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Extended Impact Assessment of a Draft EC Regulation on Medicinal Products for Paediatric Use

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Preface

In October 2003 the European Commission, Enterprise Directorate-General asked RAND Europe to conduct a study to assess the impact of a proposed Regulation to stimulate the development and testing of medicines for paediatric use. The aim of the study is to perform an analysis to enable an extended impact assessment to determine the economic, social, and environmental impacts of the proposed EC Regulation as well as its impact on sustainable development. The analysis has been based on a draft version of the proposed Regulation (dated November 2003). Since then, the text has undergone a number of revisions and the final version will no longer precisely match the version provided to us by DG Enterprise. The results will, however, be input for the extended impact assessment of DG Enterprise.

In this report we first discuss the background and methodology of the study. This discussion is followed by a description of the proposed Regulation. In Chapter 3, we analyse the current situation with respect to the prescription of medicinal products for children as well as the economics of the pharmaceutical industry. This analysis includes a projection of the current extent of the problem to the year 2015. In Chapter 4, we examine the impact of the Regulation as proposed. The summary recapitulates the main chapters and restates the conclusions of the study. In addition, recommendations regarding the design, the implementation and evaluation of the Regulation are presented in Annex 1.

The primary audience for this report is DG Enterprise of the European Commission, responsible for drafting the proposed Regulation. However, the report may also be of interest to the wide variety of stakeholders that are affected by the Regulation, such as pharmaceutical companies, health care professionals, health insurers, paediatric patients and their parents.

RAND Europe is an independent not-for-profit policy research organisation that serves the public interest by improving policymaking and informing public debate. This report has been peer-reviewed in accordance with RAND's quality assurance standards (see http://www.rand.org/about/standards/).

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Abbreviations

ADRs	Adverse Drug Reactions
BEUC	European Consumer's Organisation
BMA	British Medical Association
CBG	College ter Beoordeling van Geneesmiddelen (Dutch Medicines Evaluation Board)
CEA	Comité Européen des Assurances
CESP	Confederation of European Specialists in Paediatrics
CPME	Standing Committee of European Doctors
CPMP	Committee for Proprietary Medicinal Products (will be replaced by CHMP - Committee for Medicinal Products for Human Use)
CVZ	College voor Zorgverzekeringen (Dutch Health Care Insurance Board)
DDDs	Daily Drug Doses
EC	European Commission
EEA	European Economic Area
EFGCP	European Forum for Good Clinical Practice
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generic medicines Association
EIA	Extended Impact Assessment
EMEA	European Medicines Evaluation Agency
ENDIC	European Network for Drug Investigation in Children
EPF	European Patient Forum
EPPOSI	European Platform Patient Organisations, Science and Industry
ESCP	European Society of Clinical Pharmacy
EU	European Union
FDA	US Food and Drug Administration
FDAMA	US Food and Drug Administration Modernization Act
FDCA	US Federal Food, Drug, and Cosmetic Act
FIP	International Pharmaceutical Federation
GDP	Gross Domestic Product
GP	General Practitioner
ICU	Intensive Care Unit
IPR	Intellectual Property Right
MHRA	Medicines and Healthcare products Regulatory Agency
MICE	Medicine Investigation for the Children in Europe
NAS	New Accession States
NIH	US National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
OTC	Over-the-counter
PB	Paediatric Board

PhRMA	Pharmaceutical Research and Manufacturers of America
PPP	Purchasing Power Parity
PUMA	Paediatric Use Marketing Authorisation
R&D	Research and Development
RCTs	Randomised Clinical Trials
SMEs	Small and Medium Enterprises
SPC	Supplementary Protection Certificate
UEMO	European Association of General Practitioners
UNEPSA	Union of National European Paediatric Societies and Associations
UK	United Kingdom
US	United States
VAT	Value Added Tax
WHO	World Health Organisation

Summary

Background

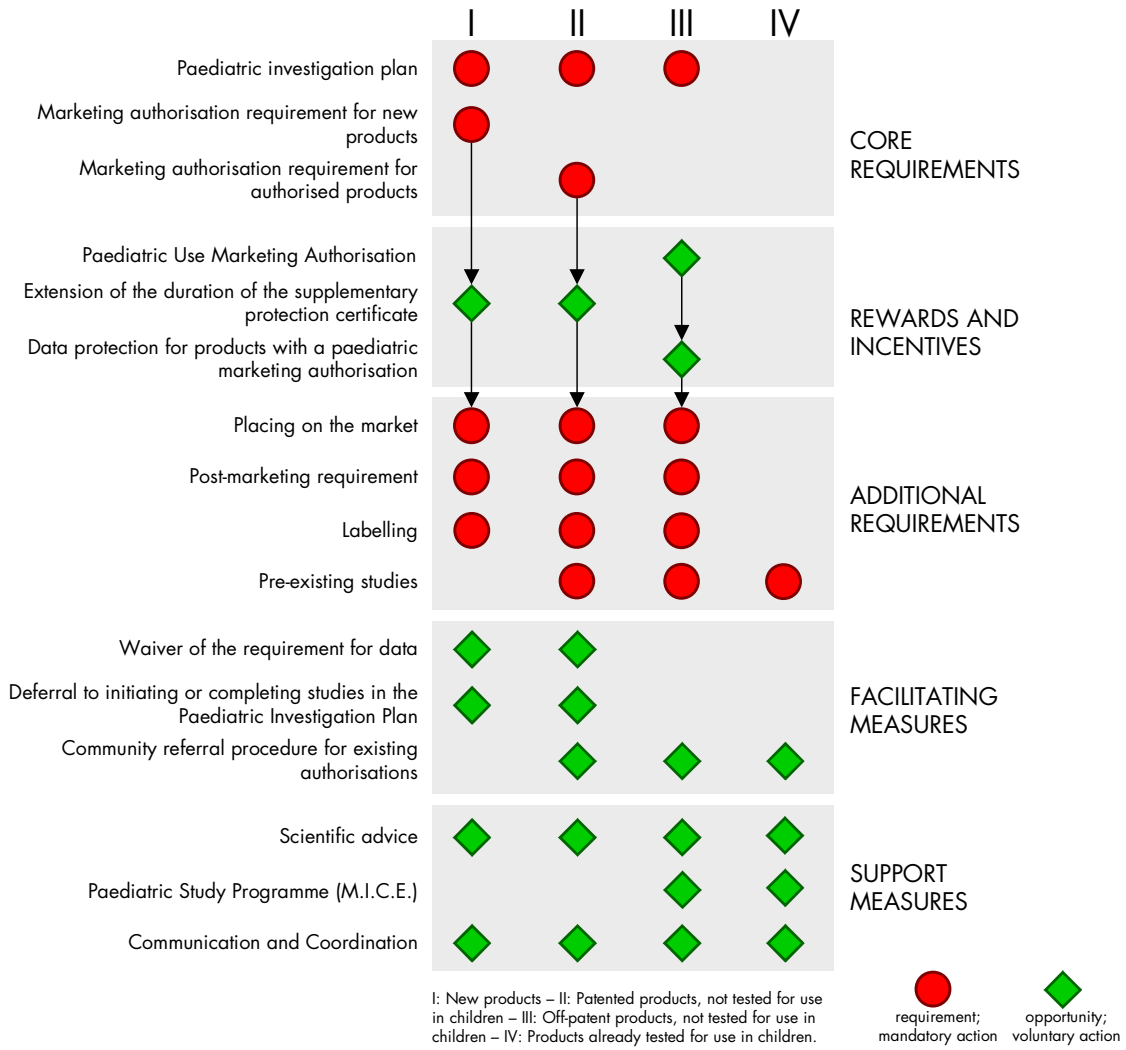
There is a serious lack of testing of medicinal products in the paediatric population. As a consequence, medication for children is often authorised for adult use only—that is, use in children is outside the terms of the product licence in terms of age, dose, route of administration or frequency. This practice exposes children to risks, the magnitude of which are not known, as their medication may be either less effective than it might be or actually dangerous.
The current market cannot fulfil the demand for paediatric medicinal products without resorting to this "less than fully authorised" delivery of medications. The reason for this lies in a combination of factors, leading to insufficient paediatric clinical pharmaceutical research.
As this is a problem that exists throughout the European Union (EU), the European Commission (EC) has attempted to provide a structural solution by drafting a Regulation to remedy the economic disincentives for appropriate research, while ensuring the long-term quality of health care for children.
The main objective of the present document is to inform an extended impact assessment of the draft Regulation to be promulgated by The EC Enterprise Directorate-General. For this purpose three main tasks have been distinguished:

1. Identifying stakeholders and mapping their views,
2. Measuring the current and future effects without policy change, and
3. Analysing the likely consequences of the Regulation on the stakeholders.

The Regulation

The higher objective of the proposed Regulation is to improve the health of the children of Europe by (1) stimulating the development of medicines for use in children, (2) ensuring that such medicines are appropriately researched and authorised, (3) improving information on the use of medicines in children of different ages, and (4) achieving these aims without delaying the authorisation of medicinal products for other segments of the population.
It aims to accomplish this by introducing two types of provision, namely substantive provisions (core requirements, rewards, incentives, and support measures that form its core) and procedural provisions (infrastructure, administrative procedures, legal and regulatory context).
Figure S.1. shows how the various provisions apply to four different groups of products: new products (not yet authorised) (I), patented, authorised products not tested for use in children (II), off-patent, authorised products, not tested for use in children (III), and authorised products already tested for use in children (IV).

Figure S.1
An overview of the way in which the Regulation applies to different types of product



The most important relations in the schema described by Figure S.1. are:

1. The reward in the form of an extension by six months of the duration of the period of supplementary patent protection provided in return for submitting and completing a paediatric investigation plan as part of an application for a marketing authorisation;
2. The incentive of data protection (i.e. exclusivity) for research done in order to obtain a paediatric use marketing authorisation (PUMA) of a drug no longer protected by patent; and
3. The rules and requirements surrounding the rewards and incentives.

The problem

We have found that the information to determine the extent of the problem is often not available or insufficient. Although on an aggregate level some types of relevant data are available, these lack the detail needed for a full extended impact assessment. Consequently, the analysis reported here

relies heavily on estimates of indicators based on assumptions and on a literature review of case studies.

Stakeholders

The Regulation on medicinal products for paediatric use may have an impact on a wide variety of different stakeholders, each of whom has their representative interest groups. These include:

- *The pharmaceutical industry*, which generally divides into the "innovative" industry undertaking research, development and manufacture of medicinal products and the "generic" industry, which manufactures medicinal products whose patents have expired.
- *Regulatory authorities*, who oversee the testing and safe conduct of clinical trials performed under the aegis of the pharmaceutical industry to establish the efficacy and safety of medicinal products. In addition, the regulatory authorities responsibilities include the authorisation of medicines and pharmacovigilance. Within the EU, the European Agency for the Evaluation of Medicinal Products (EMEA) and national competent authorities are responsible for authorisation of medical products for human and veterinary use.
- *Health care professionals,* who prescribe medications authorised for use, which may be constrained by national and insurance company formularies. These professionals can be in some circumstances legally liable for negative effects suffered by their patients.
- *Pharmacists,* who deliver the prescribed products and who may prepare tailored compounds. Their knowledge is considered key to safe delivery of medicines.
- *Health insurers and governments,* who pay the lion's share of the pharmaceutical bill. Their interest is in value for money.
- *Clinical and pharmacological researchers* (both under contract to pharmaceutical manufacturers and independently-based), who are responsible for the proper and appropriate conduct of the needed research.
- *Children* (and their parents), who are the ultimate beneficiaries or victims of the process.

Health and prescribing in the European paediatric population.

It is well known that a substantial proportion of medicines is prescribed to children in the absence of sound scientific evidence regarding the effectiveness of the drugs, but the consequences of this are less well-known. Children represent a little less than one-quarter of the European population, but generally consume a considerably smaller proportion of the health care budget than their numbers might suggest. Nonetheless, the social obligation to protect children and their sheer number mean that medicines used by children cost a lot of money and have potentially major health consequences.

Of all the medicines consumed by children, an unknown but significant percentage is unlicensed or prescribed off-label (outside the terms regarding dosage, indication for use or route of administration). Estimates of the extent of this less-than-authorised use depend on location of care (hospital vs. office-based), diagnosis, age of the child and nationality. Some studies have estimates well over 50 percent of all prescriptions.

There is a consensus that off-label use is widespread; there is less of a consensus about when this leads to harms, or what can be done about it. Reporting of adverse drug reactions (ADRs) in children is neither comprehensive nor unified, but again, there is a consensus that the incidence of ADRs is higher than would be desired. Whether unlicensed and off-label drug use leads to more ADRs is not firmly established, although the research indicates at least some effect in that direction.

The pharmaceutical industry.

In general, the EU pharmaceutical market that consists of innovative and generic drug manufacturers is very large and highly dynamic. The challenge for the pharmaceutical industry is to develop affordable medicines tested for use in children. The companies that fund and perform Research and Development (R&D) that results in new medicines are aware of their role in improving health, but in the end are driven by economics. Their investments have to be compensated for in the form of profit. However, the proposed Regulation raises concerns with respect the costs of development. Will the incentives be sufficiently attractive?

In 2001 the sales of all medicinal products in Europe is estimated at €146.8 billion. In general, sales are growing rapidly. The EU is responsible for 20% of worldwide sales**.** Although the major growth sector for the industry is geriatric products, this does not necessarily mean that the size of the market for paediatric medicines will decline, especially when more specialised medicines are made available.

To bring a product to market, a pharmaceutical company incurs considerable costs, including basic research to test a range of products, clinical research (pre and post introduction) to establish the efficacy and safety of the product, as well as appropriate doses and routes of administration, costs of preparing and submitting information to obtain marketing approval, manufacturing costs, and advertising costs. Precise data on all of these costs are hard to come by, because much of them are proprietary and related to industry competition. But we do know that research and development expenditure is generally somewhere in the tens of millions, depending on time and geography. The cost of developing a new drug can go as high as $1 billion or more. Industry survival is founded on a few numbers of highly profitable items; predicting which will be the next blockbuster is a very difficult task. Moreover, it can take over a decade to bring a newly developed product to market. Thus, the industry has considerable up-front costs, which can only be increased by requirements for testing in children. Nonetheless, our estimates are that the six-month patent protection prolongation will more than compensate for the costs that are engendered.

Generic drug manufacturers are required to adhere to the same quality, safety and efficacy standards, and to the same stringent rules of production and pharmacovigilance as their originator drug manufacturing counterparts. However, the research burden is not as great, as the nature of the active substances used has been established; their R&D intensity is less than half of that of the originator drug companies. Generics currently account for about 13% of the European market for medicinal products. The price differential and market share of patented and off-patent drugs can vary widely amongst Member States of the EU. The data exclusivity provisions of the Regulation, which apply to the generic manufacturers, are likely to be taken up by small to medium enterprises seeking to establish a niche for their products.

The individual and social costs related to paediatric medicines.

The cost of medicinal products for the population can be divided into individual and social costs. On the individual level, costs are related to (i) the amount of money that families spend on health care and medication and (ii) the additional individual costs associated with the health problems caused by inadequacies in paediatric medication. Since data to measure the costs for individuals are limited, only approximations of the related costs could be presented. From a societal perspective, the full range of costs and benefits is relevant. There are considerable gains to patients and to the community as a whole, since paediatric trials lead to a better evidence base for the paediatric use of medicines. However, there are also costs related to better medicines for children. Costs for society are related to (i) the amount of money that countries spend on health care and medication and (ii) the additional social costs associated with the health problems caused by the inadequacies in paediatric medication. The problem with these costs estimates is that data are

often aggregated and not broken down into cost components (e.g. expenditure on general practitioners, medicines, and specialists).

A projection of the extent of the problem in 2015.
If no new policies are implemented, how serious will the problem be in 2015? Throughout Europe the share of children between the ages of 0 and 19 declines both relatively and in absolute numbers. However, in 2015 there will be over 150 million children in the EU. We estimated that by 2015 the total size of the pharmaceutical market will be more than 1,000 billion dollars. Even if an increasing proportion of the market will be geared towards adults and the elderly, the paediatric population will most likely continue to be a significant market. The future costs associated with ADRs in the paediatric population as a percentage of total health care expenditure are determined to be fairly modest. However, the calculations underestimate the true extent of the costs. Outpatient care is not included and it has been suggested that the real incidence of ADRs is considerably higher. If we assume, for the moment, that the real extent of the problem is three times as high as is shown in these figures, then the costs related to the most likely scenario would be in the range of 0.1 to 0.4% of health care expenditure. In the most expensive scenarios the costs can run as high as 2% of total spending.

Assessing the impacts

An extended impact assessment within the EC must follow a specific formula. Chapter 4 of this document is based upon that formula. In this summary, we largely specify how we approached the analysis and the main findings, and refer the reader interested in details to the chapter itself.

The American experience.
In the last decade, several steps have been taken regarding medicines for paediatric use in the United States (US), seeking the same objectives as the proposed Regulation. Earlier efforts were widely regarded as not successful, but, learning from experience, a regulation promulgated in 1997 has been seen as working. The key element of this latter regulation was the six months of exclusivity added to the patent protection. This has greatly increased the number of paediatric investigations, but at an estimated increased cost of $61 million per drug. The originating drug manufacture sector is a winner and the generic sector is a loser under the US legislation.

Measuring the impacts.
In examining the potential consequences of the Regulation, we adopted a framework in which we looked at the requirements imposed by the proposed Regulation, the rewards and incentives, and the support measures to be put in place. For the requirements, we considered the legal definition of compliance, the costs of compliance, the costs of monitoring and enforcement, and the distribution of the burden. For looking at the rewards and incentives, we examined the administrative costs for government, the attractiveness of the rewards and incentives and the externalities. For the support measures, we examined their costs and benefits.
For each of the requirements, rewards and incentives, and support measures, we looked at the economic impacts, social impacts, environmental impacts and sustainability impacts. Clearly, the relative importance of these four types of impact could vary significantly, and they were accordingly given their appropriate emphases.
Within this framework, we examined each provision of the proposed Regulation separately.

The impact of the core requirements.
The three core requirements of the proposed Regulation concern the paediatric investigation plan, the marketing authorisation requirement for new products, and the marketing authorisation

for authorised medicinal products. In order to meet these requirements, the pharmaceutical companies have to develop and carry out studies, the Paediatric Board has to evaluate paediatric investigation plans, CPMP (Committee for Proprietary Medicinal Products) or the national competent authorities have to decide on a marketing authorisation, health care professionals and researchers need to provide scientific input and children need to be enrolled to do the studies. This is an ambitious undertaking that will cost between €1 million and €7 million per drug for clinical trials, as well as a lot of effort by many people. Nonetheless, it appears to be achievable with dedicated effort by all parties. The results will be increased research done on the paediatric population, leading presumably to better health care, at a cost that depends on the price elasticity of paediatric medicines and on the policy regimes of Member States. Most of the effect will be felt in new drugs; the generic drug market will be less affected. There is some risk of delay in the marketing of new paediatric medicines, and small and medium enterprises (SMEs) may not have adequate infrastructures to participate in the market. There is a chance that the industry will concentrate its added research in the most profitable areas rather than where there is a social need, especially for rare diseases. Health care professionals may not limit prescribing to tested products; success here may depend on consideration by those responsible for the delivery of health care of selectively including medicines authorised for use in children on formularies and reimbursement lists.

Box S.1
Bottom-line of the quantitative impact estimates for the core requirements

- *Impact on the budget of EMEA*: A maximum increase in EMEA's budget of €130-€195 million per year.
- *The total costs of additional paediatric testing*: An increase in the costs of Phase III clinical trials in drug development of €160-€360 million after the first year.
- *Impact of paediatric testing on the costs of drug development*: An increase in total European expenditure on drug development of 1%-2.5% after the first year.
- *Impact on consumer expenditure and industry costs*: The costs of paediatric testing add 0.1%-0.3% to consumer expenditure and 0.2%-0.7% to industrial costs.
- *Social savings through improvements in medicinal treatment*: The social savings of a complete eradication of off-label and unlicensed prescription are between €10-€36 million and €140-€252 million depending on assumptions. This excludes the value of improvements in the quality of life and the value of lives saved, both of which can be seen as considerably more valuable.
- *Impact on the affordability of medicines*: On aggregate paediatric testing will increase the price of individual medicines by less than 0.5%.

The impact of the rewards and incentives.

The reward for patented products will probably attract a lot of interest amongst the originator drug companies, but because paediatric testing is a requirement, they really do not have a choice. On the other hand, a PUMA is expected to be particularly attractive for SMEs rather than for the big players in the pharmaceutical sector. The incentive will most likely be less valuable than the six-month extension of the Supplementary Protection Certificate (SPC). Data protection extends

only to paediatric use, the incentive derives its economic value from a highly specific and generally small niche in the medicinal market, sales do not necessarily increase, and data protection does not involve market exclusivity. Moreover, the advantages will go to the first mover. In short, originator drug companies stand to gain much more than generic drug companies, as happened in the US. Households will be faced with higher average costs of medicinal products as the availability of generic drugs is delayed. In the long run insurance companies and governments will be faced with higher reimbursement costs of medicinal prescription. When the mutual recognition procedure is used, the extension will only be given if the product is authorised in all EU member states. This may prove difficult, especially when the New Accession States join the EU. On the other hand, this may act as a stimulus to shift to the centralised procedure.

Box S.2
Bottom-line of the quantitative impact estimates for the rewards and incentives

- *The value of a six-month extension of the SPC*: The value of a six-month extension of the SPC more than offsets the costs of paediatric testing. Under current conditions the pharmaceutical industry will be able to recover the costs of testing and make a profit on the SPC extension of between €63 million and €205 million (profits minus the discounted costs of testing over a ten-year period).
- *Impact on the revenues, profits and market share of generic drug manufacturers*: The producers of generic medicines will incur a one-time loss of revenue of between €86 million and €342 million or between €4 million and €51 million in profits, which represents the cost of adjusting to new market conditions during the transitional period of 2 to 5 years. After that period business will be as usual, although producers of generic medicines will have lost some of their market share.
- *The impact on social costs*: The shift in market share from off-patent medicines towards patented medicines will increase European pharmaceutical expenditure by 0.06%-0.25% and total health care expenditure by 0.01%-0.04%.

