial interests. The Paediatric Committee should be primarily responsible for the scientific assessment and agreement of paediatric investigation plans

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and for the system of waivers and deferrals thereof; it should also be central to various support measures contained in this Regulation. In its work, the Paediatric Committee should consider the potential significant therapeutic benefits for the paediatric patients involved in the studies or the paediatric population at large including the need to avoid unnecessary studies. The Paediatric Committee should follow existing Community requirements, including Directive 2001/20/EC, as well as International Conference on Harmonisation (ICH) guideline E11 on the development of medicinal products for the paediatric population, and it should avoid any delay in the authorisation of medicinal products for other populations deriving from the requirements for studies in the paediatric population.

(9) Procedures should be established for the Agency to agree and modify a paediatric investigation plan, which is the document upon which the development and authorisation of medicinal products for the paediatric population should be based. The paediatric investigation plan should include details of the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population. Since the paediatric population is in fact composed of a number of population subsets, the paediatric investigation plan should specify which population subsets need to be studied, by what means and by when.

(10) The introduction of the paediatric investigation plan in the legal framework concerning medicinal products for human use aims at ensuring that the development of medicinal products that are potentially to be used for the paediatric population becomes an integral part of the development of medicinal products, integrated into the development programme for adults. Thus, paediatric investigation plans should be submitted early during product development, in time for studies to be conducted in the paediatric population, where appropriate, before marketing authorisation applications are submitted. It is appropriate to set a deadline for the submission of a paediatric investigation plan in order to ensure early dialogue between the sponsor and the Paediatric Committee. Furthermore, early submission of a paediatric investigation plan, combined with the submission of a deferral request as described below, will avoid delaying the authorisation for other populations. As the development of medicinal products is a dynamic process dependent on the result of ongoing studies, provision should be made for modifying an agreed plan where necessary.

(11) It is necessary to introduce a requirement for new medicinal products and for authorised medicinal products covered by a patent or a supplementary protection certificate to present either the results of studies in the paediatric population in accordance with an agreed paediatric investigation plan or proof of having obtained a waiver or deferral, at the time of filing a marketing authorisation application or an application for a new indication, new pharmaceutical form or new route of administration. The paediatric investigation plan should be the basis upon which compliance with that requirement is judged. However, that requirement should not apply to generics or similar biological medicinal products and medicinal products authorised through the well-established medicinal use procedure, nor to homeopathic medicinal products and traditional herbal medicinal products authorised through the simplified registration procedures of Directive 2001/83/EC of the European Parliament and of the Council of

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6 November 2001 on the Community code relating to medicinal products for human use[(5)].

(12) Provision should be made for research into the paediatric use of medicinal products which are not protected by a patent or supplementary protection certificate to be financed under Community research programmes.

(13) In order to ensure that research in the paediatric population is only conducted to meet their therapeutic needs, there is a need to establish procedures for the Agency to waive the requirement referred to in Recital (11) for specific products or for classes or part of classes of medicinal products, these waivers being then made public by the Agency. As knowledge of science and medicine evolves over time, provision should be made for the lists of waivers to be amended. However, if a waiver is revoked, that requirement should not apply for a given period in order to allow time for at least a paediatric investigation plan to be agreed and studies in the paediatric population to be initiated before an application for marketing authorisation is submitted.

(14) In certain cases, the Agency should defer the initiation or completion of some or all of the measures contained in a paediatric investigation plan, with a view to ensuring that research is conducted only when safe and ethical and that the requirement for study data in the paediatric population does not block or delay the authorisation of medicinal products for other populations.

(15) Free scientific advice should be provided by the Agency as an incentive to sponsors developing medicinal products for the paediatric population. To ensure scientific consistency, the Agency should manage the interface between the Paediatric Committee and the Scientific Advice Working Group of the Committee for Medicinal Products for Human Use, as well as the interaction between the Paediatric Committee and the other Community committees and working groups concerning medicinal products.

(16) The existing procedures for the marketing authorisation of medicinal products for human use should not be changed. However, from the requirement referred to in Recital (11) it follows that competent authorities should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the existing validation step for marketing authorisation applications. The assessment of quality, safety and efficacy of medicinal products for the paediatric population and the granting of marketing authorisations should remain the remit of the competent authorities. Provision should be made for the Paediatric Committee to be asked for its opinion on compliance and on the quality, safety and efficacy of a medicinal product in the paediatric population.

(17) To provide healthcare professionals and patients with information on the safe and effective use of medicinal products in the paediatric population and as a transparency measure, information on the results of studies in the paediatric population, as well as on the status of the paediatric investigation plans, waivers and deferrals, should be included in product information. When all the measures in the paediatric investigation plan have been complied with, that fact should be recorded in the marketing authorisation, and should then be the basis upon which companies can obtain the rewards for compliance.

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(18) In order to identify medicinal products authorised for use in the paediatric population and enable their prescription, provision should be made for the labels of medicinal products granted an indication for use in the paediatric population to display a symbol which will be selected by the Commission on a recommendation by the Paediatric Committee.

(19) In order to establish incentives for authorised products no longer covered by intellectual property rights, it is necessary to establish a new type of marketing authorisation, the Paediatric Use Marketing Authorisation. A Paediatric Use Marketing Authorisation should be granted through existing marketing authorisation procedures but should apply specifically for medicinal products developed exclusively for use in the paediatric population. It should be possible for the name of the medicinal product that has been granted a Paediatric Use Marketing Authorisation to retain the existing brand name of the corresponding product authorised for adults, in order to capitalise on existing brand recognition, while benefiting from the data exclusivity associated with a new marketing authorisation.

(20) An application for a Paediatric Use Marketing Authorisation should include the submission of data concerning use of the product in the paediatric population, collected in accordance with an agreed paediatric investigation plan. These data may be derived from the published literature or from new studies. An application for a Paediatric Use Marketing Authorisation should also be able to refer to data contained in the dossier of a medicinal product which is or has been authorised in the Community. This is intended to provide an additional incentive to encourage small and medium-sized enterprises, including generic companies, to develop off-patent medicinal products for the paediatric population.

(21) This Regulation should include measures to maximise access by the Community population to new medicinal products tested and adapted for paediatric use, and to minimise the chance of Community-wide rewards and incentives being granted without sections of the Community paediatric population benefiting from the availability of a newly authorised medicine. An application for a marketing authorisation, including an application for a Paediatric Use Marketing Authorisation, which contains the results of studies conducted in compliance with an agreed paediatric investigation plan should be eligible for the Community centralised procedure set out in Articles 5 to 15 of Regulation (EC) No 726/2004.

(22) When an agreed paediatric investigation plan has led to the authorisation of a paediatric indication for a product already marketed for other indications, the marketing authorisation holder should be obliged to place the product on the market, taking into account the paediatric information, within two years of the date of approval of the indication. That requirement should relate only to products already authorised, but not to medicinal products authorised via a Paediatric Use Marketing Authorisation.

(23) An optional procedure should be established to make it possible to obtain a single Community-wide opinion for a nationally authorised medicinal product when data on the paediatric population following an agreed paediatric investigation plan form part of the marketing authorisation application. To achieve this, the procedure set out in

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Articles 32, 33 and 34 of Directive 2001/83/EC could be used. This will allow the adoption of a Community harmonised Decision on use of that medicinal product in the paediatric population and its inclusion in all national product information.

(24) It is essential to ensure that pharmacovigilance mechanisms are adapted to meet the specific challenges of collecting safety data in the paediatric population, including data on possible long-term effects. Efficacy in the paediatric population may also need additional study following authorisation. Therefore, an additional requirement for applying for a marketing authorisation that includes the results of studies conducted in compliance with an agreed paediatric investigation plan should be an obligation for the applicant to indicate how he proposes to ensure the long-term follow-up of possible adverse reactions to the use of the medicinal product and efficacy in the paediatric population. Additionally, where there is a particular cause for concern, the applicant should submit and implement a risk management system and/or perform specific post-marketing studies as a condition for the granting of the marketing authorisation.

(25) It is necessary in the interests of public health to ensure the continuing availability of safe and effective medicinal products authorised for paediatric indications developed as a result of this Regulation. If a marketing authorisation holder intends to withdraw such a medicinal product from the market then arrangements should be in place so that the paediatric population can continue to have access to the medicinal product in question. In order to help achieve this, the Agency should be informed in good time of any such intention and should make that intention public.

(26) For products falling within the scope of the requirement to submit paediatric data, if all the measures included in the agreed paediatric investigation plan are complied with, if the product is authorised in all Member States and if relevant information on the results of studies is included in product information, a reward should be granted in the form of a 6-month extension of the supplementary protection certificate created by Council Regulation (EEC) No 1768/92[(6)]. Any decisions by Member States' authorities as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes have no bearing on the granting of this reward.

(27) An application for an extension of the duration of the certificate pursuant to this Regulation should only be admissible where a certificate is granted pursuant to Regulation (EEC) No 1768/92.

(28) Because the reward is for conducting studies in the paediatric population and not for demonstrating that a product is safe and effective in the paediatric population, the reward should be granted even when a paediatric indication is not authorised. However, to improve the information available on the use of medicinal products in the paediatric population, relevant information on use in paediatric populations should be included in authorised product information.