The impact of the additional requirements and supporting and facilitating measures.
The additional requirements describe the conditions under which the incentives and rewards are awarded. They concern labelling, placing on the market, post-marketing requirements, and pre-existing studies. In general, the consequences of all of these will be small, as long as they are complied with. Many of the issues addressed by the supporting requirements—such as better collection of data on ADRs—are in regards to problems neither magnified nor reduced by the proposed Regulation, and the question is more of adapting implementation of the proposed Regulation to fit these issues.
The inventory of existing medicines will provide companies with an overview of the market for paediatric medicinal products and help to identify opportunities (e.g. therapeutic gaps). Knowledge will spill over from large companies to SMEs that have a narrower knowledge base. SMEs are most likely to use the opportunity to acquire free advice, because they lack in-house expertise on trial designs, pre-clinical and clinical trials, and on the centralised procedures. Larger companies generally employ experts in each area, but even they may not have sufficient expertise in the area of paediatric medicines.

The period between trials, approval, and placing on the market will become shorter. Improvements in knowledge transfers may also result in more cost-effective study designs and industrial savings and will prevent the duplication of tests. In this fashion the government contributes to a more homogeneous basis to the performance of tests.

The instruments create greater transparency in the market and provide support for the self-regulating behaviour of companies (which products to select) and health care professionals (which medicines to prescribe). For example, health care professionals as well as children, parents and guardians can use the inventory of existing medicinal products to choose between medicines (prescription or OTC; tested and untested). The network of experts can create an economy of scope considering that there are relatively few experts and they are scattered across Europe.

The Study Programme can give support to off-patent drug manufacturers for the investigations needed for a paediatric marketing application. The programme can be used to strengthen pharmaceutical R&D in Europe. It will prove particularly useful for small companies, whose work is restricted by a narrow knowledge base, small markets, and a lack of access to capital. The Study Programme can support the development of medicines for rare child diseases, support paediatric testing of orphan drugs, and thus provide health care professionals with better medicinal tools. Children with a rare disease will be given a wider range of medicinal products for treatment.

Health care professionals gain quicker access to new drugs and new forms of existing medicines and improved study designs will lower the risks for children enrolled in clinical trials. Once the Study Programme begins to generate results, it will make available tested medicinal treatments for rare childhood diseases that would otherwise remain unavailable. One such area concerns neonatal medicines. Almost all neonatal medicines are currently unlicensed and parents are highly reluctant to enlist their child in a clinical trial. Under the auspices of the Commission the Study Programme could act as a trusted party.

Three measures have been included to make it easier for companies to fulfil the requirements of the proposed Regulation. They concern the waiver of the requirement for data, deferral to initiating or completing studies in the paediatric investigation plan, and the Community referral procedure for existing authorisations. Again, each of these intended facilitating measures is likely to achieve its purpose, if properly implemented and if compliance is assured.

Box S.3
Bottom-line of the quantitative impact estimates for the additional requirements and supporting and facilitating measures

- *The value of free scientific advice*: Providing free scientific advice will cost EMEA anywhere between €0.25 million and €6.3 million in lost revenues.

Overall conclusions

The Regulation will cost money. Industry will have to pay for complying with the requirements and applying for a PUMA. Government has to provide an infrastructure and invest time and effort in handling applications, doling out rewards and incentives, and providing scientific advice and other benefits. Individuals and governments will have to pay a little bit more for their medicines. But a likely outcome is that the health of children will improve and that the pharmacological research infrastructure will be better. The generic drug manufacturers will be the main losers, and some thought should be given to whether ways to compensate the generics industry are necessary. But on margin, the wins will outweigh the losses.

This will not necessarily come easily. In general, rewards for compliance produce a stronger effect than response to incentives, and this is true in the present case. Enforced compliance for new drugs will happen, but the incentive to attract off-patent medicines to the PUMA is not as strong. Regarding the PUMA, research and development will be drawn to where the money is to be earned rather than where benefit is maximised, and it is not clear that supplemental research funds through the Study Programme will fully remedy that situation. The extent to which health practitioners will fully utilise the newly available information in order to provide best practice is open. Here, and in many other cases, the devil will be in the details—and not only details inherent in the Regulation.

The measures proposed in the Regulation do not have any substantial environmental impacts. Similarly, the sustainability impacts are minor with the exception that special attention to the medical needs of children fulfils part of the sustainability mandate to care for the wellbeing of succeeding generations.

Will the Regulation achieve its higher objectives?

Our assessment indicates that the proposed Regulation will achieve its objectives. The effect on each objective will, however, vary:

- **Stimulating the development of medicines for use in children.** This objective will be achieved, albeit at a price. Producers of patented medicines will benefit substantially more than producers of off-patent products. Households, health care professionals, insurers and governments will be faced with slightly higher drug prices, due to a delay in the marketing of generic medicines and as a result of the costs of paediatric testing. This may be offset by lower overall health care costs due to improvements in the care of children. Our main doubt concerns the attractiveness of the PUMA and the impact on producers of generic medicines.
- **Ensuring that such medicines are appropriately researched and authorised**. The proposed Regulation will unequivocally achieve this objective. Marketing authorisations become conditional upon agreement on a paediatric investigation plan and the performance of paediatric studies. The additional requirements and facilitating and supporting measures provide strong support for research by smoothing procedures, providing information, and ensuring availability.
- **Improving information on the use of medicines in children of different ages.** The mechanisms proposed in the Regulation will contribute to the creation of a firm knowledge base on the medicinal treatment of children and on clinical trials in children. The Regulation will introduce a potential force for standardisation, cooperation, and prioritisation. Whether this improved information directly leads to improved prescribing is beyond the scope of the proposed Regulation.
- **Achieving these aims without delaying the authorisation of medicinal products for other segments of the population**. Some of the main risks and uncertainties relate to possible delays in drug development, marketing and authorisation. The proposed Regulation provides adequate instruments to prevent most of these from materializing. Waivers single out products for which paediatric testing is deemed unnecessary. Deferrals allow the adult version of a medicine to be marketed, while testing for the use in children continues. Thus, this objective is likely to be achieved.

The higher objective of the Regulation –the very reason why it was drafted in the first place– is **to improve the health of the children of Europe**. The proposed Regulation provides one half of

the solution. By changing the economics and legal preconditions of the production of medicines, the Commission hopes to steer consumers (health care professionals and households) towards tested and, hence, safer medicines. If the tested medicines are indeed prescribed, children will receive better treatment, involving shorter hospitalisation and lower drug consumption, and enjoy a higher quality of life. A number of risks and uncertainties remain, but the most likely ones do not substantially threaten the impact of the Regulation. Choice remains the most uncertain factor: the readiness of the industry to focus on the development of paediatric medicines, the response of generic drug manufacturers to the incentives of the PUMA, and the willingness of health care professionals to prescribe tested medicines. The final piece –regulating prescription practices– will have to be provided by policy makers in the health care domain.

Final observations.

The assessment of the potential impact of the proposed Regulation shows there are a number of risks and uncertainties, as well as time-dependent considerations that would endanger their desired effects. With the exception of generic companies that would most strongly disagree with the proposed mechanisms of reward for originator companies, individual stakeholder groups have favoured many of the individual policy measures and agreed that the desired effects could be achieved if the complexity of the existing health care market for children is taken into consideration. Our conclusions show that these complexities, with particular view to the social and economic impacts, can be summarised under the following headings:

- **Consultation with all stakeholders.** For this Regulation to satisfy the shortcomings of the paediatric market, often highly time consuming consultation processes need to be put in place with the range of stakeholders identified in this study. Whilst the incentives and rewards address the market constraints from a global perspective, an in-depth, case-by-case review of the needs and desired effects within the proposed framework will ensure stakeholders views, in particular those of patients and advocates, but also those of pharmaceutical companies are taken into account.
- **Membership in the Paediatric Board (PB).** Because of the power of the PB in determining the adequacy of paediatric plans, waivers, and deferrals, it is important that the PB be both in fact and in perception seen as neither favouring nor discriminating against any stakeholder group.
- **Balancing need and cost.** Our assessment of stakeholders' views showed that the current framework requires wider consideration of investment costs into existing and new medicines. The proposed Regulation intends to adjust medicinal consumption from the supply-side (the production of tested medicines) but does not target prescription and over-the-counter (OTC)-sales directly. Health professionals may not be convinced of the need to use licensed drugs, when independent studies or clinical judgement determines use of existing medications. The investment costs for new medicines are substantial, and at this stage we have no guarantee that newly licensed drugs will always be the preferred option. In addition, the costs and benefits appear to be unequally distributed between originator and generic drug companies. However, the investment considerations need to be balanced against the potential long-term public health benefits in society, and the increased knowledge and understanding that would be created for this market.
- **Ethical considerations need to respect patient views.** Although our assessment showed that the majority of stakeholders, with the exception of generic companies, welcome the main measures proposed provided to stimulate originator companies to invest in this market, there are ethical considerations that need to be taken into account. Clinical trials require recruitment in the paediatric population. Whilst this may not

present concerns in the population affected by severe diseases, because the focus of attention and care is much increased during that period, children who are not affected by serious disease may be exposed to risks in clinical trials. However, any *theoretical* risks from clinical trials have to be balanced against the current situation where everyday children across Europe are exposed to *proven* risks of treatment with untested, unlicensed medicines.

- **Cost-effectiveness considerations affecting European health care systems.** European health care systems are striving towards responsive as well as affordable and cost-effective health care provision. This will require a careful balance of incentives and rewards between innovator and generic companies. The promotion of generic drugs has increasingly been viewed as an attractive costs saving option for European reimbursement systems, because these drugs are cheaper. However, this requires both short-term and long-term views of stimulating and rewarding research efforts in the immediate future, and ensuring access to medicines in the long run. The proposed Regulation achieves the opposite effect in that it delays the entry into the market of generic drugs and seems to disproportionately reward the originator drug companies for their compliance with the requirements.
- **Methods for Post-marketing surveillance.** The use of new medicines requires close surveillance of their effectiveness and potential adverse effects on childrens' health, potentially over long time periods. This requires a large amount of resources be spent on reporting schemes. At this stage, many reporting schemes have failed to account for accurate adverse drug events and wider health implications. Therefore, adequate surveillance methods and resources need to be put in place to ensure we learn of the benefits and risks of paediatric medicines

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- Aventis Pharma
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- BLISS (United Kingdom)
- British Medical Association, General Practitioners Committee (BMA, United Kingdom)
- Dutch Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen (CBG), The Netherlands)
- Dutch Health Care Insurance Board (College voor Zorgverzekeringen (CVZ), The Netherlands)
- Confederation of European Specialist in Paediatrics (CESP)
- Direzione Generale dei Farmaci e dei Dispositivi Medici (Italy)
- European Agency for the Evaluation of Medicinal Products (EMEA)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- European Generic medicines Association (EGA)
- European Network for Drug Investigation in Children (ENDIC)
- European Organisation for Rare Diseases (Eurordis)
- European Society of Clinical Pharmacy (ESCP)
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CHAPTER ONE
Introduction

Objective

There is a serious lack of testing of medicinal products in the paediatric population, i.e. the population between 0 and 18 years. As a consequence, paediatric medication is often a variation on medicines authorised for adult use only. Many drugs prescribed to children are not licensed for use in children or are prescribed off-label (i.e. outside the terms of the product licence; e.g. off-label for age, for dose, route of administration and frequency, or for indication).

Without detailed knowledge of the effect of medicines in paediatric use, children are exposed to an unnecessary level of risk. There is little or no information on the type and incidence of adverse drug reactions (ADRs) related to dosage, age or frequency of administration. Such reactions can be life threatening or at the very least require additional treatment. Children may receive ineffective or second-best treatment when the dosage is not optimal or when new medication has not been approved for paediatric use.[1] The low rate of paediatric testing consequently can reduce the quality of life of affected children, raise the costs of health care (e.g. through longer hospitalisation) and increase child mortality.

The market and current regulations apparently cannot fulfil the demand for paediatric medicinal products without resorting to "less than fully authorised" delivery of medications. Full authorisation can only come from evidence based upon clinical trials in the paediatric population, but there are currently no appropriate incentives for pharmaceutical producers, and no regulations that encourage or enforce the testing of medicines in children. In addition, paediatric drug research is considered difficult. Some of the main obstacles are patient recruitment and consent (of parents *and* children), uncertain long-term toxic effects resulting in risks, ethical and human rights issues, and the difficulties in designing paediatric clinical trials. Moreover, the lack of expertise in this area, for instance in paediatric pharmacology, requires an appropriate infrastructure to be put in place. A structural solution is needed that remedies the short-term problems *and* ensures the long-term quality of health care for children.

Overall, the lack of tested medicinal products adapted to paediatric use is a complex problem with multiple aspects. It involves economic problems (e.g. lack of proper incentives), ethical and legal issues (e.g. the liability of health care professionals), and practical problems (related to paediatric testing). Consequently there is no single solution.

As the abovementioned problems exist throughout the European Union (EU), the European Commission (EC) aims to address the problems at a EU-level. The integration of the New Accession States (NAS) –with a younger population and fewer resources– in the EU in 2004 makes it even more urgent to address these problems.

[1] For example, in the 1960s many drugs that had not been studied in children were labelled as "not to be used in children" even though they were also effective against childhood diseases ('t Jong, 2002: p. 12).

In the beginning of 2002, two regulations were drafted to stimulate the development of medicines for paediatric use, one regulation focusing on patented products and one on off-patent products. In November 2003 the two proposed Regulations were merged into one draft Regulation on medicinal products for paediatric use (hereafter called the Regulation), after which it was discussed within the ad hoc group on paediatrics of the Pharmaceutical Committee. Chapter 2 of this report describes the draft Regulation in more detail.
The main objective of this research is to conduct an extended impact assessment; that is to examine the economic, social, and environmental impacts of the proposed EC Regulation as well as to examine the impact on sustainable development. For this purpose three main tasks have been distinguished:

1. Identifying stakeholders and mapping their views,
2. Measuring the current and future effects without policy change, and
3. The impact assessment itself.

Methods used

The value chain of medicinal products – innovation, production, and marketing – includes a wide variety of stakeholders. Not every group will be equally affected by the proposed Regulation. In order to make reliable and complete predictions of the impact and the associated risks and uncertainties of the proposed measures, a good understanding of the views and constraints (or disincentives) of the stakeholders that are affected by the Regulation is required. Without such understanding the impact assessment will most likely fall short. An analysis of views and constraints helps to identify where markets may fail and regulation may be ineffective. It will help identify possible risks of non-compliance and outline the scope for self-regulation as opposed to the need for intervention.
We have used a number of different methods to identify stakeholders and map their views. For identifying stakeholders we studied the literature on (1) medicines for paediatric use[2] and on (2) the regulation of pharmaceuticals (for paediatric use) in EU-countries[3] (Jakubowski and Busse, 1998; Kavanos, 2002a; 2002b). To map the views of relevant stakeholders we (3) interviewed a selection of stakeholders (a total of 23 persons, interviewed by telephone and/or face-to-face), and (4) studied position papers and statements regarding medicines for paediatric use (EFGCP News, 2002; EFPIA, 2003; EFPIA Paediatric Workshop, 2003; EFPIA Position Paper, 2002a; 2002b; 2003; EGA, 2002; EMEA, 2002; 2003; FIP, 2000; UK Neonatal and Paediatric Pharmacists, 2002).
To measure the current and future effects without policy change, we have performed a literature review regarding the off-label and unlicensed use of paediatric medicines. Quantitative estimates of the number of children affected and the costs involved were made on the basis of statistical information in existing publications and databases (e.g. OECD Health Data and WHO Data – European Health for All Database).
To gain a better understanding of the potential impact of the Regulation, we have used the interviews with representatives of different groups of stakeholders (e.g. regulatory agencies, health

[2] We began with a literature review, which we performed for a study on pharmaceutical drug use in children (Geesink, Van Beusekom, Van het Loo et al, 2002). This literature review was updated for the years 2001-2003.
[3] We made a description of the pharmaceutical regulation in all EU Member States countries, which is available upon request. The information is almost integrally taken from the study 'Health Technology Assessment and the European Union', which was financed by and prepared for the use of the European Commission, Directorate-General for Employment, Industrial Relations and Social Affairs in 1998 (Banta and Oortwijn (eds.), 2000).

care professionals, and pharmaceutical companies) as well as a range of position papers. In addition, we have reviewed existing databases and the literature to gain insight in the possible economic and social impacts of the proposed Regulation.
The intention was to identify different stakeholders at EU level, in the United Kingdom (UK), Germany, the Netherlands, and Italy. The final selection of key informant interviews was discussed with the European Commission and based on informant availability. Given the large number of stakeholders and the limited time available, we decided to interview a selection of stakeholders, with a focus on stakeholders at EU-level. In those instances where we were not able to interview a representative of a stakeholder group at EU-level, we contacted a representative of that group in a sample of Member States. Almost all stakeholders responded positively to our invitation.
To this information, we applied our own quantitative projection analyses and qualitative stakeholder analyses.

Outline of report

This report describes the results of the study, divided into three tasks:

- Identifying stakeholders and mapping their views
- Measuring the current and future effects without policy change
- The extended impact assessment

These first steps in our analysis concern a description of the context in which the Regulation is to be applied. We list the stakeholders that are directly and indirectly affected by the proposed Regulation, and map their views. In addition, we identify the extent of the problem. The outcomes of the first two tasks serve as input for the impact assessment.
Chapter 2 presents the Regulation, which has been proposed to stimulate the development of medicines for paediatric use. In Chapter 3 we describe the extent of the problem regarding the use of medicines in children (at this moment and in 2015). The extended impact assessment itself is presented in Chapter 4. Recommendations regarding the design, the implementation and evaluation of the Regulation are presented in Annex 1.

CHAPTER TWO
The Regulation

Objectives

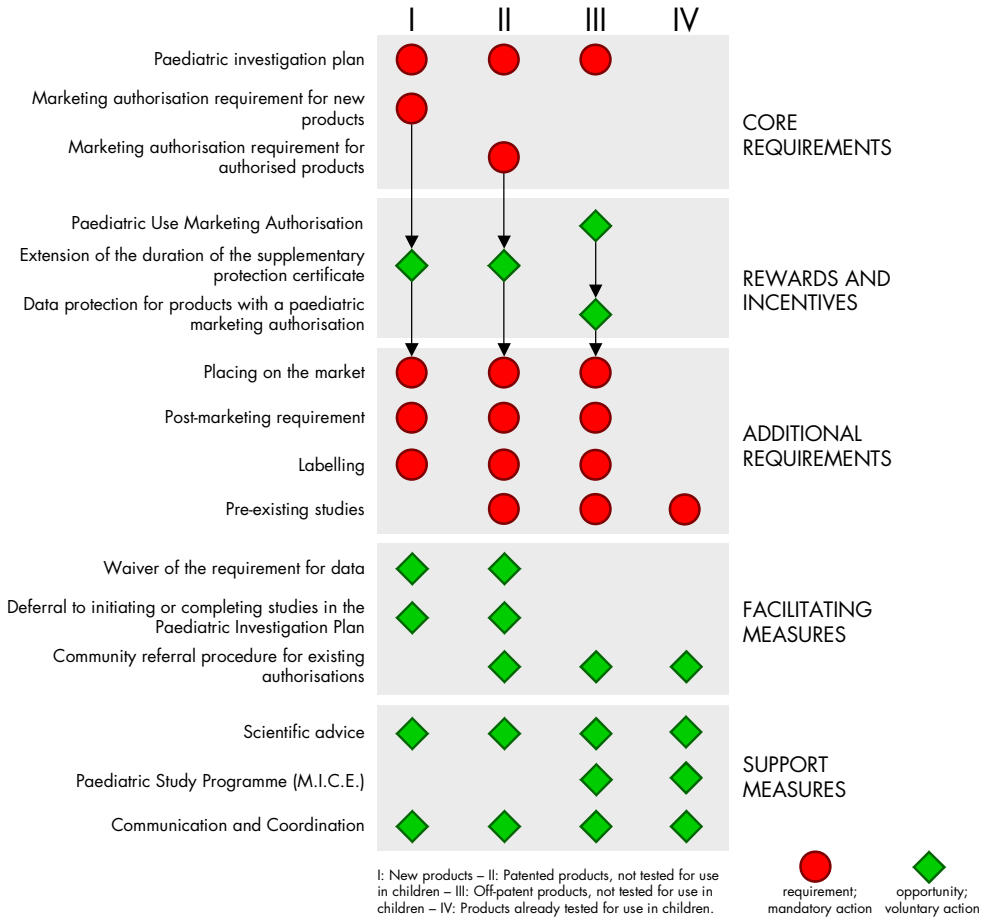
The proposed Regulation aims to provide incentives where the market is able to self-regulate and set requirements where market failures are more likely to persist and government intervention is needed. Moreover, the Commission has tried to find ways to balance individual and social costs and benefits, to avoid outright losers and distributional inefficiencies but work for a win-win solution, and to prevent new regulatory and market failures from occurring.
The higher objective of the proposed Regulation is to improve the health of the children of Europe. It aims to achieve this objective by (1) stimulating the development of medicines for use in children, (2) ensuring that such medicines are appropriately researched and authorised, (3) improving information on the use of medicines in children of different ages, and (4) achieving these aims without delaying the authorisation of medicinal products for other segments of the population.

How will the proposed Regulation work?