(29) Under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products[(7)], medicinal products designated as orphan medicinal products gain ten years of market exclusivity on the granting of a marketing authorisation for the orphan indication. As such products are frequently not patent-protected, the reward of supplementary protection certificate extension cannot

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be applied; when they are patent-protected, such an extension would provide a double incentive. Therefore, for orphan medicinal products, instead of an extension of the supplementary protection certificate, the ten-year period of orphan market exclusivity should be extended to twelve years if the requirement for data on use in the paediatric population is fully met.

(30) The measures provided for in this Regulation should not preclude the operation of other incentives or rewards. To ensure transparency on the different measures available at Community and Member State levels, the Commission should draw up a detailed list of all the incentives available, on the basis of information provided by the Member States. The measures set out in this Regulation, including the agreement of paediatric investigation plans, should not be grounds for obtaining any other Community incentives to support research, such as the funding of research projects under the multi-annual Community Framework Programmes for Research, Technological Development and Demonstration Activities.

(31) In order to increase the availability of information on the use of medicinal products in the paediatric population, and to avoid unnecessary repetition of studies in the paediatric population which do not add to the collective knowledge, the European database provided for in Article 11 of Directive 2001/20/EC should include a European register of clinical trials of medicinal products for paediatric use comprising all ongoing, prematurely terminated, and completed paediatric studies conducted both in the Community and in third countries. Part of the information concerning paediatric clinical trials entered into the database, as well as details of the results of all paediatric clinical trials submitted to the competent authorities, should be made public by the Agency.

(32) An inventory of the therapeutic needs of the paediatric population should be established by the Paediatric Committee after consultation with the Commission, the Member States and interested parties, and should be regularly updated. The inventory should identify the existing medicinal products used by the paediatric population and highlight the therapeutic needs of that population and the priorities for research and development. In this way, companies should be able easily to identify opportunities for business development; the Paediatric Committee should be able better to judge the need for medicinal products and studies when assessing draft paediatric investigation plans, waivers and deferrals; and healthcare professionals and patients should have an information source available to support their decisions as to which medicinal products to choose.

(33) Clinical trials in the paediatric population may require specific expertise, specific methodology and, in some cases, specific facilities and should be carried out by appropriately trained investigators. A network, which links existing national and Community initiatives and study centres in order to build up the necessary competences at Community level, and which takes account of Community and third country data, would help facilitate cooperation and avoid unnecessary duplication of studies. This network should contribute to the work of strengthening the foundations of the European Research Area in the context of Community Framework Programmes

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for Research, Technological Development and Demonstration Activities, benefit the paediatric population and provide a source of information and expertise for industry.

(34) For certain authorised products, pharmaceutical companies may already hold data on safety or efficacy in the paediatric population. To improve the information available on the use of medicinal products in the paediatric populations, companies holding such data should be required to submit them to all competent authorities where the product is authorised. In this way the data could be assessed and, if appropriate, information should be included in the authorised product information aimed at healthcare professionals and patients.

(35) Community funding should be provided to cover all aspects of the work of the Paediatric Committee and of the Agency resulting from the implementation of this Regulation, such as the assessment of paediatric investigation plans, fee waivers for scientific advice, and information and transparency measures, including the database of paediatric studies and the network.

(36) The measures necessary for the implementation of this Regulation should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission[(8)].

(37) Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 should therefore be amended accordingly.

(38) Since the objective of this Regulation, namely improving availability of medicinal products tested for paediatric use, cannot be sufficiently achieved by the Member States and can therefore be better achieved at Community level, given that this will make it possible to take advantage of the widest possible market and avoid the dispersion of limited resources, the Community may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve this objective,

HAVE ADOPTED THIS REGULATION:

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(**1**) OJ C 267, 27.10.2005, p. 1.

(**2**) Opinion of the European Parliament of 7 September 2005 (OJ C 193 E, 17.8.2006, p. 225), Council Common Position of 10 March 2006 (OJ C 132 E, 7.6.2006, p. 1) and Position of the European Parliament of 1 June 2006 (not yet published in the Official Journal). Council Decision of 23 October 2006.

(**3**) OJ L 121, 1.5.2001, p. 34.

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

(**5**) OJ L 311, 28.11.2001, p. 67. Directive as last amended by Directive 2004/27/EC (OJ L 136, 30.4.2004, p. 34).

(**6**) OJ L 182, 2.7.1992, p. 1. Regulation as last amended by the 2003 Act of Accession.

(**7**) OJ L 18, 22.1.2000, p. 1.

(**8**) OJ L 184, 17.7.1999, p. 23. Decision as amended by Decision 2006/512/EC (OJ L 200, 22.7.2006, p. 11).

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