The Regulation is a regulation for *all* medicines (adult and paediatric). The requirements in the Regulation will not apply to marketing authorisation applications that are ongoing when the Regulation enters into force. However, once those medicines are licensed the Regulation will apply to them. The Regulation consists of two types of provision, namely substantive provisions (the requirements, rewards, incentives, and support measures that form its core) and procedural provisions (infrastructure, administrative procedures, legal and regulatory context). In our analysis we have primarily focused on the substantive provisions and included the procedural provisions where they have a relevant impact on one or more stakeholder.
The articles in the proposed Regulation have been rearranged to reflect their nature. We have identified five groups of provisions:

- *Core requirements*: The requirement to include the results from studies carried out according to an agreed paediatric investigation plan in a marketing authorisation forms the core of the Regulation.
- *Rewards and incentives*: In exchange for the costs and effort involved in meeting the core requirements the producers of originator medicines are given a form of IPR (intellectual property right) protection, an extension of the Supplementary Protection Certificate (SPC). There is no requirement for drug manufacturers of medicines not covered by patent or SPC. For these companies (generic and innovative) it is possible to apply for a paediatric use marketing authorisation (PUMA). This is a specific marketing authorisation exclusively for paediatric use, associated with a period of data protection.

Figure 2.1
An overview of the way in which the Regulation applies to different types of product



- *Additional requirements*: In order to guide the effects of the core requirements in the right direction, a number of additional requirements has been included. For example, for products already on the market which gain a paediatric indication the marketing authorisation holder must market the tested product within 12 months of the date of approval of the application for a marketing authorisation, so that the paediatrically tested product also becomes available.
- *Facilitating measures*: The two main facilitating measures concern waivers and deferrals. Waivers will be granted to avoid unnecessary testing. Deferrals govern the period of transition, and – when the Regulation is established and working –ensure that the requirement for paediatric data never delays a product being made available for adults (e.g. when it is considered safer to study the use of a drug in adults before children). In addition, the Commission will provide pharmaceutical companies with a direct path to the centralised procedure. Facilitating measures can be requested, although the PB can grant both waivers and deferrals without such a request.
- *Support measures*: The Regulation will lead to investment in the creation and exchange of knowledge about paediatric medicines, clinical trials involving children, and in a study fund to advance the development of medicines for use in children. Support measures are available when needed.

Figure 2.1. shows how the various provisions apply to four different groups of products: new products (not yet authorised) (I), patented, authorised products not tested for use in children (II), off-patent, authorised products, not tested for use in children (III), and authorised products already tested for use in children (IV).
This overview also shows to some extent how the provisions of the proposed Regulation are connected. The most important relations have been marked with arrows and concern (1) the rewards provided to compensate for the core requirements, (2) the incentives (related to the PUMA), and (3) the additional requirements that are conditional on the rewards and incentives.

The key provisions of the Regulation

To understand the nature of the Regulation and its economic, social and other impacts, the contents of the proposed Regulation need to be explained. We have used the draft version of the Regulation to describe the key provisions. *It must be emphasized that this is not a final or otherwise approved version of the text.* The descriptions merely serve to help the reader understand the various provisions of the Regulation.

Core requirements

Paediatric investigation plan A paediatric investigation plan will be submitted and shall include details of the timing and the measures proposed to assess the quality, safety and efficacy of the medicinal product in all paediatric populations that may be concerned. In addition, all measures to adapt the medicinal product to make its use more acceptable, easier or more effective for different paediatric subpopulations shall also be described.
The paediatric investigation plan is the plan for a set of studies that must be conducted for a product to be permitted to enter the market (unless a waiver has been granted). The results of the studies will include details regarding the safety, quality and efficacy of a product and when applicable information about how to make the product more acceptable, easier or more effective for specific target groups. Submission and discussion of the plans is expected to contribute to raising the standards of paediatric investigations throughout the EU.
Marketing authorisation requirement for new products In order to obtain a marketing authorisation for a medicinal product for human use that is not authorised when the proposed Regulation enters into force, the application shall include the data determining the conditions in which the medicinal product may be authorised to treat the paediatric population or certain of its subpopulations.
New indications, dosage forms or routes of administration for authorised medicinal products The requirement to include the data determining the conditions in which the medicinal product may be authorised to treat the paediatric population or certain of its subpopulations may also be applied to applications for authorisation of new indications, new pharmaceutical forms and new routes of administration concerning authorised medicinal products. This does not apply to products authorised via the generic licensing route.
As indicated above, the requirement is to include the results from studies carried out according to an agreed paediatric investigation plan, and not for the investigation to prove that the medication in question is safe and effective for use in children. The proposed Paediatric Board (PB) of the EMEA will be responsible for the evaluation of the proposed plan and, in many cases, for evaluation of compliance of the application for a marketing authorisation with the agreed plan. The Committee for Proprietary Medicinal Products (CPMP) or national competent authorities will assess the quality, safety and efficacy of paediatric medicines. The CPMP may discuss the results of the paediatric investigation plan with the PB and then decides whether or not to grant a

market authorisation. The EMEA is the responsible actor to coordinate the activities of the PB with other committees.

Reward and incentives

Extension of the duration of the Supplementary Protection Certificate This provision applies to products that are covered by a patent or by a SPC. When an application for a marketing authorisation includes the results of all measures taken in accordance with an agreed paediatric investigation plan, the applicant shall benefit from a six-month extension of the SPC. The extension is also awarded when the completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, the patient information leaflet of the concerned medicinal product.

The reward is given for additional paediatric investigation, but applies to the marketing of paediatric *and* adult medicinal products. The measure is consequently more than mere compensation, but represents a real financial gain for the pharmaceutical industry. This measure adjusts the difference between individual costs and social benefits (an externality) by lengthening the period during which producers can recover the costs of their investments. A longer duration of patent protection increases the returns to investments, thus providing a monetary incentive compensating for the requirement of paediatric testing. To receive the reward the product should be authorised in all Member States and the product should be marketed within 12 months.

Paediatric Use Marketing Authorisation A PUMA concerns a marketing authorisation granted to a medicinal product for a paediatric use which does not fulfil the criteria set out in the first two requirements (*marketing authorisation requirement for new products and new indications, dosage forms or routes of administration for authorised medicinal products*), including a new formulation of that product. This shall cover only those therapeutic conditions, which are relevant for use in paediatric populations. The expectation is that a PUMA will be particularly attractive for small and medium enterprises (SMEs) rather than for the big players in the pharmaceutical sector.

Data protection for products with a paediatric use marketing authorisation Companies that (successfully) apply for a PUMA are rewarded with 10-year data exclusivity for licensing purposes that means that only these companies can use the data collected in the paediatric investigation. If another company performs its own research (in clinical trials) in order to meet the conditions for a PUMA, then it too will receive a period of data exclusivity. The instrument is therefore not guaranteed to provide market exclusivity: it offers companies the opportunity to buy market access and capture a niche.

Additional requirements

Placing on the market When an agreed paediatric investigation plan has led to the authorisation of a paediatric indication and if the product is already marketed for other indications, the marketing authorisation holder shall market the product taking into account the paediatric indication within 12 months of the date of approval of this indication. A product granted a PUMA shall be marketed within 12 months of the grant of the marketing authorisation. This measure focuses on placing medicines on the market within 12 months of the date of marketing approval. Presumably, if the product is not yet marketed, the paediatric indication will be taken into account upon the launch of a new product.

Post-marketing requirements As part of an application for a marketing authorisation that includes a paediatric indication, the applicant shall indicate how it proposes to ensure follow-up efficacy and possible adverse reactions to the specific use of the medicinal product in the paediatric indication in addition to the normal requirement for post-marketing monitoring. The marketing authorisation holder will submit an annual report to the PB that provides an update on progress with paediatric studies compared with the agree paediatric investigation plan.

This requirement refers to pharmacovigilance, i.e. the monitoring of suspected adverse reactions, which is already a requirement under Regulation EC/2309/93 and Directive 2001/83, but which would have to be operationalised in such a way as to ensure adequate information on the youngest children, neonates in particular. Pharmacovigilance focuses on safety after medicines are placed on the market. A company needs to show how they will perform the additional post-marketing monitoring. In the case of a deferral of paediatric testing (see below), marketing authorisation holders are obliged to present an annual report on their progress with paediatric studies. The European Commission is currently developing a separate article on fines to enforce compliance.

Labelling The name of the medicinal product for which the PUMA is granted shall include a superscript of the letter "P" in blue lettering surrounded by the outline of a star, also in blue. This measure aims to increase the visibility of medicines tested for paediatric use.

Pre-existing studies Any paediatric studies completed before the entry into force of this Regulation, which have already been submitted for evaluation in a country outside the Community, shall not be taken into consideration for the incentives. Any studies, which concern products authorised in the Community, shall be submitted to the concerned Competent Authority for evaluation within one year of entry into force of this Regulation.

This measure is to dissuade companies from withholding data of completed studies at the time of coming into force of this Regulation, which has already been used to gain incentives in the US. Studies completed after entry into force of the Regulation are eligible for both US and EU incentives. In addition, all companies are compelled to submit data on paediatric use, implying that the competent authorities can assess the data and product information can be updated.

Facilitating measures

Waivers The PB may agree to waive the requirement in order to apply for a marketing authorisation for the data determining the conditions in which the medicinal product may be authorised to treat the paediatric population or certain of its subpopulations according to an agreed paediatric investigation plan. The PB may agree such a waiver if an applicant can provide evidence suggesting that the concerned medicinal product is likely to be ineffective or unsafe in the paediatric population, or that the disease or condition for which the medicinal product is intended occurs only in adult populations or if the product does not represent a therapeutic benefit over existing treatments for paediatric patients.

If the PB considers that the medicinal product for which a waiver is requested may produce a significant therapeutic benefit in one or more specific paediatric indication(s) different from that proposed by the applicant, the waiver shall not be agreed in respect of the concerned paediatric indication(s). The PB may also decide to waive the requirement for a class or part of a class of medicinal products, taking into consideration the inventory and without any request from an applicant.

Deferrals The applicant may include a request for a deferral to initiating or completing some or all of the studies in the paediatric investigation plan. A deferral focuses on those situations in which paediatric information may be submitted until after approval, e.g. when paediatric studies should be delayed because safety and/or effectiveness data in adults should be collected first, or when awaiting the completion of paediatric studies would delay the availability of a product to adults (FDA, 1998).

Community referral procedure for existing authorisations For a medicinal product that is already authorised via the mutual recognition procedure, an applicant may submit directly an application to the centralized procedure. The Community referral procedure allows the CPMP, through the Commission, to dictate to the Member States what the national marketing authorisation, or part of the national authorisations, should state. When the CPMP reaches an opinion on paediatric use, it is forwarded to the European Commission. The Commission issues a decision, which

directs the Member States to update their authorisations with regard to specific wording on paediatric use.

Support measures

Paediatric Study Programme; Medicines Investigation for the Children of Europe (MICE)
A Community programme shall be created to support studies relating to existing medicinal products or existing active substances not covered by a patent or Supplementary Protection Certificate (SPC), to be used in support of applications for a paediatric marketing authorisation. This programme is to stimulate research into off-patent drugs and will ideally lead to licensing action but such licensing action is not a necessary result. The requests for funds will probably have to meet the requirements for EU support, most particularly principles of subsidiarity and proportionality. For the study programme, separate legislation is needed, and therefore it will take some years (after the Regulation enters into force) before the study programme will be operational.
Scientific advice Prior to submission of a paediatric investigation plan and during its implementation, the sponsor of a medicinal product for paediatric use may request advice from the Agency on the design and conduct of the various tests and studies necessary to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population. This specific paediatric scientific advice shall be provided by the Agency without the payment of fees.
Other support measures concern Communication and Coordination issues. Communication and Coordination measures would (1) encourage and facilitate the collection by and exchange of information between companies and research institutes, (2) enhance transparency of testing and regulation, and (3) to prevent the duplication of trials in children which is considered unethical. In the Regulation, three measures of Communication and Coordination can be distinguished:
Communication and Coordination: survey of existing paediatric uses Within two years of the entry into force of the proposed Regulation, Member States shall collect available data on all existing uses of medicinal products by health care professionals in paediatric indications and provide these data to the Agency.
Communication and Coordination: inventory The data collected in the survey of existing paediatric uses shall be assessed by the Agency in order to identify research priorities. The PB will use this information to make a first inventory of therapeutic needs. The inventory shall take into account the prevalence of conditions to be treated in the paediatric population, the seriousness of the conditions to be treated, the availability and suitability of alternative treatments for the conditions in the paediatric population, including the efficacy and the adverse reaction profile (including any unique paediatric safety issues) of those treatments.
This measure focuses on identifying which medicines there are, which are off-label, and where there are therapeutic gaps that need closing. The inventory may help in focusing the attention of policy makers, pharmaceutical companies and health researchers. About half of all medicinal products have not been tested for paediatric use. Many of those products do not require such testing, although many of these may still require the relevant information to be included in marketing authorisations. For those that do require testing some products are in greater need than others. A careful selection of priority medicines ensures that scarce public resources and regulatory interventions are applied as efficiently as possible, that is, where they are most urgently needed and where they will be most effective. This does require careful selection on the basis of a precisely defined set of criteria.
Communication and Coordination: network for the performance of clinical trials on paediatric population The Agency shall contribute to the coordination of research and comparative studies relating to medicinal products for the paediatric population, the development of interdisciplinary networks, the exchange of information on clinical practice and the co-ordination of clinical trials

in the area of paediatric medicine by establishing a European network with specific expertise in the performance of trials in the paediatric population.
Communication and Coordination: the exchange of information Appropriate details of all trials carried out in the Community shall be entered into a database and part of the information that derives from an agreed paediatric investigation plan will be made accessible to the public. Appropriate details of trials that are part of an agreed paediatric investigation plan and that are carried out in third countries shall also be entered into the database. Details of the results of all studies conducted in accordance with an agreed paediatric investigation plan, whether conclusive or not, shall be published with all relevant conclusions for medicinal products in the same therapeutic class that cover the same proposed paediatric use.
The creation of knowledge databases and the search for best-practice solutions is a key element in the public policy research of the European Community and of the national governments of Member States. The PB will play a central role in the establishment of a network: EMEA will coordinate/facilitate a network for the performance of clinical trials. The benefits will be to coordinate academic research and to provide a coordinated network of centres to conduct industry sponsored studies. The measure does not put the infrastructure in place, but merely prepares it or expresses an intention. The Member States, the industry, and academia have the responsibility of setting it up and making it work.

Summary of the Regulation

In 2002, two regulations were drafted to stimulate the development and testing of medicines for paediatric use, one regulation focusing on patented products and one for off-patent products. In the end of 2003, these draft regulations were integrated into one draft Regulation on medicinal products for paediatric use.
The draft Regulation, which focuses on (i) new products (not yet authorised), (ii) patented, authorised products not tested for use in children, (iii) off-patent, authorised products, not tested for use in children, and (iv) authorised products already tested for use in children, consists of *substantive* provisions (requirements, rewards, incentives, and support measures) and *procedural* provisions (infrastructure, administrative procedures, legal and regulatory context).

The most important provisions of the proposed Regulation concern:

1. the reward *(an extension by six months of the duration of the period of supplementary patent protection)* provided to compensate for the core requirements (paediatric investigation plan and the requirement to include the results from studies carried out according to an agreed paediatric investigation plan as part of an application for a marketing authorisation or (in specific cases) an application for a new indication, new route of administration or new dosage form);
2. the incentive (data protection (i.e. exclusivity) for products with a paediatric use marketing authorisation - PUMA); and
3. the additional requirements that are conditional to the rewards and incentives.

CHAPTER THREE
The Problem

Defining the problem and identifying risks

The Regulation on medicinal products for paediatric use may have an impact on a wide variety of different stakeholders (such as pharmaceutical companies, insurers, hospitals, doctors, other health care professionals, and children and their parents or guardians). They interact in the market for paediatric medicines[4], especially in phase III and phase IV of a drug testing life cycle[5].
In essence the Regulation tries to balance two basic needs:

- Maintaining and protecting the health and quality of life of children
- The economic viability and sustainability of the pharmaceutical industry

Children need safe medication to provide them with appropriate treatment and to avoid adverse drug reactions (ADRs) and –possibly– death. The lack of safe medicines puts children at potential and actual risk of suffering undesirable health effects. Paediatric medicines have to be tested, developed and produced, which is only possible if the right incentives are provided to the pharmaceutical industry. Children and the pharmaceutical industry are the most important parties in this Regulation. The Regulation indirectly but significantly affects other stakeholders involved in paediatric medicine, such as general practitioners (GPs) and other professionals providing medical care, pharmacies, government departments and regulatory agencies, researchers in academia and other research institutions and insurance companies (see section 3.2). The views of those who prescribe medicines are particularly important, as they are involved in judging the effectiveness of medicines on a day-to-day basis.
In this Chapter, the extent of the problem is described on the basis of the incidence of health problems in the paediatric population (3.3), the role of the pharmaceutical industry (3.4), the individual and social costs related to paediatric medicines (3.5) and a projection of the extent of

[4] By "paediatric medicines" we mean pharmaceutical products whose appropriate use, dosage, route of administration and duration of use have been established through scientific evidence for paediatric populations.

[5] Phase III (takes around three years): Randomised trials in larger patient groups with the purpose of determining the short and long term safety/efficacy balance of the active ingredient, as well as to assess its overall and relative therapeutic value when compared with established therapies (i.e. effectiveness). The pattern and profile of more frequent adverse reactions must be investigated and special features of the therapy must be explored (e.g. clinically relevant drug interactions, factors leading to differences in effects such as age etc.). See: http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/goodclin_e.pdf
Phase IV (varies in length): Phase IV trials are conducted after initial granting of marketing authorisation. The purpose of these trials is monitoring effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use (NIH, 2004). In addition, Phase IV trials studies often compare a drug with other drugs already in the market, and may also establish the cost effectiveness of approved treatments (JM Clinical Trials, 2004).

the problem in 2015 (3.6).[6] In our analysis of the current situation, we focus on the EU-15 and the 10 NAS countries of 2004 (Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic and Slovenia). Bulgaria and Romania were included when projecting the extent of the problem to 2015.

We have found that the information to determine the extent of the problem is often not available or insufficient. For example, information on medical treatment and medicinal consumption is not sufficient to make a complete estimate. There are little or no data to identify the number of individuals that receive treatment or that suffer the consequences of inadequacies in medication. Similarly, there is a lack of age-specific information on medicinal consumption. On an aggregate level some types of relevant data are available. For example, data on the number of doctors' visits per inhabitant, the number of admissions into hospitals, and the total daily consumption of different types of medicinal product are available, although rarely specified by age.

The analysis will consequently have to rely heavily on estimates of indicators based on assumptions (e.g. the assumption that the age distribution of the general population applies equally to the aggregate statistical data available) and on a literature review of case studies.

Stakeholder analysis: who is affected?

To understand the potential impact of the proposed Regulation for the different stakeholder groups, it is important to first identify who the key stakeholders are, and to assess the impacts of the Regulation on these stakeholders. We have identified the following key stakeholders in the field of medicines for paediatric use:

- Pharmaceutical industry (innovative and generic);
- Regulatory authorities (on EU and national level);
- Health care professionals (paediatricians, general practitioners, pharmacists, and nurses); and
- General public (advocate groups; patient groups).
- In addition, there are other actors that play a role in this market, such as the medical research community and health insurers.

Pharmaceutical industry

The pharmaceutical industry takes a leading role during the innovation phase and throughout the drug development period. The industry has close contacts with the research community and government agencies to establish the viability of investments. Once a marketing authorisation has been granted, the pharmaceutical companies are heavily involved in the marketing phase, involving private and public healthcare purchasers and providers. Throughout the patented period, the industry is still involved in ensuring the safe production and supply of the drug, although the responsibility of ensuring safety and effectiveness also lies with healthcare professionals, healthcare purchasers, regulatory bodies and consumers. Generic companies and wholesalers will play an important role in the continued use and promotion of the drug in the off-patent period. Generic companies, that provide cheaper drugs, may have an important role to

[6] In this report, the paediatric population comprises all individuals up to and including the age of 17. The data generally refer to different age groups (e.g. 0 to 19 years old). We have not tried to adjust the data to fit in with the official definition of the paediatric population.

play in the development and testing of existing paediatric therapies that are currently used off-label.
At the EU-level, the following organisations represent pharmaceutical companies based in Europe.

- **European Federation of Pharmaceutical Industries and Associations (EFPIA).** EFPIA is an organisation representing the innovative pharmaceutical industry operating in Europe. The members of EFPIA are pharmaceutical companies undertaking research, development and the manufacture of medicinal products for human use. Its mission is "to promote pharmaceutical research and development and the best conditions for companies to bring to market medicines that improve human health and the quality of life around the world." EFPIA has published a position paper in which it presents its views regarding the draft Regulation on medicines for paediatric use. (www.efpia.org)
- **European Generic medicines Association (EGA).** EGA is an organisation representing European pharmaceutical companies producing generic medicines. The members of EGA include national pharmaceutical industry associations (from both EU Members States and the Accession Countries) and companies. Regarding the development of pharmaceutical legislation and guidelines, EGA is in constant dialogue with various international and national agencies, including the EU. (www.egagenerics.com)

As the impact of the proposed Regulation may be different for different types of pharmaceutical companies (manufacturers of originator medicines versus manufacturers of generic medicines) both of the above organisations are key stakeholders. In addition, the successful introduction of a drug depends on marketing companies to promote the product to the right audience and as widely as possible.

Regulatory authorities

Regulatory authorities have an important role to play in the initial innovation phase, as they approve clinical trials and also offer scientific advice (on a voluntary basis) to the pharmaceutical industry. The environment for testing and safe conduct of trials requires the approval of regulatory authorities, as well as monitoring of test results and filing procedures for new drug applications. In Europe, there are two routes for gaining a marketing authorisation for medicinal products: a centralised procedure (at the European level) and a decentralised or mutual recognition procedure (at the national level). In the centralised procedure, applications are submitted directly to the European Agency for the Evaluation of Medicinal Products (EMEA) to be evaluated by the Committee for Proprietary Medicinal Products (CPMP) regarding quality, safety and efficacy.

- European Agency for the Evaluation of Medicinal Products (EMEA). EMEA is a European Agency responsible for the regulation of medicinal products in Europe. EMEA's main task is to co-ordinate the licensing system and the scientific evaluation of the safety, quality and efficacy of medicinal products for human and veterinary use throughout the EU. The CPMP is EMEA's scientific committee responsible for human medicines. (www.emea.eu.int)

If an authorisation is granted under the centralised procedure, it is valid throughout the whole of the EU. The centralised procedure is compulsory for biotechnological products, and optional for other new and innovative products. The mutual recognition procedure applies to the majority of conventional medicinal products and is based on the existing multi-state procedure. It works on the principle of mutual recognition by EU Member States of their respective national marketing

authorisations. Purely national authorisations remain available for medicinal products to be marketed in just one Member State. Often the mutual recognition procedure is seen as an advantage for small companies wishing to access niche markets. From a public health viewpoint the main disadvantage is that the mutual recognition procedure means that products do not have to be authorised in all European Member States (and therefore a product will not be available throughout whole of Europe).

Health care professionals

Health care professionals are increasingly involved when we move down the value chain. Whilst health care professionals assume an important role in guiding pharmaceutical companies with respect to the need for development of paediatric drugs, this stakeholder group starts to be more seriously involved at phase IV, when manufacturers want to establish the potential impact of the drug on the current market. Pharmaceutical companies closely liaise with health professionals towards the end of the trial period for marketing purposes.

The crucial role health care professionals play in the on- and off-patent periods lies with their preference in delivering health care using high-quality products, and promoting drugs through pharmacists. In the absence of licensed medicines that are tested specifically for their use in children, doctors can prescribe drugs that are not licensed for use in children (Guiton, Reith, Isitt, 2002). Furthermore, these drugs prescribed by doctors can be dispensed by pharmacists and administered by nurses or midwives. Liability is an issue for health professionals, especially when product manufacturers are only likely to be found liable if harm results from a defect in the product. Therefore legal responsibility for prescribing falls to the doctor who signs the prescription (MTRAC, 2004). Doctors' decisions concerning the type of medicine they prescribe is based upon clinical judgement. MTRAC (2004) states that a doctor will not be found negligent in a court of law if he can convincingly demonstrate that "he acted in accordance with a responsible body of relevant professional opinion". If problems arise after receiving a drug that was not licensed for use in children, doctors are unlikely to be found negligent if they have

- taken steps to become familiar with the effects and side-effects of the drug,
- are able to monitor that drug completely, and
- have access to effective consultant support (MTRAC, 2004).

The main groups of health care professionals dealing with medicines for paediatric use are medical doctors (general practitioners, paediatricians, etc.) and pharmacists. Organisations representing these groups at the EU-level include:

Medical doctors

- **Standing Committee of European Doctors (CPME).** CPME is the umbrella organisation representing European doctors. The members of CPME are the national associations of medical doctors in the 17 EU/European Economic Area (EEA) Member States and in 14 other European countries. CPME's aim is to promote the highest standards for public health and medical practice at the EU level. (www.cpme.be)
- **European Union of General Practitioners (UEMO).** UEMO is an organisation of national, nongovernmental, independent organisations representing general practitioners in the countries of Europe. UMEO encompasses organisations from all EU member states and several other European countries. As a recent Dutch study ('t Jong, Eland, Sturkenboom et al, 2002) showed that off-label and unlicensed prescription of medicines to children is also frequent in general practice (15.3% unlicensed prescriptions and

13.6% off-label prescriptions), general practitioners form an important stakeholder group. (www.uemo.org)

- **Union of National European Paediatric Societies and Associations (UNEPSA).** The primary objective of UNEPSA is to "encourage cooperation between national paediatric societies/associations in Europe in their task to promote child health and comprehensive paediatric care." Furthermore, it aims to improve dissemination of information, and to encourage the conduct of research in paediatrics. Its members are national paediatric associations. (www.unepsa.org)
- **Confederation of European Specialist in Paediatrics (CESP).** CESP is a subgroup of the Union of European Medical Specialists (UEMS) and is the mechanism by which specialist medical services are recognised within the EU. CESP has set up a European Board of Paediatrics (EBP), which is responsible for developing guidelines for common standards of training for paediatricians within the EU. (www.uems.be)

Pharmacists:

- **European Society of Clinical Pharmacy (ESCP).** ESCP is an international association founded by clinical practitioners, researchers and educators from several European countries. Its overall mission is to develop and promote the rational and appropriate use of medicines by the individual and by society. Members include clinical pharmacists, hospital pharmacists, community pharmacists, researchers and educators from 53 countries. (www.escpweb.org)
- **International Pharmaceutical Federation (FIP).** FIP is a worldwide federation of national pharmaceutical (professional and scientific) associations, which has a mission "to represent and serve pharmacy and pharmaceutical sciences around the globe". Although FIP is a federation of associations, any pharmacist or pharmaceutical scientist can apply to become a member of FIP. FIP's has an important role in the education in and development of the practice and science of pharmacy. (www.fip.org)

Public/patient organisations

Patients/public are the ultimate stakeholders. Their main interest is to receive safe and effective drugs, which are convenient to take. In addition to health care professionals, the general public plays a crucial role in stimulating demand for paediatric drugs. In Phase IV, the public has a role in evaluating the drug's effectiveness and use in the market, and patients and their families are crucial parties in raising awareness thus contributing to the successful application of certain drugs. They have power to advocate and stimulate the innovation process of drugs and, at later stages, the widespread coverage of effective drugs on the market.
There are different advocate groups that represent patients at a European level, including:

- **European organisation for rare diseases (Eurordis).** Eurordis is an alliance of patient associations and individuals dedicated to improving the quality of life of all people in Europe with rare diseases and their families and supporters. Its mission is "to build a strong pan-European community of patient organisations and people living with rare diseases, to be their voice at the European level, and - directly or indirectly - to fight against the impact of rare diseases on their lives". (www.eurordis.org)
- **European Patient Forum (EPF).** EPF was created in early 2003, by 12 European patient organisations. The aim is to establish one European patient body to address issues concerning the interests of patients in the European healthcare debate. (www.europeanpatientsforum.org)

- **European Consumers' Organisation (BEUC).** BEUC is a Brussels based federation of 36 independent national consumer organisations from the EEA countries, i.e. the EU countries, the Accession Countries, and Norway, Liechtenstein and Iceland. Their mission is to "try to influence, in the consumer interest, the development of EU policy and to promote and defend the interests of all European consumers". (www.beuc.org)
- **European Platform Patient Organisations, Science and Industry (EPPOSI).** EPPOSI is the European partnership of patients' organisations, science and industry working on health care policies towards treatment and prevention of serious diseases. The platform is concentrating its activities in the field of health care policy making, with a focus of attention on the promotion of patients' interests. They are particularly interested in "finding ways to promote funding and facilitate the development and availability of innovative medical solutions to all individuals in need". (www.epposi.org)
- **European Forum for Good Clinical Practice (EFGCP).** EFGCP is a not-for-profit organisation established by, and for, those with a professional involvement in clinical research. It is dedicated to promoting the interests of patients in clinical research through the development of European ethical and scientific standards. (www.efgcp.org)

As the above list indicates, there is no European patient organisation specifically aimed at representing the interests for children that need medical care. These organisations are, however, involved in several specific issues that are relevant to the prescription of medicines to children. The proposed Regulation may have an impact on the quality of the medical care available to children, on research and development of medicines for both common and rare diseases, and on the way in which research is being conducted.

Health insurers

Another group of stakeholders that may be affected by the Regulation are health insurers. Health insurers are involved in the reimbursement of prescribed drugs. The way in which national health care systems have arranged the reimbursement of health care costs in general (e.g. public and/or private health insurance system) differ. At the European level the following organisation focuses on insurance issues:

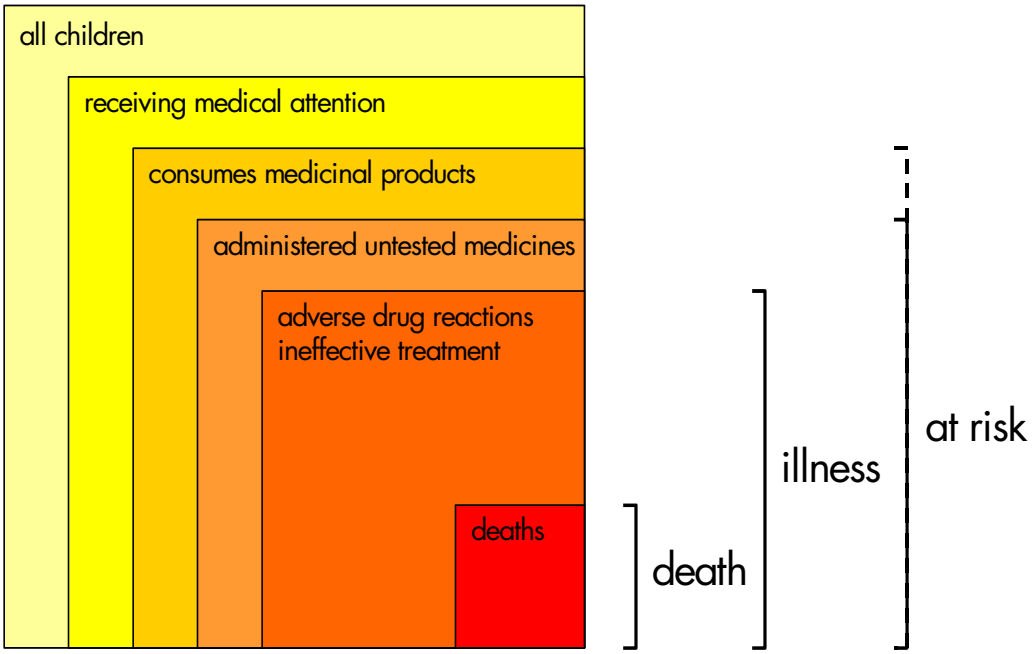
- **Comité Européen des Assurances (CEA).** CEA is the European federation of national insurance associations. The CEA represents the common interests of European insurers by promoting, defending and illustrating their views in international bodies, encourages cooperation between member national associations. CEA's involvement in the field of medicinal products for paediatric use is very limited. However, its members may be impacted by the draft Regulation. (http://www.cea.assur.org/)

Research community

Finally, we identified the research community as a group of stakeholders that may be affected by the Regulation. The following organisation represents the medical research community on a European level:

- **European Network for Drug Investigation in Children (ENDIC).** ENDIC is a European professional organisation facilitating both clinical and scientific research into medicines for children. Its primary objectives are to "promote research in the field of paediatric pharmacology" and to "offer a forum for exchanges between pharmacologists and clinical physicians about more adequate drug administration in this population". (www.vct.be/demo/ esdp/homeset.html)

Figure 3.1
The composition of the child population relevant to the use of untested paediatric medicines



The current extent of the problem

Lack of paediatric testing and the size of the affected paediatric population

A substantial proportion of medicines is prescribed to children in the absence of sound scientific evidence regarding the effectiveness of the drugs (Geesink, Van Beusekom, Van het Loo et al, 2002). Recent studies (e.g. Turner, Nunn, Fielding et al, 1998; Conroy, McIntyre, Choonara, 1999) have shown that many drugs prescribed to children in paediatric and especially neonatal care are not licensed for children or are prescribed off-label ('t Jong, Eland, Sturkenboom et al, 2002). Although off-label does not necessarily cause adverse events, there are certainly examples of situations in which ADRs have occurred ('t Jong, Eland, Sturkenboom et al, 2002).

The purpose of licensing a drug is to ensure that adequate standards of quality, safety and efficacy are met. In the absence of paediatric drug research, a product licence is not granted and scientific evidence regarding the quality, safety and efficacy may be lacking.

The availability of a licensed product does not guarantee appropriate prescription of medicines to children. Medicines may also be prescribed off-label –i.e. outside the terms set in the product licence– and may be prescribed off-label in relation to age, indication, dose or frequency, route of administration, or formulation.

For children the nature of the problem has three degrees of severity:

- *Risk*: the consumption of untested medicines can but need not lead to illness or death.
- *Illness*: adverse drug reactions (for example, when dosage or frequency are inappropriate for use in children); sub-optimal or ineffective treatment (for example, when more effective but untested medication is denied or when dosage is too low).
- Death or severe long-term impairment.

Table 3.1
Size of the population in the age groups between 0 and 19 in the total population of the EU-15 and the 12 NAS-countries in 2003 (millions)

	EU-15	NAS-10	Bulgaria Romania
0-4	19.9	3.7	1.5
5-9	20.4	4.0	1.5
10-14	21.8	5.0	1.9
15-19	22.2	5.6	2.2
Total	84.3	18.3	7.0
Population	380.1	74.8	29.8
Population share of 0-19	22.2%	24.5%	23.6%

Note: The paediatric population comprises the age groups from birth to 18 years, so the estimates in this table slightly overestimate the size of the paediatric population.
Source: US Census Bureau, International Database.

How many children fall into each of the categories of the types of effect and the degrees of severity? The first task of the measurement of the extent of the problem would be to obtain estimates of the numbers of children that are put at risk by the use of unlicensed and off-label medicines, those experiencing a decline in their quality of life due to adverse drug effects and ineffective treatment, or those who died as a direct result of the use of medicines untested in children or because effective medicines were not available. Figure 3.1. provides a schematic view of the paediatric population relevant to this problem.
The EU, the NAS countries, and Bulgaria and Romania combined have over 100 million children in the age range of 0 to 19. This represents 22.2% of the EU population and 24.2% of the population of the NAS-12 countries in 2003 (Table 3.1.).
Since every child is occasionally ill and needs some form of medication, the population that is potentially affected by the Regulation is substantial.

Health care services provided to the paediatric population

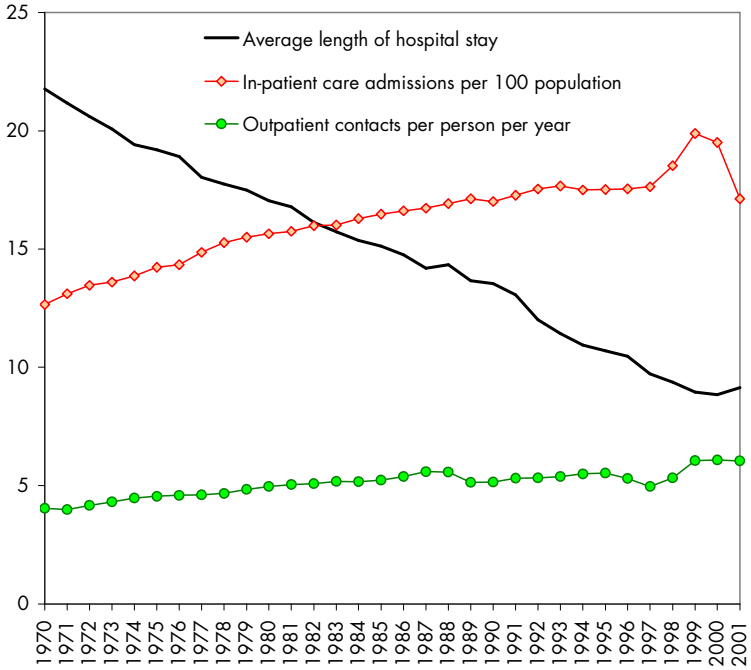
Statistical information about medical treatment on a high level of aggregation generally relates to the total population that receives health care. In addition, it is fairly difficult to estimate the number of individual patients rather than the number of cases. However, for some specific disorders there are data regarding resource utilisation in children (e.g. in-patient resource utilisation in asthmatic children: Valovirta, Kocevar, Kaila et al, 2002).
The best age-specific aggregate data are available for the United Kingdom. Table 3.2. presents a summary for the year 2001. The data show that adults – and especially those over 55 – account for the greater part of hospital treatment in terms of the number of patients, persons and bed-days. Children in the age groups 1-4, 5-14 and 15-24 comprise 14.6% of hospitalised patients, 17.2% of hospitalised persons, and only 7.7% of bed-days. Similar data for Spain show that patients under the age of 24 represent 16.6% of the total hospital population.
More useful is the comparison of hospitalised persons with the number of people in each relevant age group. In the United Kingdom, the rate of hospitalisation, the annual number of hospitalisations per person, and the average duration of treatment clearly go up with age. In 2001 about 5.5 per 1,000 persons younger than 24 years received hospital treatment.

Table 3.2
Total number of admissions in hospitals by age in the United Kingdom, 2001

Age	Hospitalised patients [a]		Number of persons hospitalised		Hospitalisations per person	Number of bed-days		Average bed-days per patient	Persons hospitalised per 1,000 persons in the age group
	Number	% of total	Number	% of total		Number	% of total		
1-4	46,984	4.6	30,040	5.0	1.6	129,817	2.4	2.8	8.9
5-14	42,958	4.2	30,396	5.1	1.4	111,991	2.1	2.6	4.0
15-24 [b]	58,518	5.8	42,462	7.1	1.4	173,450	3.2	3.0	5.5
25-34	131,434	13.0	94,809	15.9	1.4	451,092	8.4	3.4	11.7
35-44	105,920	10.5	70,966	11.9	1.5	391,739	7.3	3.7	7.6
45-54	108,647	10.7	64,108	10.7	1.7	497,048	9.2	4.6	8.3
55-64	139,237	13.8	74,036	12.4	1.9	767,430	14.2	5.5	11.0
65-74	152,820	15.1	75,324	12.6	2.0	1,010,901	18.7	6.6	15.3
75-84	154,757	15.3	77,507	13.0	2.0	1,227,762	22.7	7.9	23.0
85 and over	70,948	7.0	38,191	6.4	1.9	636,990	11.8	9.0	33.6
TOTAL	1,012,223	100	597,839	100	1.7	5,398,220	100	5.3	9.9

[a] The number of hospitalised patients is equal to the number of persons hospitalised multiplied by the number of hospitalisations per person.
[b] This high figure, as well as the next one to a lesser extent, includes maternity admission.
Source: Annual Statistical Abstract 2003.

Figure 3.2
The average annual number of out-patient contacts per person, in-patient care admissions per 100 inhabitants, and the average length of a hospital stay in days in the EU-15, 1970-2001



Note: The estimates are the un-weighted average of the data for the countries for which information is available. When the time series for a specific country stopped short of 2001, it was extrapolated by applying the ratio between its values and the values for the countries for which the data were complete in the last five years of the country's time series.
Source: WHO Health for All Database, 2003.

In the last thirty years the average length of a hospital stay has steadily declined from more than 20 days per patient in 1970 to just under 10 days in 2001. At the same time the number of health care contacts inside and outside the hospital has gradually increased (See Figure 3.2.). This reflects two tendencies in health care:

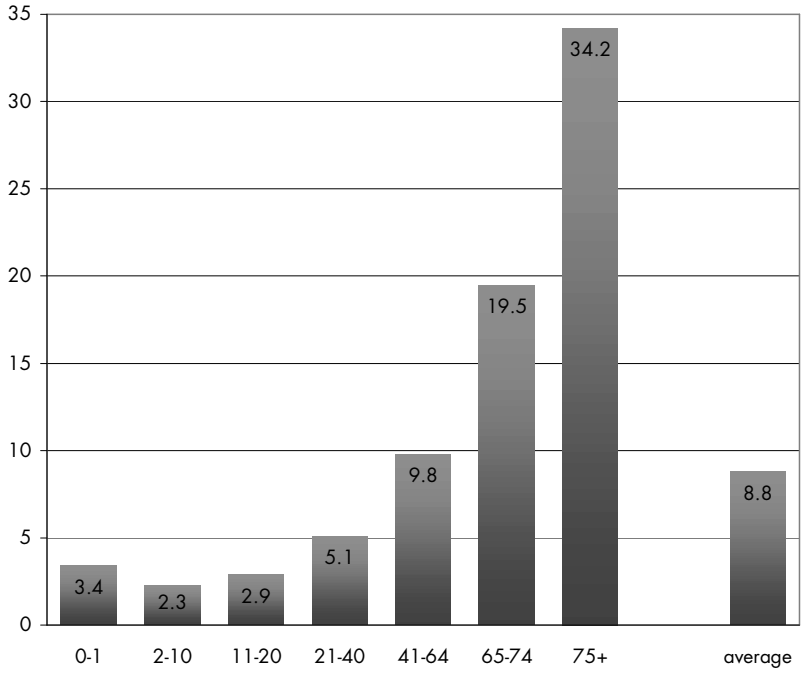
- *Demographic ageing* continuously increases the population share of the age groups that require more frequent and more intensive treatment. It is quite likely that demographic ageing partially explains the increasing number of health care contacts.
- *Increases in health care efficiency and advances in medical technology* have made it possible to treat patients quicker, more effectively, and in their own home rather than in a hospital. This may account for the reduction in in-patient days and for the decline in the average length of hospital stay.

It is, however, important to note that neither tendency significantly affects the problems surrounding the medicinal treatment of the paediatric population. However relatively small their population share may be or may become, children still require adequate and safe medication, and so this remains an important problem.

The consumption of medicinal products

There exist aggregate data on daily drug doses (DDDs) by type of medicine (OECD Health Data, 2003), but to get more specific information on individual products and on the type of medicines (licensed, not licensed for children, and off-label), case studies and piece-meal statistics have had to be used.

Figure 3.3
Annual number of prescriptions by age in the Netherlands, 2002



Source: Stichting Farmaceutische Kengetallen, Data en feiten 2003, p. 17.

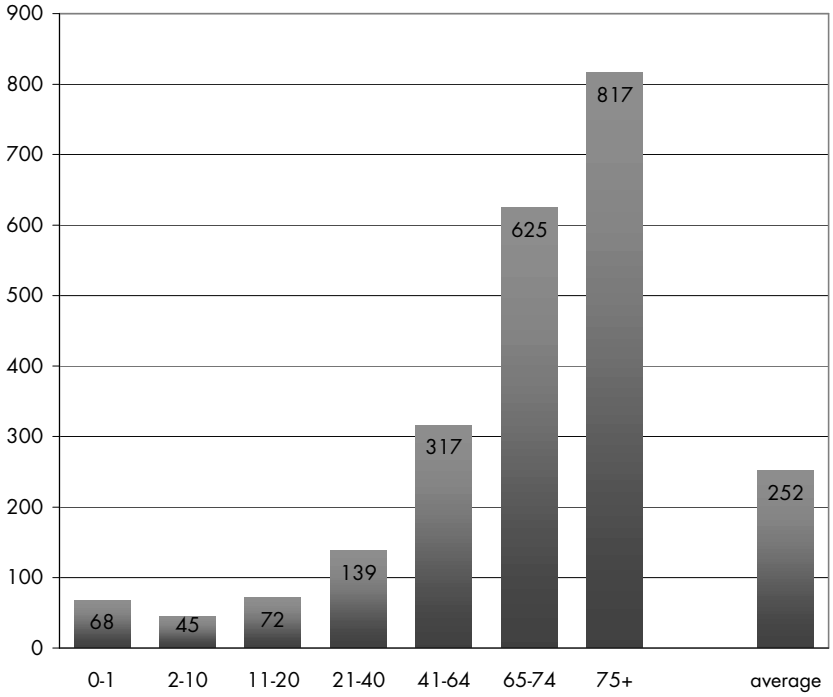
The figure below presents the number of prescriptions by age in the Netherlands. It appears that the number of prescriptions in children (the age groups between 0 and 20) is relatively low compared to that of the elderly. Similar numbers were found for the US: in 1997 the annual number of prescriptions by age was 4.13 for children under the age of five years and 1.50 for children and adolescents (5-24).;
Expenditure on pharmaceuticals by age is presented in the Figure 3.4. These data show that the average amount spent on pharmaceuticals per child is well below average spending per capita (roughly 70 to 80% lower).

Off-label and unlicensed use of medicines

Health care professionals throughout Europe use medicines that are either not licensed for use in children (hereafter called unlicensed) or that are prescribed off-label, i.e. outside the terms of a product licence (i.e. at a different dose, for a different indication, or by an alternative route) (Geesink, Van Beusekom, Van het Loo et al, 2002).[7] It also appears that off-label prescriptions are more common than prescriptions of medicines that are not licensed for use in children (Hekster, Lisman, Heijmenberg et al, 2000). Several studies describe off-label prescription and use in paediatric wards and general practice, of which some are summarised in the following table.

[7] Examples of off-label drugs include diazepam rectal solution used in children younger than one year (not licensed for age group), amiloride tablets in all children (formulation), rectal injection of lorazepam used in a child with an acute seizure (route). An example of unlicensed use is the preparation by the hospital pharmacy of a suspension made of crushed tablets (Conroy, Choonara, Impicciatore et al, 2000).

Figure 3.4
Expenditure on pharmaceuticals by age in the Netherlands, 2002 (€)



Source: Stichting Farmaceutische Kengetallen, Data en feiten 2003, p. 17.

It can be concluded from Table 3.3. that the share of off-label prescription is higher than the share of unlicensed prescriptions, both in hospitals and in general practice. It also appears that the percentage of patients receiving unlicensed or off-label treatment is higher in hospitals than in general practice.

More specific information can be found in the articles. Choonara and Conroy (2002) have investigated studies throughout Europe and have found that at least one-third of children in hospital and up to 90% of neonates in a neonatal intensive care unit receive either an unlicensed or off-label drug. The medicines that are most frequently used off-label include analgesics, antibiotics and bronchodilators. Other studies found varying degrees of unlicensed and off-label use of medications in children. Off-label and unlicensed prescriptions in hospitals occur in percentages ranging from 7% (Thompson and Heflin, 1987) to 52.9%, while the median percentage is around 40% (Chalumeau, Treluyer, Salanave et al, 2000).

Hospitals off-label prescriptions are much higher compared to off-label prescriptions in general practice ('t Jong, Eland, Sturkenboom et al, 2002). For example, in a study in a single general practice amongst all prescriptions (3347) for children (12 years and under), 1175 were analysed retrospectively for one year. The authors found that 84.5% of the prescriptions were for licensed medicines. Unlicensed use was reported for 0.3% of the prescriptions. From 361 unlicensed or off-label prescription items, 320 (89%) were off-label with respect to dose, representing 9.6% of the total prescription items (McIntyre, Conroy, Avery et al, 2000).

Table 3.3
Summary statistics based on a number of case studies of unlicensed and off-label prescriptions to children

	Mean	Standard deviation	Median	Minimum value	Maximum value	Number of studies
HOSPITAL WARDS						
Mean number of prescription per patient, #	4.6	2.0	4.2	2.1	9.0	11
Unlicensed prescriptions, %	14.5	17.0	7.0	0.3	48.0	11
Off-label prescription, %	36.6	18.8	38.0	7.0	66.0	12
Patients receiving unlicensed or off-label treatment, %	63.1	26.4	62.0	16.0	91.6	10
GENERAL PRACTICE						
Mean number of prescription per patient	3.2	0.5	3.2	2.6	3.8	6
Unlicensed prescriptions, %	16.4	11.6	16.6	0.3	33.0	5
Off-label prescriptions, %	18.2	7.1	16.9	10.5	29.0	6
Patients receiving unlicensed or off-label treatment, %	35.0	29.8	35.0	13.9	56.0	2

Source: Table 3.4.

However, exact numbers and data about the most frequently prescribed drugs differ enormously both between countries and between studies performed within a single country.[8] This is also true for the kind of unlicensed drugs prescribed. In addition, studies differ in incidence figures of unlicensed and off-label prescriptions of age groups (e.g. McIntyre, Conroy, Avery et al, 2000 could not identify a difference in the incidence of unlicensed or off-label prescribing between age groups in general practices). Schirm, Tobi and De Jong-Van den Berg (2003) found evidence that unlicensed drug use in Dutch children outside the hospital is the highest among 0-1 years old, and off-label drug use is the highest among 12-16 year olds. In Germany the proportion of off-label prescriptions in primary care was highest for 1-2 year olds and lowest for 7-11 year olds (Bücheler, Schwab, Mörike et al, 2002).

Table 3.4. gives an overview of recent studies that have reported on the extent of unlicensed and off-label prescription in the paediatric population. The table shows that unlicensed and off-label prescription of medicines was found in all studies, but that differences in the extent of unlicensed and off-label prescription exist among countries, among hospitals within a country, and among hospital departments (e.g. paediatric wards and intensive care units - ICUs).

[8] E.g. In the Netherlands, the drugs most often prescribed unlicensed or off-label in general practices were fusidic acid (opthalmological gel), salbutamol (aerosol), deptropine citrate, amoxillin and flucticasone (aerosol) ('t Jong, Eland, Sturkenboom et al, 2002). In the UK, the ten most often prescribed unlicensed or off-label drugs were penicillin, beclometasone, amoxillin, chloramphenicol and paracetamol (McIntyre, Conroy, Avery et al, 2000). These are all established drugs for which there is a large amount of clinical information available. Little information is available about the risk of such off-label prescribing, but the authors suggested that there is an increased risk of toxicity (Geesink, Van Beusekom, Van het Loo et al, 2002).

Table 3.4
A survey of studies reporting the use of off-label and unlicensed medicines in children

Author	Setting	Age group	Mean No of prescriptions per patient	No (%) of unlicensed prescriptions	No (%) off-label	No (%) of patients receiving unlicensed or off-label treatment	Indication (diagnosis)
Conroy, Choonara, Impicciatore et al, 2000	General paediatric medical wards in UK + Italy (general), Sweden + Germany (mixture of general and respiratory cases) and Netherlands (cardiac, oncological, renal and respiratory disease) (cardiac, oncological, renal and respiratory disease)	Derby: 21 days-16 years	4.2	58 (7)	181 (23)	109 (57)	Was studied, but not reported
		Uppsala: 4 days –15 years	2.1	8 (4)	49 (26)	37 (43)	
		Marburg: 28 days – 16 years	2.6	8 (4)	83 (37)	46 (54)	
		Bergamo: 30 days –12 years	3.4	1 (0.3)	263 (66)	101 (86)	
		Rotterdam: 4 days – 16 years	4.6	89 (14)	296 (45)	128 (90)	
		Total	3.6	164 (7)	872 (39)	421 (67)	
Turner, Longworth, Nunn et al, 1998	Regional children hospital in the UK: Paediatric medical and surgical wards	4 days-20 years	2013 for 609 patients: median number of drugs was 2 on surgical and 1 on medical ward	Total: 139 (7) Surgical ward: 64 Medical ward: 75	Total: 367 (18) Surgical: 201 Medical: 166	36% of children in 707 admissions – one or more drugs in 256 admissions	Diagnosis was recorded
Turner, Nunn, Fielding et al, 1999	Five different paediatric wards in a regional children's hospital for 13 weeks		4455 courses to 936 patients in 1046 admissions	Total: 507 (48%)			
't Jong, Vulto, de Hoog et al, 2000	Children hospital in the Netherlands: one	0-17 years	2139 for 238 children	1024 (48)	390 (18)	218 received one or more	Not described

Table 3.4
A survey of studies reporting the use of off-label and unlicensed medicines in children

Author	Setting	Age group	Mean No of prescriptions per patient	No (%) of unlicensed prescriptions	No (%) off-label	No (%) of patients receiving unlicensed or off-label treatment	Indication (diagnosis)
	medium care and three intensive care units					courses of an unapproved drug	
Thompson, Heflin, 1987	Paediatric hospital		951 drug orders		62 (7)		
Avenel, Bomkratz, Dassieu et al, 2000	Neonatal intensive care unit (1998)	0-128 days	40 babies: 257 prescriptions relating to 55 drugs	26 (10)	Premature infants (62) Newborns (64)		
McKinzie, Wright, Wrenn, 1997	US University Hospital: Paediatric Emergency Department		359 children		(43)	Of 296 children discharged with medication, 16% received off-label prescriptions	
Conroy, McIntyre, Choonara, 1999	Neonatal intensive care (1998)	26 weeks-37 or more weeks gestation	455 prescriptions for 70 babies: median: 3.5	45 (9.9)	249 (54.7)	63 (90)	Diagnosis was recorded, not published
Chalumeau, Treluyer, Salanave et al, 2000	French office based paediatric practice in Paris area (n=95): private practitioners in non-hospital settings	2 days-15 years	2522 prescriptions for 989 patients	99 (4) Total: 844 (33)	745 (29) Off label use in age groups: Neonates: 70% Infants: 27%	550 (56) received one or more off-label prescriptions	Vaccination: 63/385 Fever: 19/328 Common cold: 106/259 Rickets prevention:

Table 3.4
A survey of studies reporting the use of off-label and unlicensed medicines in children

Author	Setting	Age group	Mean No of prescriptions per patient	No (%) of unlicensed prescriptions	No (%) off-label	No (%) of patients receiving unlicensed or off-label treatment	Indication (diagnosis)
					Children: 31% Adolescents: 36%		49/253 Dental caries prevention: 15/172 (off-label/ prescriptions)
Schirm, Tobi, de Jong-van den Berg, 2002	Community in Netherlands (pharmacist database)	0-16 years	Total: 68019 for 19283 children	11288 (16.6)	15453 (22.7)	Unknown	Not available, and therefore not studied
Bücheler, Schwab, Mörike et al, 2002	Primary care in Germany	0-16 years, divided by age groups: 0-11 months 1-2 years 3-6 years 7-11 years 12-16 years	Total 1.74 million for 455661 children 1-2 years: 68791 (17.9) 7-11 years: 40539 (10.5)	Not specified in database – not reimbursed	210528 (13.2)	Not described	No diagnosis in database
' t Jong, Eland, Sturkenboom, et al, 2002	Primary care in Netherlands (150 general practitioners)	0-16 years	17453 prescriptions for 6141 (45.7) children	2667 (15.3)	2381 (13.1)	Overall risk of receiving unlicensed or off-label prescription was 13.9 per consultation	Not described
Schirm, Tobi, de	Community in the	0-16 years divided	66222	11288 (16.6)	13659 (20.6)	Unlicensed	Not available

Table 3.4
A survey of studies reporting the use of off-label and unlicensed medicines in children

Author	Setting	Age group	Mean No of prescriptions per patient	No (%) of unlicensed prescriptions	No (%) off-label	No (%) of patients receiving unlicensed or off-label treatment	Indication (diagnosis)
Jong-van den Berg, 2003	northern part of the Netherlands	into age groups: 0-1 years 2-5 years 6-11 years 12-16 years	prescriptions for 18943 children	0-1: 13226 (34.7) 2-5: 15668 (17.3) 6-11: 19140 (12.0) 12-16: 18171 (8.4)	0-1: 13226 (18.9) 2-5: 15668 (16.4) 6-11: 19140 (18.8) 12-16: 18171 (27.4)	drug use is highest among 0-1 years Off-label highest among 12-16 years	
McIntyre, Conroy, Avery et al, 2000	Single general practice (suburban) in English Midlands	0-12 years 0-5 years: 865 6-12: 1807	3347 prescriptions for 1175 children Status of 158 prescriptions unknown Median no of prescription per child: 2	10 (0.3) 0-1 yr: 491 prescriptions: 76 unlicensed/off-label	351 (10.5)	No significant difference in the incidence of off-label/ unlicensed between age groups	Not possible to determine whether drugs were used for licensed indication
Martin, Wilton, Mann et al, 1998	General practices (100) in the UK (1992-1996)	Prescription of SSRI to children aged 12 and under	25 children who met criteria	Most common prescribed antidepressant is not recommended by the British National Formulary			Reason for prescription

Adverse drug reactions (ADRs) and ineffective treatment

Due to well-known difficulties in the access to and expense of testing diverse populations, most drugs are developed and tested in young to middle-aged adults (Conroy, McIntyre, Choonara et al, 2000). Differences exist between young and old people regarding their response to medicines (pharmaco-dynamics) and the way they handle medicines (pharmacokinetics). The dosage of the drug is one of the factors that determines whether its effect is therapeutic or toxic, while the route and interval of administration may have a sizeable impact on the onset and duration of the pharmacological effects of each given dose. Unlicensed and off-label prescriptions do not necessarily threaten the health of a child, but the risk of ADRs is high, since adequate dosing schemes have often not been assessed (Turner, Nunn, Fielding et al, 1999). Moreover, inadequate doses may lead to insufficient therapeutic effects and therefore do not effectively treat patients. Often doses for children are derived from adult doses, simply by reducing the dose (based upon surface area or body weight). This can lead to therapeutic accidents (e.g. overdose of morphine). The effects of medication (particularly when used chronically) on physical and cognitive development are also of concern (Geesink, Van Beusekom, Van het Loo et al, 2002).
ADRs are undesired effects arising from the appropriate use of medications, which may have profound immediate, delayed, and long-term implications regarding neurological and somatic development of a child. There is an ongoing discussion in the medical literature on the classification of ADRs. A simple, often used, classification is that between Type A and Type B reactions (Rawlins and Thompson, 1977):

- *Type A*: dose-dependent and predictable from the known pharmacology of the drug.
- *Type B*: not dose-dependent and unpredictable.

This classification has gradually been expanded to other alphabetically labelled types, including Type C (dose- and time-dependent (chronic) reactions), Type D (delayed reactions), Type E (withdrawal reactions), and type F (failure of therapy) (Aronson, 2002). In a recent study, Aronson and Ferner (2003) propose a three-dimensional classification system based on dose relatedness, timing and patient susceptibility.
There is a lack of systematic attention to ADRs in children, and incidence estimates (mostly limited to hospitalised children in the US and UK) differ widely (Impicciatore, Choonara, Clarkson et al, 2001). The recording of the prevalence of ADRs for off-label and unlicensed drugs in terms of percentage of related prescriptions is limited. However, there are some articles that describe this issue, based upon spontaneous reporting. Menniti-Ippolito, Raschetti, Da Cas et al (2000) studied ADRs in children in general practice. The report rate (not equal to incidence due to underreporting) was 15.1 ADRs per 1.000 children in the period April 1996 to March 1997 in a population of 24.000 registered children. None of the ADRs resulted in a hospital admission. Table 3.5. shows that ADRs in children (0-14) in Spain are most frequently reported in the age group 1-4 years old (Morales-Olivas, Martinez-Mir, Ferrer et al, 2000).

Table 3.5
The reporting of ADRs by age in Spain, 2000

Age (years)	% of reports
<1	12.8
1-4	37.9
5-9	25.0
10-14	24.3

Source: Morales-Olivas, Martinez-Mir, Ferrer et al, 2000

This study also gave an impression of the medicines associated with frequent ADRs. Antibiotics had the highest number of reports (about 40%) followed by respiratory tract drugs (23%) and digestive tract drugs (10%). The authors suggest that this is due to the fact that antibiotics and respiratory tract drugs are widely used in children. In addition, the authors state that these data may be "biased and incomplete", because the Sistema Espanol de Farmacovigilancia is a voluntary reporting scheme. Because sometimes there is ambiguity about whether the reporting schemes cover off-label and unlicensed use, this may discourage reporting.

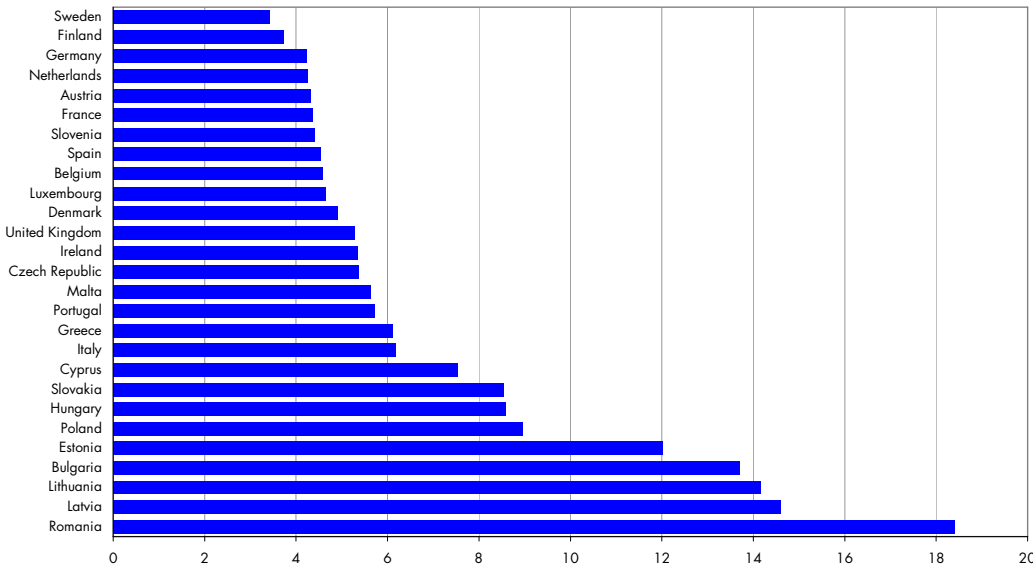
Turner, Nunn, Fielding et al (1999) carried out a study to determine the incidence of ADRs to unlicensed and off-label drugs used in five different paediatric wards in a regional children's hospital in the UK. The authors found a small statistically non-significant increase in ADRs when medicines were used off-label or unlicensed - that is interesting but may be due to chance or because the study was not of sufficient size to detect a statistically significant difference. It appeared that ADRs occurred in 116 (11%) of the 1046 patient admissions. The ADRs were associated with 112 (3.9%) of the 2881 licensed drug prescriptions and with 95 (6%) of the 1574 unlicensed or off-label drug prescriptions.

Lazarou, Pomeranz, Corey (1998) conducted a meta-analysis of prospective studies on the incidence of ADRs in hospitalised patients in the US. Although the study did not focus on children, it gives an impression of the incidence of serious and fatal ADRs in hospital patients. The study concluded that the overall incidence of serious ADRs was 6.7% (95% CI, 5.2%-8.2%) and of fatal ADRs was 0.32% (95% CI, 0.23%-0.41%) of hospitalised patients. The authors estimate that in 1994 overall 106,000 (76,000 – 137,000) patients in the US had fatal ADRs, making these reactions between the fourth and sixth leading cause of death.

In a more recent article by Choonara and Conroy (2002), studies focusing on the effect of unlicensed and off-label drug use, in relation to toxicity have been reviewed. Although the results of some studies suggest that the percentage of unlicensed and off-label drug use was associated with the risk of an ADR (one out of three studies found a significant relation), the risk of prescribing off-label and unlicensed drugs in children is not clear from the limited data available. It is, however, recognised that ADRs resulting from unlicensed or off-label drug use are a considerable problem because it generates more ADRs among children (Turner, Nunn, Fielding et al, 1999).

Conroy, McIntryre, Choonara et al (2000) discuss the lack of a framework to collect information on ADRs to unlicensed and off-label drugs. Data sources for the conduct of pharmacovigilance include: spontaneously reported ADRs, periodic safety update reports from pharmaceutical companies, data on the use of medicines, clinical trials and epidemiological studies. The current EU pharmacovigilance system is organised with some functions, responsibilities and accountability falling to the Member State competent authorities and others falling to the EMEA and European Commission. The Member States currently play a key role in the collection of data, from health care professionals, from academic institutions and from pharmaceutical companies. The EMEA also collects data particularly from pharmaceutical companies and the

Figure 3.5
Infant Mortality Rate in European countries in 2003 (per 1,000 in relevant age groups)



Source: US Census Bureau, International Data Base.

Member States. Although Member States are responsible for many aspects of data management, a Community pharmacovigilance database, Eudravigilance, is operational and being further developed.

Although there are some systems in place to collect information on ADRs, these systems generally depend on spontaneous reporting by healthcare professionals. It is known from the literature (e.g. Eland, Belton, van Grootheest et al, 1999; Hasford, Goettler, Hunter et al, 2002) that ADRs are underreported for several reasons. These reasons include uncertainty as to whether the reaction was caused by the drug, the ADR being too well known, or the ADR being trivial. Although there is no evidence to support this, it is also considered that reporting for off-label and unlicensed use of medicines may be reduced because of concern by medical practitioners about the legal liability they may face from an ADR resulting from off-label or unlicensed use of a medicine.

Mortality rates and ADRs as a cause of death

The causes of death by age group are readily available (e.g. from the WHO *Health for All Database* 2003 and the WHO *Statistical Information System*), although some of the main categories directly relevant to our objectives are often hidden in compound categories (see Figure 3.5. below). An additional problem is that the international data are not entirely comparable, especially for such ambiguous causes as accidental poisoning and ADRs.

The available statistics on the causes of death by age group suggest that very few children die as a result of ADRs (see Table 3.6.). The figures also show that there are considerable national differences within the EU-15. Some countries record almost no ADR-related deaths (Austria, Denmark, Finland, Greece, Ireland, Italy), while large countries such as France and Germany report hundreds, and Italy and the UK – countries of comparable size – report only a few dozen (19 and 46 cases).

The large international differences are to an important degree due to the quality of the statistical material. Statistics on the causes of death cannot be used without mentioning two major shortcomings:

Table 3.6
Adverse drug effects as a cause of death in the EU-15, 1999 (deaths per million population)

	Entire population	0-24 year olds
Austria	0.12	0.00
Belgium	3.05	0.00
Denmark	0.19	0.00
Finland	0.00	0.00
France	11.07	0.32
Germany	6.27	0.50
Greece	0.00	0.00
Ireland	1.34	0.00
Italy	0.33	0.13
Luxembourg	18.48	0.00
Netherlands	2.72	0.62
Portugal	1.30	0.31
Spain	3.94	0.49
Sweden	8.13	0.00
United Kingdom	0.77	0.11

Source: WHO Mortality Database.

- Underreporting and misrepresentation of causes can distort the numbers. It is quite likely that hospital errors in medication that lead to ADRs are classified under the patient's main disease for which he or she received medication. The motives for underreporting can be related to current medicinal practices (deaths are recorded under the disease rather than the ADR, because ADRs are seen as an accepted risk of treatment) or to concerns over liability over an ADR-related death. The real number of deaths is most likely considerably higher.
- The data relating to different countries are not comparable. Although there is general agreement on a classification of causes of death, the various countries seem to use their own interpretation, especially of the more ambiguous causes (such as adverse drug effects).

Data from the WHO *Statistical Information System* show that in the EU in 1999 only a small number of people of 18 years or younger died as a result of ADRs. However, the study by Lazarou, Pomeranz, Corey (1998) regarding ADRs in hospitalised patients in the US draws the opposite conclusion, stating that ADRs are the fifth largest cause of death. Although the data from Lazarou, Pomeranz and Corey suggest that ADRs represent an important clinical issue, its value to the European context is limited. The authors explicitly state: "the studies included in the meta-analysis were only representative for the United States" (p. 1202). More importantly, they do not distinguish between children and adults. Even though it is unclear to what extent the hospital populations of the US and the EU are comparable, it is safe to assume that the true magnitude of the problem is considerably larger than mortality data indicate. In short, currently available evidence for the EU consequently does not allow for definitive conclusions on the incidence of ADRs in children.

Table 3.7
Hospital and retail sales of pharmaceuticals in the EU and other non-EU countries for the years 2000-2002 (in million Euros)

	2000	2001	2002	Increase 2000-2002
Austria	2,713	4,701	5,127	89%
Belgium	3,161	4,944	5,296	68%
Denmark	1,563	1,690	1,920	23%
Finland	1,632	1,768	1,955	20%
France	21,617	29,996	30,942	43%
Germany	28,070	34,591	37,336	33%
Greece	2,572	2,108 [a)]	2,659 [a)]	3%
Ireland	879	1,050 [a)]	1,234 [a)]	40%
Italy	15,857	22,795	24,088	52%
Luxembourg	[b)]	[b)]	[b)]	
Netherlands	3,949	4,579	5,022	27%
Portugal	2,408	2,610 [a)]	2,821 [a)]	17%
Spain	9,140	13,260	14,657	60%
Sweden	2,576	2,748	2,958	15%
United Kingdom	13,267	19,946	21,959	66%
Total EU-15	**109,404**	**146,786**	**157,974**	**44%**
Czech Republic	792	1,084	1,307	65%
Hungary	917	1,355	1,700	85%
Poland	3,488	4,133	4,110	18%
Romania	469	568	647	38%
Slovak Republic	521	599	631	21%
Slovenia	292	349	362	24%
Croatia	710	634	844	19%
Norway	1,269	1,419	1,511	19%
Switzerland	2,909	3,752	4,174	43%
Other non-EU countries	**11,367**	**13,893**	**15,286**	**34%**
EUROPE	**120,773**	**160,679**	**173,260**	**43%**

[a)] retail sales only; [b)] missing data.
Sources: AESGP, 2003; IMS Health, 2001; 2002.

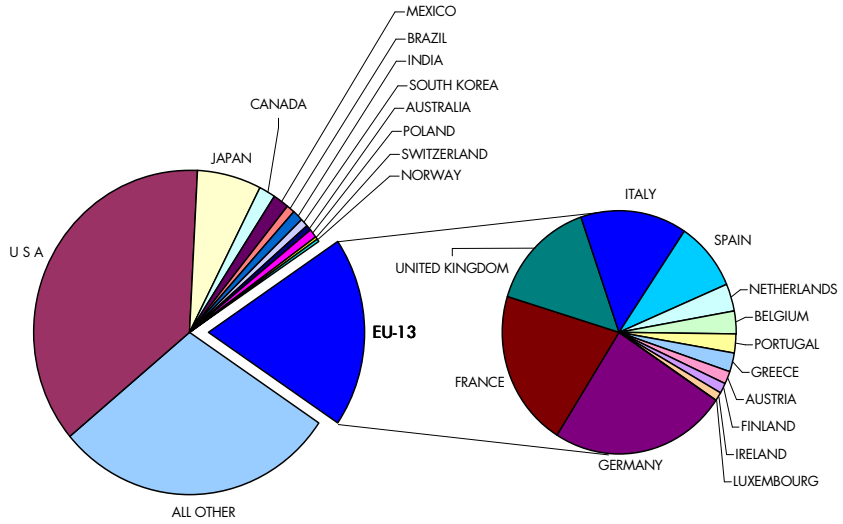
The pharmaceutical industry

The companies that fund and perform R&D that results in new medicines are aware of their role in improving health, but in the end are driven by economics. Their investments have to be compensated for in the form of profit. The challenge for the pharmaceutical industry is to develop affordable medicines tested for use in children. However, the proposed Regulation raises concerns with respect the costs of development. Will the incentives be sufficiently attractive?
The size of the potential market for paediatric medicines appears to be shrinking in relative terms as a result of decreasing birth rates. However, it does not necessarily shrink in absolute terms. The total market for pharmaceutical products will most definitely grow, as it has consistently in recent history, and the enlargement of the EU with the NAS in Central and Eastern Europe will unlock new markets for EU producers and NAS producers alike. In the long run growth will probably be stronger in the market for medicines for geriatric use.

Supply and demand in the pharmaceutical market

Demand for pharmaceuticals can be measured on the basis of total health care expenditure, expenditure on medicines (total and paediatric), and expenditure on hospitals and other health care professionals. Aggregate data on health expenditure (Table 3.13.) have been used to estimate total expenditure in the 15 Members States of the EU in 2001 at:

Figure 3.6
Total pharmaceutical retail sales in 2002



WORLD SALES: C. $400 BILLION
EUROPEAN SALES: C. $88 BILLION

Note: The EU-13 refers to the EU-15 without Denmark and Sweden.
Source: IMS Data Overview.

- 862.8 billion Purchasing Power Parity (PPP)[9]$ in total health care expenditure (378.4 million people and 2,280 PPP$ per capita)
- 148.4 billion PPP$ in pharmaceutical expenditure (17.2% of health expenditure)

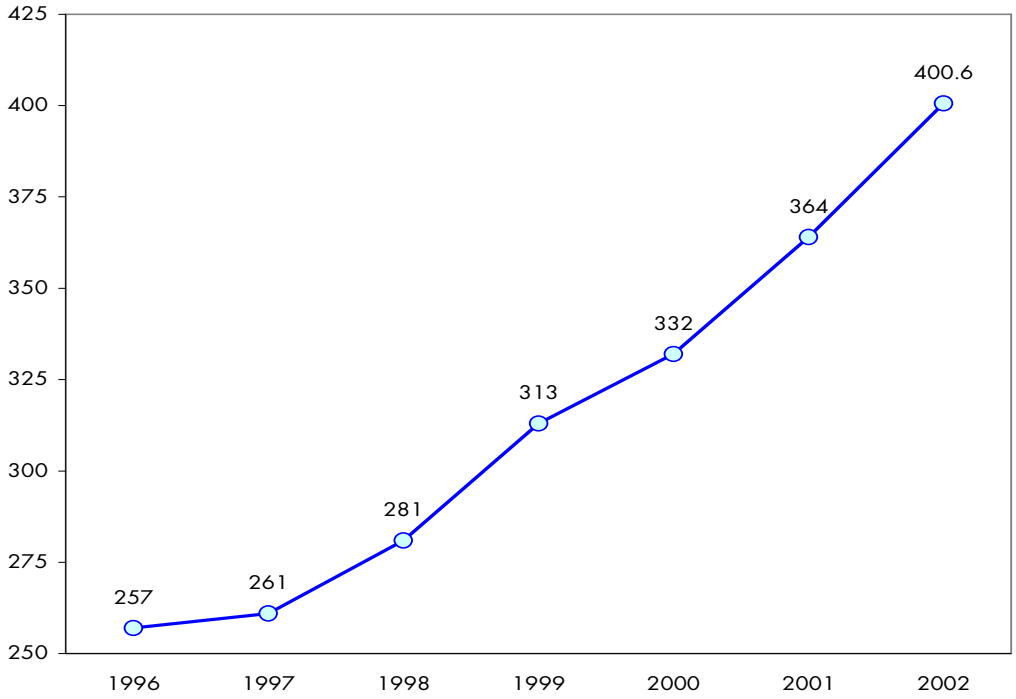
The estimate of pharmaceutical demand matches the available figures on wholesale and retail sales in the EU (Table 3.7.). In 2001 the sales of all medicinal products (including hospital sales) at public price levels (extrapolated from pharmacy purchase prices) and including Value Added Tax (VAT) in the EU amounted to €146.8 billion.

With a few exceptions (notably Greece, Sweden, and Portugal), pharmaceutical sales have increased rapidly since 2000. Overall sales have grown by 44%; some of the largest markets (Spain, Italy, the UK) have experienced above-average growth rates. Even though these figures are at current prices and therefore include inflation, the increase in pharmaceutical prices can only explain a modest proportion of the sales increase. In short, the pharmaceutical market is very large and highly dynamic.

The EU is responsible for 20% of worldwide sales (see Figure 3.6.). The US is the largest market. It dominates the world market in terms of total pharmaceutical sales, it is the largest market for generic medicines, and produces the largest proportion of new drugs (57% as against 25% for Europe). In 1997 the Food and Drug Administration Modernization Act (FDAMA) amended the Federal Food, Drug, and Cosmetic Act (FDCA), introducing the possibility of obtaining six

[9] Purchasing Power Parity refers to the equalisation of price levels across countries. The exchange rate between two countries should equal the ratio of the two countries' price level regarding a fixed number of goods and services. When the price level of a country increases (i.e. due to inflation), that country's exchange rate must depreciate in order to return to PPP (via fx.sauder.ubc.ca/PPP.html).

Figure 3.7
The development of the global pharmaceutical market, 1996-2002 (billions of dollars at constant prices)



months extension of market exclusivity or patent protection if a manufacturer submitted the proposed paediatric studies together with a Written Request to the FDA (FDA, 2001). This rule, known as the Paediatric Exclusivity Provision, will have aided US pharmaceutical companies in their competition with EU companies. Offering a similar incentive in the EU would contribute to reducing the declining opportunities presented by the domestic market of EU companies.

Government policies, i.e. the Paediatric Exclusivity Provision, that lead to longer periods of market exclusivity increase the amount of sales revenues; increased sales revenues lead to greater profits and potentially more funding for R&D (US International Trade Commission, 1991). The US paediatric market exclusivity provisions provided companies with the incentive to reap greater profits for R&D investment in this market, also because it granted market protection of the overall use of the drug. The Family Rights Association claims that the pharmaceutical industry was able to increase profits by billions of dollars[10]. In addition, US companies were able to build up a knowledge base and infrastructure for the conduct of clinical trials that put US companies at a competitive advantage to European companies. Europe's infrastructure for carrying out early-stage clinical trials in children is fragmented. Clinical centres may participate in multi-centre trials initiated in the US, but they would not necessarily have the expertise to carry out the trials alone. The proposed extension to SPCs[11] in the European market will provide a commercial incentive to pharmaceutical companies, and give some guarantee that profits may be redistributed to the development of a sound R&D infrastructure basis and general expertise that would put Europe in a more equal competitive position with the US. This is also because SPCs provide five years of marketing exclusivity after expiry of the patent, at a time when sales are high.

[10] http://familyrightsassociation.com/info/drugs/billions_testing_drugs_on_kids.htm

[11] A SPC is a compensation for the delays caused by the fact that pharmaceuticals have to go through clinical trials and an authorisation process.

Figure 3.7. shows the recent development of the world market for pharmaceutical products. In the future geriatric products will become a major growth sector. However, demographic ageing will not necessarily mean that the size of the market for paediatric medicines will decline, especially when more specialised medicines are made available.

The competition between originator and generic drugs

The producers of originator drugs –essentially the pharmaceutical companies that do fundamental research to discover new active substances, develop new drugs, new methods of administering medicines, etcetera– consider generic medicines as a major threat to their economic viability. Generic drug manufacturers begin their R&D process –which is based on the work of the producers of originator drugs– during the period of patent protection, so that their competition starts almost as soon as the patent has expired. Competition from generic drugs is increasing and the originator drug companies are concerned that the period during which they can exploit their patents and recover their R&D investments is shortening. On the other hand, once a patent runs out, the brand can continue. The originator drug company can then produce a generic version of its own innovative products and can consequently apply for a paediatric use marketing authorisation.

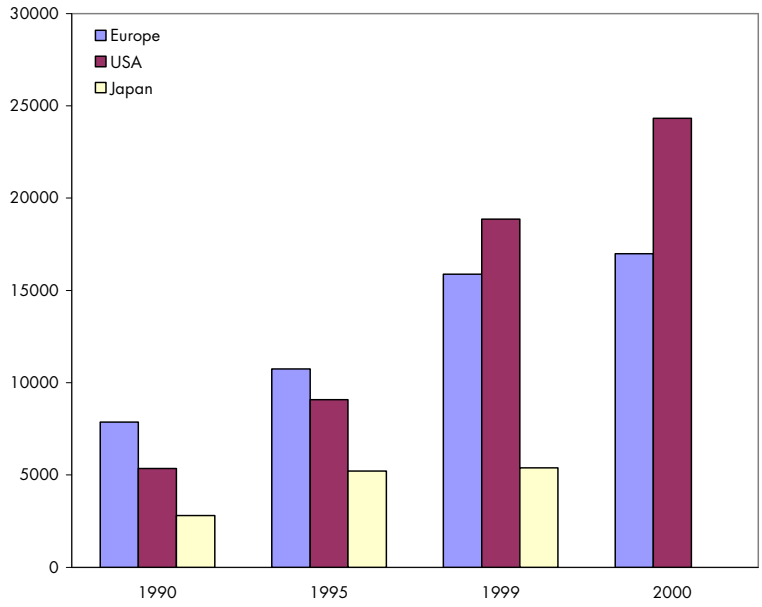
Generic drugs having the same active substance, are required to adhere to the same quality, safety and efficacy standards, and to the same stringent rules of production and pharmacovigilance. Since they contain the same active substances, preclinical and clinical trials are not needed. Producers of generics are, however, required to do a bioequivalence study to show that the generic drug is therapeutically equivalent with the original product. They must show that their product has no significant differences in the rate and extent of absorption into the human body. This may involve separate tests for the use in children. The difference in requirements between originator and generic drugs translates into the burden of R&D spending on turnover: originator drug manufacturers in the US spend about 16 to 18% of their turnover on R&D as against 6 to 8% for generic drug manufacturers. The production of patented and off-patent medicines is not separated strictly between originator drug companies and generic drug companies. However, manufacturers of originator drugs generally do not become generic drug manufacturers because of the hurdles in drug development.

Generics currently account for about 13% of the global market for medicinal products. Assuming that the same market share applies to Europe, the market for generic medicines amounts to c. €11.4 billion. This leaves 87% (or c. €76.6 billion) for patented products. The share of paediatric products in the total European market is estimated at 15% or c. €13.2 billion. Assuming that this percentage applies to both segments of the market, annual sales of off-patent paediatric medicines can be estimated at €1.7 billion and those of patented products at €11.5 billion.

The importance of generic products is not uniform throughout the EU. Their market shares vary widely between Member States. In Germany (41%), Sweden (39%), Denmark (22-40%), the UK (22%) generic products have captured a substantial proportion of the market. In the Netherlands generic products account for a modest share of medicinal sales (12%), while they make up 3 to 4% of the market in France and only 1% or less of the market in Italy, Spain and Portugal. Such national differences are intimately related to policy. For example, in such countries as the UK, Germany, the Netherlands and Denmark the use of generic products is encouraged as an instrument to counter the rise in pharmaceutical costs. In other countries (Spain, Greece, Italy and France) prices are low and the use of generic products is not actively promoted by health insurance organisations.[12]

[12] http://www.euractiv.com/cgi-bin/cgint.exe?204&OIDN=2000564&-tt=hh

Figure 3.8
Pharmaceutical R&D Expenditure 1990-2000 (millions of dollars)



Source: www.pharma-outsourcing.com/open/library

The costs of developing new medicines

A pharmaceutical company in the process of obtaining a licence for a new product, that will be marketed afterwards, has to make the following trade-off: do the additional earnings that will result from licences for paediatric indications justify the costs and risks of sponsoring the trial and of developing and maintaining the new paediatric formulation?

When trying to obtain a paediatric indication, a pharmaceutical company has to consider the following cost:

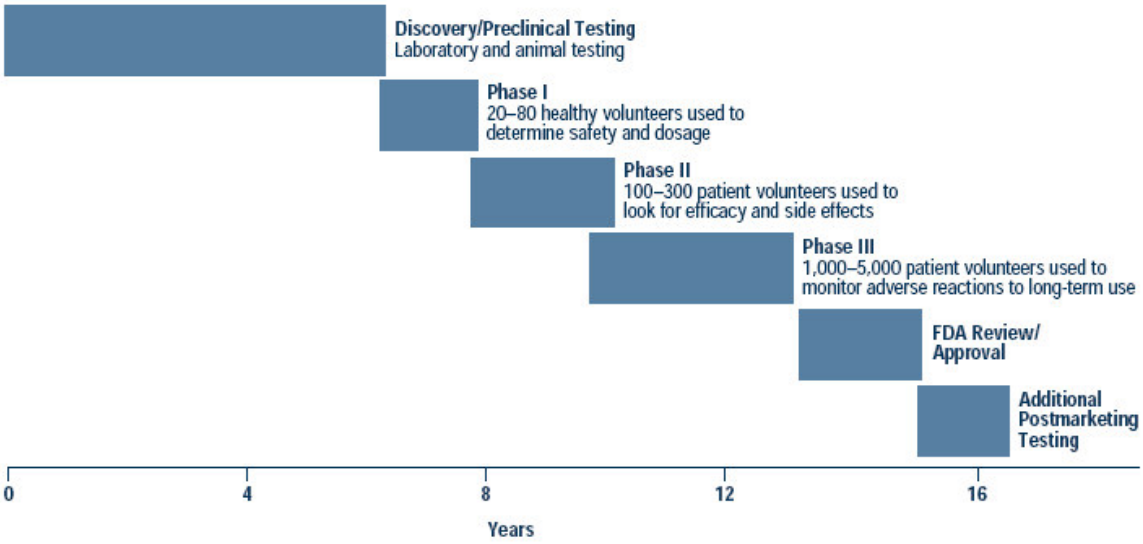
- The costs of developing and testing a range of paediatric formulations
- The costs of performing the trial
- The costs of preparing and submitting data
- Manufacturing costs
- Long-term follow-up costs

The main challenge in trying to make the above-mentioned trade-off concerns the availability and quality of information. Industry or its associations (such as PhRMA [Pharmaceutical Research and Manufacturers of America] and EGA) provide most of the available data on costs and finances. The pharmaceutical industry generally does not provide highly specific data on its expenditure unless it has a very good reason. This means that industrial data are by their very nature suspect.

How much do different companies invest in the development of new medicines and what is the average cost of a new drug? Figure 3.8. presents an overview of pharmaceutical R&D expenditure of pharmaceutical companies based in Europe, the USA and Japan for the years 1990, 1995, 1999 and 2000.

R&D expenditure is currently higher in the US than in Europe or Japan. Moreover, the growth in European R&D spending has lagged behind that of the US, turning a lead in 1990 into a lag in 2000. Expressed as a percentage of production, EU expenditure on R&D fluctuated between 8.3% (1986) and 10.1% (1990), and levelled off at 8.9% in 1995. The US achieved a ratio of

Figure 3.9
Phases in drug development



Source: PhRMA Profile 2003, p. 3.

11.3% (1986), which increased to 14.4% in 1995 (Gambardella, Orsenigo, Pammolli, 2001: Table 5, p. 16).

The costs of developing an average new drug have increased from $138 million in 1975 to $318 million in 1987 and $802 million in 2000 (DiMasi, Hansen, Grabowski, 2003). These costs include the failures of R&D (which do not result in a marketed product), investments in the long process of drug development (which includes the costs of preclinical, clinical and other research), and the cost of capital. The main reason why the estimates are so high is that the pharmaceutical industry has to consider the aggregate costs per successful drug rather than the real costs of developing one individual drug. The risk premiums and real rates of capital used to raise actual costs to aggregate costs are such that the figures reported by the industry and the academics it sponsors (such as DiMasi, Hansen, Grabowski, 2003) are staggering. Love (1997) concludes that the real costs of drug development are much lower. In an interview with EMEA it was suggested that the real costs of a new drug are two to three times lower than the estimates of the pharmaceutical industry. In a recent article, Maeder (2003) states that the costs of developing orphan drugs are substantially lower than those for non-orphan drugs. In accordance with the abovementioned figures, he states: "according to a recent industry analysis it costs about one fourth as much [as for a non-orphan drug] to develop a drug for rare diseases".

In addition, it has been suggested that many pharmaceutical products fail to make a profit and that the financial stability of the industry depends on a few highly successful products.[13] The PhRMA –an interest group representing the producers of originator drugs– points out that pharmaceutical R&D has become longer, more complex, and more expensive as a result of "more sophisticated science, more complex disease targets, more intensive regulatory process, and a growing need for accurate data". Phase III trials –which is where paediatric examinations would presumably be concentrated– have become increasingly complex due to "more stringent pre-market requirements, more refined subgroups of patients to meet regulatory requirements and to

[13] PhRMA Profile 2003, p. 5. The 20% of products with the highest returns generate 70% of revenues. Companies are often dependent on a limited number of highly successful drugs to finance the R&D for new products. Only three of every 10 prescription drugs available in the US generate revenues that exceed average R&D costs (data from Grabowski and Vernon, 1994).

Table 3.8
Expenditure on domestic R&D by stage on ethical Pharmaceuticals by PhRMA Member Companies, 2001 (millions of dollars)

	Domestic R&D ($)	Share (%)
Pre-human/Preclinical	9647.4	32.5
Phase I	1659.2	5.6
Phase II	3151.2	10.6
Phase III	4502.2	15.1
Approval	2307.9	7.8
Phase IV	3286.9	11.1
Uncategorised	5167.9	17.4
Total	29722.7	100

Notes: Company-financed R&D only.
Source: PhRMA Annual Membership Survey, 2003; cited in PhRMA Profile 2003, p. 78.

better adjust medicines to distinct needs of specific groups of patients". In the US the number of Phase III procedures has increased by 20% between 1995 and 2000.[14]

Of every 5,000 potential pharmaceutical products developed, only five are tested in clinical trials and only one is approved for use in patients. The revenues from medicines that ultimately emerge onto the market must also cover the costs of dead-ends and failures in research. The process of drug development and the distribution of R&D expenditure between its various segments show where the money disappears.

Figure 3.9. shows that the greater part of research and testing takes place before a product enters the market. In the US it takes 12 to 13 years before a newly discovered drug enters the market as a complete pharmaceutical product. Table 3.8. shows that this period accounts for roughly 64% of total domestic R&D spending on pharmaceuticals in the US. If the distribution of expenditure between phases is assumed to be the same for all medicines, then the price of an unsuccessful development exercise can be anywhere from a third (for developments abandoned before testing in humans) to two-thirds (for drugs rejected by the FDA) of the development costs of successful products. The impact of paediatric testing will depend on the manner in which the investigation is organised within the process of clinical trials and post-marketing testing as well as on the specific formulation of the proposed Regulation.

For the purposes of our project, the full costs per approved new drug may not be the most relevant costs to consider, as the requirement to do paediatric studies will only occur for medicines that have been developed for adults anyway. The risk premiums associated with drug development are consequently much lower than those applied by the industry (Table 3.9.), while the cost to industry of the paediatric regulation is the cost of doing specific paediatric studies, such as a Phase III clinical trial or a pharmacokinetic study in children. The risk premium is relevant to the objectives of this impact assessment, because the requirements of the Regulation target the incentives of pharmaceutical producers and the associated rewards and incentives must be attractive from their perspective. Unfortunately, there do not appear to be public studies on the costs of Phase III clinical trials in the paediatric population.

[14] This may, in part, be related to the Paediatric Exclusivity Provision.

Table 3.9
Probability of entering Phases I, II and III (%)

	Probability of entering phase (%)
Phase I	100
Phase II	71.0
Phase III	31.4

Source: DiMasi, Hansen, Grabowski, 2003: p. 163-165.

Information used to provide a rough estimate of the turnover and profits required to offset development costs (Table 3.10.) are:

- The costs of developing a new drug (failures included) are $800 million in 2000. This is a figure calculated by the industry that reflects aggregate costs rather than the actual costs of any individual drug.
- Time-to-market (from basic research to market launch) is estimated at 12 to 15 years by PhRMA, but the EGA states that it has decreased from 109 months in 1986-1990 to 96 months in 1991-1995 and 71 months in 1996-2000 (EGA, 2002).
- The profit margins of the top eight companies are 11 to 25%. The median profit margin of Fortune 500 pharmaceutical companies has increased from an average of about 9% in the 1970s and early 1980s to more than 18% in the early 21st century. Companies continue to make large amounts of money after the patent has expired. Once a patent has expired the innovator product does not disappear, and if there is high brand recognition and brand prescribing, the innovator product will continue to make large amounts of money.
- In the US the R&D expenditure of PhRMA members amounts to about 16-18% of their sales, while other information suggests that one of every five dollars of revenue is poured backed into R&D.
- Generic drug manufacturers allocate 6 to 8% of their turnover to R&D.
- Generic medicines account for 13% of the world market for medicinal products.
- Paediatric medicines comprise c. 15% of the European market for medicines.
- Patent protection lasts for 20 years.

Three assumptions form the basis of the estimates: (1) that the R&D costs of developing a new drug will be recovered during the period between official approval and the end of patent protection, (2) that the profit margin can vary between 10 and 25%, and (3) that new R&D will be funded from current turnover.[15] The estimates have been made for two scenarios: the aggregate costs of $800 million per drug and estimated actual costs of $200 million.
Table 3.10. presents two types of information: (i) the annual amount of turnover that must be generated in order to recover the development costs between marketing approval and patent expiry, and (ii) a (lower range) estimate of the profits generated if this turnover is achieved. The data are by their very nature limited, but they serve to create an impression of the magnitude of the potential profits associated with a six-month extension of patent protection. The calculations only relate to the actual patent life, and exclude the period of the SPC.

[15] The only item that cannot be included for lack of information is that of production costs.

Table 3.10
Estimates of the amount of turnover required to recover the costs of drug development, make a profit and invest in new R&D under different assumptions, 2000 (millions of dollars)

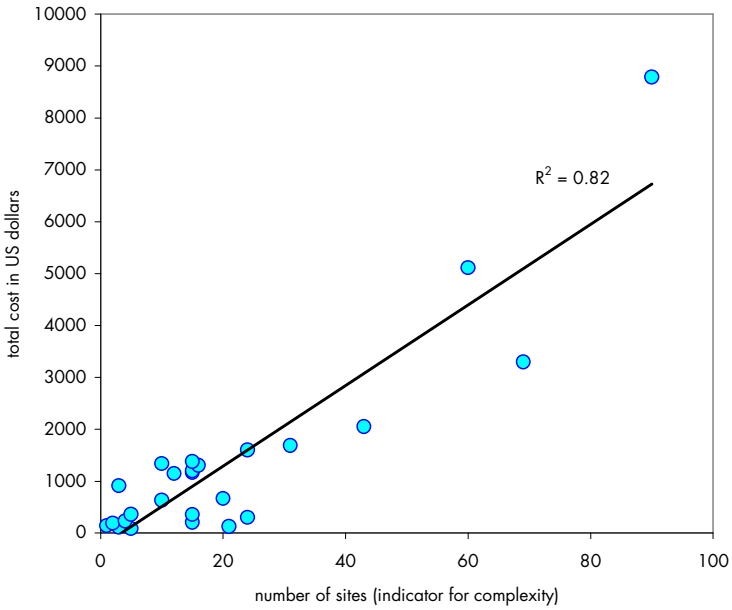
(A)	Time to develop new drug assuming development costs of $800m				
	15 (USA)	12 (USA)	107m	96m	71m
Profit margin	**Required annual turnover to recover R&D costs**				
Break-even	184.0	115.0	83.0	76.7	65.3
10	202.4	126.5	91.3	84.3	71.9
15	211.6	132.3	95.5	88.2	75.1
20	220.8	138.0	99.6	92.0	78.4
25	230.0	143.8	103.8	95.8	81.7
Profit margin	**Estimated profits per 6 months**				
10	10.1	6.3	4.6	4.2	3.6
15	15.9	9.9	7.2	6.6	5.6
20	22.1	13.8	10.0	9.2	7.8
25	28.8	18.0	13.0	12.0	10.2
(B)	**Time to develop new drug assuming development costs of $200m**				
	15 (USA)	**12 (USA)**	**107m**	**96m**	**71m**
Profit margin	**Required annual turnover to recover R&D costs**				
Break-even	46.4	29.0	20.9	19.3	16.5
10	51.0	31.9	23.0	21.3	18.1
15	53.4	33.4	24.1	22.2	18.9
20	55.7	34.8	25.1	23.2	19.8
25	58.0	36.3	26.2	24.2	20.6
Profit margin	**Estimated profits per 6 months**				
10	2.6	1.6	1.2	1.1	0.9
15	4.0	2.5	1.8	1.7	1.4
20	5.6	3.5	2.5	2.3	2.0
25	7.3	4.5	3.3	3.0	2.6

Explanation of calculations: The method used to estimate the amount assumes that the costs will be fully recovered in the period between drug approval and the end of its patent life. For example, if it takes 15 years to develop a new drug and the patent is valid for 20 years, the costs of drug development have to be recovered in five years; if the costs are $800 million, the company achieves a 10% profit and ploughs back 15% of turnover in R&D, then the amount to be recovered in five years is $1,012 million. At 10% profit this results in $20.2 million per year or $10.1 million per six months.
Sources: EGA, 2002; PhRMA, 2000.

Similar calculations could not be made for the value of the 10-year period of data protection (i.e. data exclusivity) awarded to manufacturers of medicines not covered by patent or SPC in exchange for paediatric testing. There are virtually no data, other than those provided by the industry.

With respect to the impact of the proposed Regulation, the costs for the industry are determined by the costs of performing a paediatric evaluation. The benefits concern the financial rewards of a patent on paediatric medicines, either a six-month extension of the duration of the SPC related to marketing authorisation of new products or data protection related to products with a Paediatric Use Marketing Authorisation (PUMA).

Figure 3.10
Total cost of full-service paediatric studies compared with the complexity of the studies (as indicated by the number of test sites)



Source: Data provided by EGA.

The costs of paediatric testing

The EGA has presented us with data taken from an independent company that performs paediatric studies.[16] The data concern 25 set price tenders for full-service paediatric studies in Europe and the US, covering a range of therapeutic areas. In this sample the average cost of a full-service paediatric studies was €1.1 million. Figure 3.10. shows the relationship between the cost and complexity of the study.

Love (1997) presents data on costs of US National Institutes of Health (NIH)-funded trials. He concludes that the average costs of trials are close to US$ 7 million (and the average expected cost is US$ 16 million). For the revised analysis in the preamble to the 1998 Paediatric Final Rule, FDA assumes that a pharmacokinetic study of 15 patients will cost US$ 100,000 per affected age group and that an efficacy study of 50 patients will cost US$ 150,000 per affected age group. In the same document (http://www.fda.gov/ohrms/dockets/98fr/120298c.txt) the FDA reports that a major industry association reported the development of a paediatric formulation cost US$ 500,000 to US$ 3.5 million.

A US survey in 2002 of applicants who had conducted paediatric studies in response to FDA Written Requests found that the average costs for off-patent products (per active substance) amounted to $3.87 million per Written Request and $20,405 per patient. The costs of a total paediatric study range from $500,000 to $20 million. The National Institute of Health estimates

[16] The company works in a competitive market and its prices can be considered representative of those of other contract research organisations.

that cost at between $1 million and $7.5 million, while a study by the Wall Street Journal arrived at a range between $200,000 and $3 million. Given this information, a reasonable range for the costs of paediatric testing is between €1 million and €7 million, with €4 million as a fair average.[17]

The process and economic value of Intellectual Property Rights (IPR)

Patenting and data exclusivity are part of the entire process of R&D regardless of the nature of the product. The originator drug companies are highly anxious to preserve IPR:

> "Patents provide the opportunity to recoup the time and money invested in innovation. They are essential to research-intensive industries such as pharmaceuticals, for which long, risky, and expensive research and development (R&D) represents the primary cost of bringing a product to market. Without patents, a competitor could immediately produce a less expensive copy of a new medicine, preventing the innovator from recouping its large R&D investment. [...] Patents also increase a society's knowledge base; a patent holder must disclose all aspects of the invention to the world in order to receive a patent. However, patents do not guarantee a return on investment, the right to market an invention, or the obligation to market an invention, and they do not stop someone else from creating a competing invention" [PhRMA, 2003: p. 58-59].

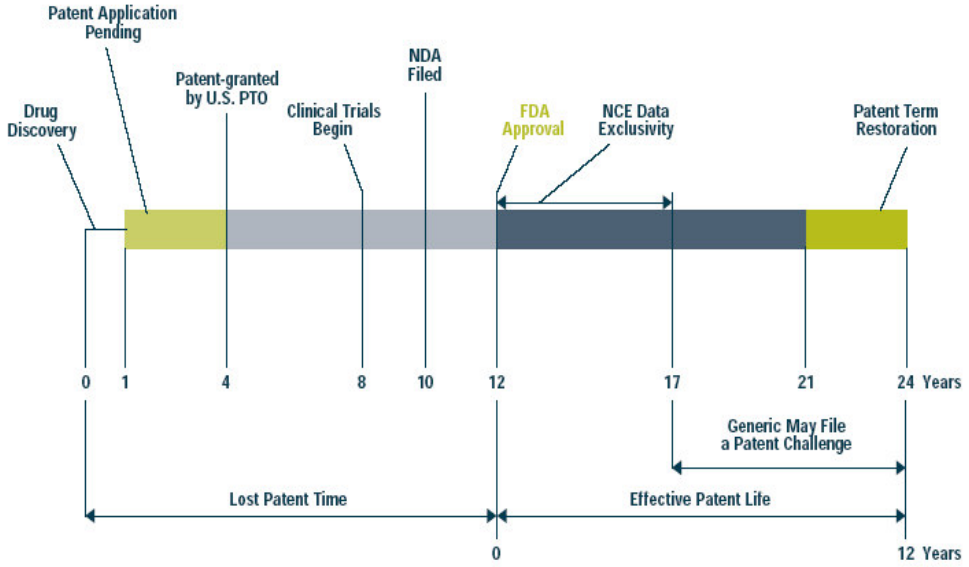
Whichever form they take, intellectual property rights are essential to the process of innovation. In many ways, data exclusivity provides a similar incentive for adjustments and refinements made after the original patent has expired, albeit in a different manner. Where patents essentially provide *market exclusivity* (the holder of the patent is the only entity who can produce or licence for production the item that is described in the patent), *data exclusivity* means that data upon which a licence application was based, can be used for licensing purposes exclusively by the company involved. It is the existing pharmaceutical legislation, which sets up the framework for data exclusivity. The legislation determines that regulators can't use the data to license the generic drug for a certain period of time.

The brief history of pharmaceutical IPR in Europe shows how the framework of protection has gradually been strengthened since the 1980s:

1980s	15/17-year **product patents** rose to 20 years in most of Europe
1987	6-year or 10-year **data exclusivity** regimes introduced to compensate for lack of protection on biotech products
Early 1990s	20-year **product patents** in Spain, Greece, Portugal, Finland, and Central and Eastern Europe
1992	**Supplementary Protection Certificates** (SPC) increase 20-year EU pharmaceutical patents up to more than 5 years
1990s	**Patents** granted for uses, dosages, salts, and changes in formulations
1994	TRIPS agreement grants worldwide 20-year **patent** protection for all pharmaceutical products except biotech

[17] EFPIA argues: "Costs are very variable, depending on the nature of the disease, the extent of the programme needed and the duration of the trials. On a per-patient basis, and as a general rule, direct costs are similar to those for trials in adult patients. However, indirect costs can be much higher due to the difficulties in performing the necessary studies, as outlined above. Paediatric pharmaceutical formulations, specifically developed for various age categories, are expensive. However, rather than costs, it is the greater risk and difficulty of conducting research in children that constitutes the primary barrier" (EFPIA, 2003).

Figure 3.11
Patent timeline



Source: Gregory, Glover, Kuhlik. "Patents and Hatch-Waxman: Understanding the Debate Between Innovative Drugs and Generic Copies," presentation to The National Governors Association (Washington, DC), 19 April 2002; taken from PhRMA Profile, 2003.

1995	10-year **data exclusivity** applied to products using the EU Centralised Procedure
1998	EU Biotech Patent Directive introduces **patents** for biotech inventions
2001	European Patent Convention establishes stronger usage **patents** (Swiss claims)
2001	Candidate Countries adopt 6-year **data exclusivity** and 5-year **SPCs** in advance of EU membership
2001	Proposal of the EC to increase **data exclusivity** to 11 years for innovative new indications
Late 2003	Commission to propose further **market protection** to encourage testing on children for paediatric indications
2004	EU and US brand industry to propose plans for another extension of **market protection** for geriatric trials

(Source: EGA, 2002).

The Regulation, which sets the legal basis for SPCs was inspired because of the necessity of the pharmaceutical industry to conduct studies and go through an authorisation process before they can place pharmaceuticals on the market. The term of patent protection is not equal to the period during which the innovation can be economically exploited. It also covers the entire development process from the discovery of the active substance (or combination of different substances) to final market approval. The effective patent life is consequently much shorter. In the US the effective patent life for drugs is estimated at 11 to 12 years (which includes a period of extension or patent term restoration) (PhRMA, 2003: p. 58). The American process of patenting and drug development is shown in Figure 3.11.

Strong competition and the intricacies of patent law have resulted in a situation where an individual pharmaceutical product is no longer covered by a single patent (for the active

substance), but by as many as 20 to 40 different patents. The additional patents cover different versions of the product, different manufacturing processes, patents for usage, formulation, for the salts, esters and isomers used, and for the size, shape, colour and markings of the product. In addition, in the EU the SPCs provide an additional period of market exclusivity of five years or more (up to as much as 15 years) (EGA, 2002). Protection is therefore stronger than is suggested by the data on the duration of patent life.

Originator and generic drug manufacturers hotly debate the issue of whether IPR should be strengthened or reduced. The EGA suggests that the reduction in protection in the US has increased competition from generic medicines and has resulted in more innovation, while the EU has greatly increased its IPR protection for pharmaceuticals since 1980 at the cost of declining innovation. It adds that "..each year of market exclusivity after patent expiry can cost European patients and healthcare systems up to €100 million per drug" and that the US has produced 66% more new treatments over the past 20 years than the EU (EGA, 2002)[18].

The PhRMA argues that IPR is vital to support innovation. It states that "replacing an older drug with a drug 15 years newer increases spending on drugs by $18, but reduces overall health costs by $111." As a representative of the originator drug manufacturers it understandably argues fiercely to maintain and strengthen IPR (PhRMA, 2000: p. 24).

The value of patent protection depends upon the length of the period of exclusivity and the size of the market. Patent life is fixed by international agreement at 20 years from the date on which the patent application is filed. However, in practice, due to the delay between patenting and obtaining marketing approval, the "effective life" of a patent is less than 20 years. Both the US and the EU have adopted legislation extending the life of pharmaceutical patents. When a patent is expired, the patent-holder can no longer prevent other manufacturers from producing and distributing copies of the patented drug (generics). The competitive impact of generics can be quite substantial and prices, after their introduction, can fall by 30-50%. Pharmaceutical companies therefore try to impede or delay entry by generics manufacturers. Legislation to prevent this has therefore emerged (Heimler, 2000).

Individual and social costs

The cost of medicinal products for the paediatric population can be assessed on two levels:

- Households, hospitals, and other stakeholders (*individual costs*)
- Society (social costs)

Individual costs

Individual costs related to the paediatric population can be determined by answering the following questions:

1. How much do families spend on health care and medication, and how much costs are related to time off from work in order to care for a child?
2. How high are the additional individual costs associated with the health problems caused by inadequacies in paediatric medication? What if every child spent one day less in hospital or had to make one less visit to a GP due to better medicines?

[18] EGA is a special interest group; even if totally honest, the data and analyses they present must be seen in the context of its mission and objectives: to reduce IP protection for pharmaceutical companies so that more generic drugs can be produced and sold. In the preface of its report, the EGA voices its support to the profitability and protection of the producers of original pharmaceutics, but also speaks out against strong market protection.

Table 3.11
Estimated cost per bed-day in ten EU Member States, 2000

	Number of admissions (thousands)	Average duration of hospital stay, 2000 (days)	Estimated number of bed-days (thousands)	Population (thousands)	Expenditure on in-patient care (PPP$ per capita)	Total expenditure in-patient care (mln PPP$)	Expenditure per estimated bed-day (PPP$)
Austria	2,371	7.6	18,019	8,110	926	7,510.0	416.8
Belgium	2,078	9.9	20,568	10,161	797	8,098.3	393.7
Denmark	1,026	6.6	6,770	5,293	1,301	6,886.2	1,017.2
Finland	1,383	10.3	14,240	5,176	678	3,509.5	246.4
France	13,727	9.4	129,033	59,079	1,010	59,669.8	462.4
Germany	19,318	11.9	229,880	82,187	1,017	83,584.8	363.6
Italy	9,514	7.6	72,305	57,762	849	49,039.9	678.2
Netherlands	1,489	12.9	19,206	15,926	1,048	16,689.9	869.0
Portugal	1,190	8.2	9,757	10,211	425	4,339.5	444.8
Spain	4,525	8.6	38,915	39,629	625	24,768.1	636.5
Unweighted average							552.9
Weighted average							472.7

Note: The numbers for Belgium, France, Luxembourg, Portugal and Spain are calculated on the basis of the ratio between average values for the other six countries in the last five years for which data was available.
Source: WHO Health for All Database, 2003.

To answer these questions we need data on such variables as household expenditure on health care and medication, the average daily costs of hospitalisation, expenditure on and the price of paediatric medicines. Not all the information is available, so that the end result will be an approximation rather than a complete estimate.

Table 3.11. presents WHO estimates of hospitalisation and expenditure on in-patient care, which we have used to estimate expenditure per bed-day. Per capita expenditure on in-patient care is given. It was assumed that the number of admissions multiplied by the average duration of a hospital stay is a good indication of the volume of in-patient treatment (estimated number of bed-days).

On the basis of the data on the daily costs of hospital treatment, the average duration of a hospital stay, the information (taken from the literature) on the incidence of ADRs and the share of unlicensed and off-label medicinal products in the total number of prescriptions, we have calculated a number of "cost estimates" (see Table 3.12.). The numbers present (1) the best cost-estimate based on the most reliable or acceptable data, together with (2) extreme margins of the estimates in order to given an indication of the sensitivity of the calculations.

Table 3.12
Three estimates for the effect on the costs of hospitalisation and the number of unlicensed and off-label prescriptions, c. 2000

	Assumptions closest to literature		Lower range estimate		Upper range estimate	
	Assumption	Result	Assumption	Result	Assumption	Result
Total number of children in the EU		84,300,000 children		84,300,000 children		84,300,000 children
Percentage of children hospitalised annually	0.5%	421,500 children	0.25%	210,800 children	1.0%	843,000 children
Percentage of patients that received unlicensed or off-label medicines	60%	252,900 children	35%	73,800 children	90%	758,700 children
Incidence of adverse drug reactions – lower estimate	4.5%	11,400 children	2%	1,500 children	15%	113,800 children
Incidence of adverse drug reactions – upper estimate	17%	43,000 children	10%	7,400 children	27%	204,800 children
Number of prescriptions per child	4	1,686,000 prescriptions	3	632,300 prescriptions	5	4,215,000 prescriptions
Percentage of prescriptions unlicensed	7%	118,000 prescriptions	2%	3,200 prescriptions	25%	2,023,200 prescriptions
Percentage of prescriptions off-label	38%	640,700 prescriptions	20%	44,300 prescriptions	45%	2,781,900 prescriptions
Cost per bed-day	470 PPP$		250 PPP$		690 PPP$	
Cost if all children stay in hospital for one more day		198.1 million PPP$		52.7 million PPP$		571.7 million PPP$
Cost if children who suffer ADR have to stay in hospital X days longer - lower estimate	2	10.7 million PPP$	1	0.4 million PPP$	3	157.0 million PPP$
Cost if children who suffer ADR have to stay in hospital X days longer - upper estimate	2	40.4 million PPP$	1	3.7 million PPP$	3	282.6 million PPP$

Table 3.13
Aggregate data on health expenditure and pharmaceutical expenditure in the EU-15, 2001 (PPP$)

	Total per capita health expenditure	Total health expenditure as % of GDP	Pharmaceutical expenditure per capita (2000)	Pharmaceutical expenditure as % of total health expenditure	Public pharmaceutical expenditure as % of total pharmaceutical expenditure
Austria	2,233 [a]	8.0 [a]			
Belgium	2,293 [a]	8.7 [a]	323 [c]		
Denmark	2,503	8.6	208	8.9	50.5
Finland	1,841	7.0	264	15.7	51.8
France	2,561	9.5	486	21.0	65.9
Germany	2,808	10.7	379	14.3	70.6
Greece	1,511	9.4	221	14.0	75.5
Ireland	1,935	6.5	191	10.3	93.7
Italy	2,212	8.6 [b]	457	22.4 [b]	51.7 [b]
Luxembourg	2,719 [a]	5.6 [a]	329		
Netherlands	2,626	8.9	237	10.1	60.6
Portugal	1,613	9.2	308		
Spain	1,600	7.5			
Sweden	2,270	8.7	305	13.5	69.1
UK	1,992	7.6	238		
EU-15 (est.)	**2,280**	**8.9**	**362**	**17.2**	**63.4**

[a] 2000; [b] 2002; [c] 1997
Note: Aggregate data on health expenditure and pharmaceutical sales are available for most but not all countries. Empty fields in the table represent missing values.
Source: WHO Health for All Database, 2003. OECD Health Data, 2003.

The cost estimates show that the most likely effect of ADRs in in-patient care is roughly 10 to 40 million PPP$. The costs could even be as high as 150 to 300 million PPP$. The real number of ADRs will be higher still, mainly due to underreporting. It is considerably more difficult to make a similar calculation for outpatient care or for the consequences of inadequate treatment on the quality of life, health and life of children.

Social costs

From a societal perspective, the full range of costs and benefits is relevant. There are considerable gains to patients and to the community as a whole, since paediatric trials lead to a better evidence base for the paediatric use of medicines. However, there are also costs related to better medicines for children.
The social costs related to the problem can be determined by answering the following questions:

1. How much do countries spend on health care and medication?
2. How high are the additional social costs associated with the health problems caused by the inadequacies in paediatric medication?

Data on national health expenditure and on pharmaceutical sales and consumption give an indication of the importance that is assigned to health in different countries. Information about

Table 3.14
Trends in the number and population share of children under the age of 20, 2003-2013

	European Union	New Accession States
Total number 2003-2013	-6.6%	-13.0%
Population share 2003	22.2%	29.3%
2013	20.4%	24.7%

Source: US Census Bureau, International Database.

household expenditures can be obtained from national studies of household budgets and aggregate statistics on private consumer expenditure. One problem is that such data are rarely if ever broken down into cost components (e.g. expenditure on GPs, medicines, specialists, etc.). An indication of individual expenditure on health care, medication and on in-patient care is found in the WHO *Health for All* Database (see Table 3.13.).
The average values for the EU-15 give an idea of the magnitude of the health care sector and of the pharmaceutical market from the viewpoint of the consumer. On average almost 9% of Gross Domestic Product (GDP) is allocated to health care expenditure; circa 17% of that expenditure or close to 1.5% of GDP is spent on pharmaceutical products. Unfortunately the data do not allow us to distinguish between adults and children.
The national figures reflect differences in reimbursement systems. The overall importance assigned to health care is more or less similar in every country of the EU-15: only two countries spend less than 7% and only four spend more than 9% of GDP on health care. Variation is somewhat more pronounced in the share of pharmaceutical expenditure, with Italy and France as considerable outliers (more than 20% of total health care expenditure). The share of public expenditure is consistently above 50%. Changes in the price of medicinal products will consequently also have an impact on public finance, via systems of public health insurance.

The future under a "no policy change" scenario

How serious will the problem be in 2015, if no new policies are implemented? We will predict the extent of the problem in 2015 using an analysis of trends in:

- The volume of children affected by the lack of paediatric medicinal products
- The costs of treatment in real terms and discounted
- Pharmaceutical R&D and retail sales

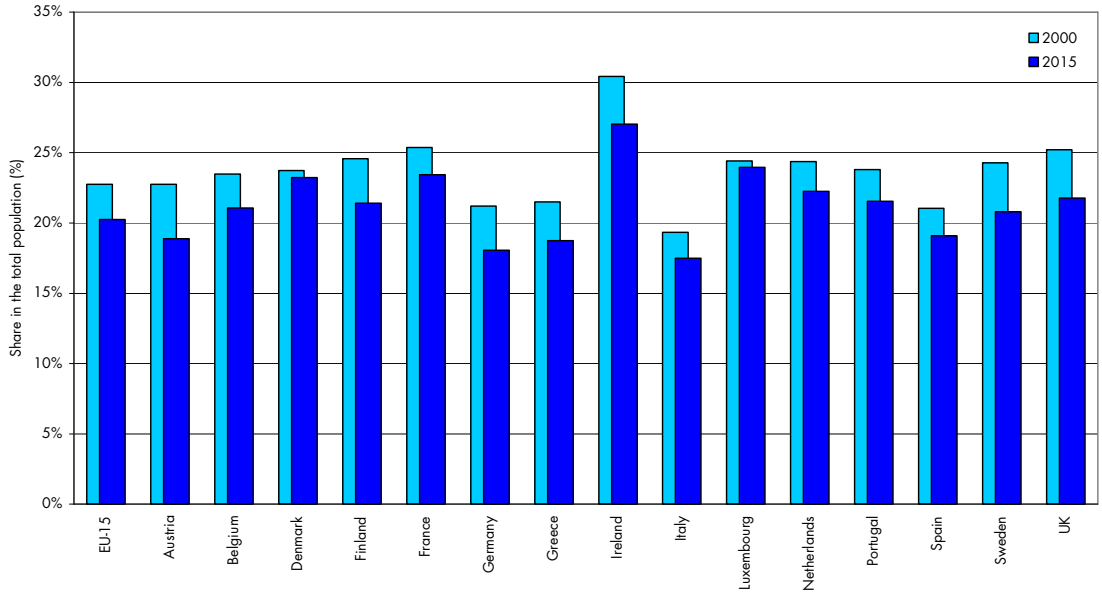
The quantitative prediction is based on demographic trends, recent developments in the level of health care costs (e.g. 1995-2003), and additional information on possible developments in the institutional and technological context of health care. Data on health care spending from the WHO Health for All database and the OECD Health Data 2003, and population data from the International Database of the US Census Bureau were used to extrapolate trends in the period 1970-2002 forwards to 2015.[19]

Number of children

The total number of children under 20 is expected to decline, although in 2013 they will still account for over 20 percent of the population (Table 3.14.).

[19] All data were calculated using linear trend extrapolation (based on coefficients derived from a regression of indicator values with time). Only the average duration of a hospital stay was calculated using loglinear trend extrapolation.

Figure 3.12
National trends in the population share of children in the ages of 0 through 19 in the EU-15, 2000 and 2015 (%)



Source: US Census Bureau, International Database.

Typical patterns of demographic ageing result from the extrapolation of population developments. Throughout Europe the share of children between the ages of 0 and 19 declines and there will even be a decline in absolute numbers (Figure 3.12.). However, even in 2015 there will be over 150 million children in the EU-25.

Costs of treatment

The extrapolation of the cost for in-patient care per bed-day was calculated as follows:

- *Population* data were taken from the US Census Bureau's International Database;
- Time series for the period 1970-2002 on the *number of hospital admissions per 100 inhabitants*, the *average duration of hospital stay in days*, *per capita expenditure on in-patient care*, and *per capita total health expenditure* were extrapolated;[20]
- The estimated *total number of bed-days* was calculated by multiplying the *number of admissions* (*population* times *admissions per 100 inhabitants*) with the *average duration of a hospital stay*;
- *Total expenditure on in-patient care* was calculated by multiplying *population* with *per capita expenditure on in-patient care*;
- The costs per bed-day were then equal to total expenditure on in-patient care divided by the total number of bed-days.

Linear extrapolation always produces debatable results; predictions for the future are only reliable under the assumption that there will be no fundamental changes in the health care system, in the

[20] Missing data on per capita expenditure for in-patient care for Greece, Ireland, Sweden and the UK were estimated by applying the ratio between total per capita health care expenditure and per capita expenditure for in-patient care for all the other countries to total per capita health care expenditure for Greece, Ireland, Sweden and the UK.

Table 3.15
Estimated costs per bed-day of in-patient care, 1990-2015

	Costs in PPP$						Index 2000=100					
	1990	1995	2000	2005	2010	2015	1990	1995	2000	2005	2010	2015
EU-15	**219**	**345**	**471**	**565**	**704**	**866**	**46**	**73**	**100**	**120**	**149**	**184**
Austria	282	329	417	413	461	518	68	79	100	99	111	124
Belgium	160	284	359	459	577	717	44	79	100	128	160	200
Denmark	504	787	1017	1487	1971	2581	50	77	100	146	194	254
Finland	142	199	199	273	334	402	72	100	100	138	168	203
France	229	350	464	534	657	803	49	76	100	115	142	173
Germany	162	269	364	425	516	617	44	74	100	117	142	170
Greece	244	420	617	658	826	1023	39	68	100	107	134	166
Ireland	265	452	654	785	987	1223	41	69	100	120	151	187
Italy	311	395	679	843	1113	1448	46	58	100	124	164	213
Luxembourg	113	199	333	323	397	480	34	60	100	97	119	144
Netherlands	412	615	869	1169	1530	1974	47	71	100	135	176	227
Portugal	170	341	460	622	814	1041	37	74	100	135	177	227
Spain	302	449	566	698	856	1034	53	79	100	123	151	183
Sweden	185	489	829	965	1406	2026	22	59	100	116	170	244
UK	189	357	449	547	704	895	42	79	100	122	157	199

general health of the population, in the economy, and in government finances and health insurance.

Table 3.15. presents the results. On average the costs per bed-day are predicted to increase by 84 percent between 2000 and 2015. The rate of increase until 2015 is a function of the rate of increase between 1970 and 2000 and consequently only reflects current cost trends. If those trends persist, in-patient care costs will increase especially in Belgium, Denmark, Finland, Italy, the Netherlands, Portugal and Sweden.

Extrapolating cost scenarios

We have combined the population trends, future (in-patient) health care cost levels and the data on unlicensed and off-label drug consumption and the frequency of ADRs in the paediatric population as presented in the cost estimates (see Table 3.12.).[21] The result is a number of different projections of the future costs associated with ADRs in the paediatric population as a percentage of total health care expenditure.

Five scenarios have been tested:

- (1) a most likely scenario, based on data close to those in the latest literature;
- Two scenarios with fixed values for the consumption of unlicensed and off-label medicines in children and for the incidence of ADRs, but with (2) an increase or (3) a decrease in the rate of hospitalisation;
- Two scenarios in which all variables changed, namely (4) a decrease in hospitalisation, a decline in the consumption of unlicensed and off-label medicines in children, and a decline in the incidence of ADRs, and (5) an increase in hospitalisation, an increase in the consumption of unlicensed and off-label medicines in children, and an increase in the incidence of ADRs

[21] And assuming an additional hospitalisation of two days for every ADR.

Figure3.13
The projected costs of ADRs related to the consumption of unlicensed and off-label medicinal products in the paediatric population, 2000-2015: assuming a high incidence of ADRs (as a percentage of total health care expenditure)

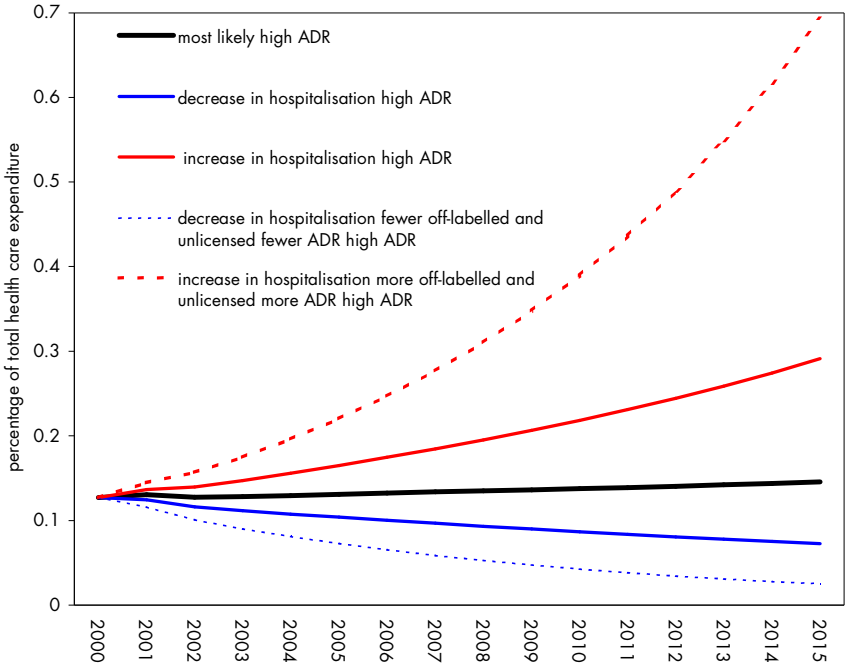


Figure 3.14
The projected costs of ADRs related to the consumption of unlicensed and off-label medicinal products in the paediatric population, 2000-2015: assuming a low incidence of ADRs (as a percentage of total health care expenditure)

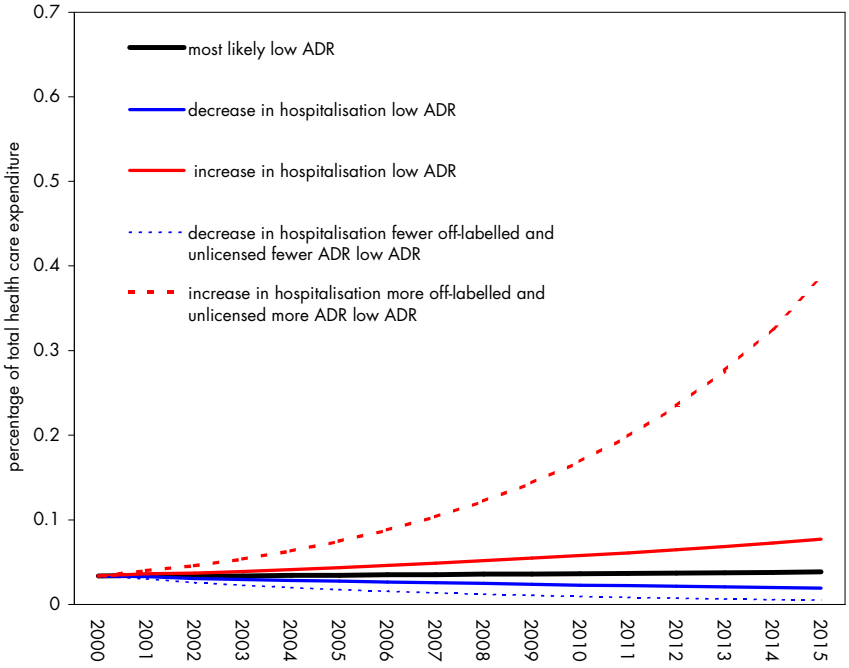
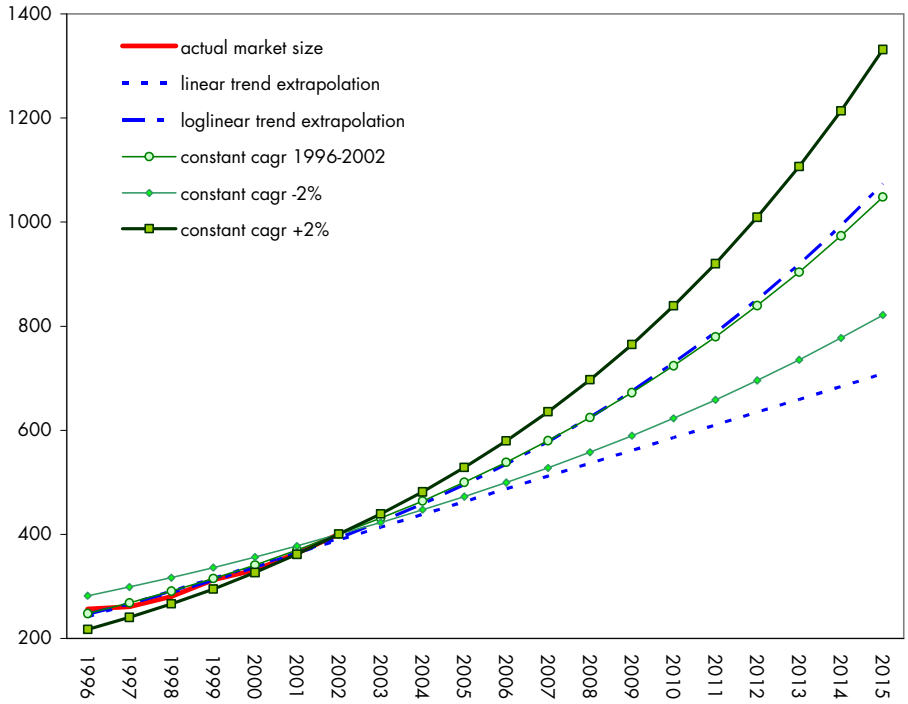


Figure 3.15
Projections of worldwide pharmaceutical sales, 1996-2015 (billions of dollars)



Figures 3.13. and 3.14. present the future trends for two types of scenario: one starting from a high level of ADRs and one starting from a low level of ADRs. The results show that the costs are fairly modest compared to the total value of all health care expenditure. On the other hand, the calculations underestimate the true extent of the costs. Outpatient care is not included and it has been suggested that the real incidence of ADRs is considerably higher. If we assume, for the moment, that the real extent of the problem is three times as high as is shown in these figures, then the costs related to the most likely scenario would be in the range of 0.1 to 0.4% of health care expenditure. In the most expensive scenarios the costs can run as high as 2% of total spending.

Pharmaceutical sales

Finally, we have extended the recent development of pharmaceutical sales into the future. To do so, we have employed two different kinds of method in different versions:

- Constant compound average growth rates with a sensitivity analysis based on adjusted growth rates of +2% and –2%;
- Trend extrapolations on a linear and log-linear basis.

Figure 3.15 presents the different results.
Growth is more likely to be exponential than linear. The two middle estimates suggest that by 2015 the total size of the pharmaceutical market will be more than 1,000 billion dollars. Even if an increasing proportion of the market will be geared towards adults and the elderly, the paediatric population will most likely continue to be a significant market.

Summary of the extent of the problem

The Regulation on medicinal products for paediatric use may have an impact on a wide variety of different stakeholders, including children (and their parents), the pharmaceutical industry, general practitioners and other professionals providing medical care, pharmacies, government departments and regulatory agencies, researchers in academia and other research institutions and insurance companies. Of these stakeholders, *children and the pharmaceutical industry* are the most important parties.

Children are at risk when taking medicines not tested for them because of potential negative effects regarding taking the drug at all, the dosage, and the route of administration. Negative consequences can be short-term or long-term. The population of children that is potentially affected by the Regulation is sizable (about 23% of the total population in the EU and the 12 NAS-countries). In this population many drugs are not licensed for children or are prescribed off-label. It appears that the share of off-label prescription is higher than the share of unlicensed prescriptions, both in hospitals and in general practice. The percentage of patients receiving unlicensed or off-label treatment is higher in hospitals than in general practice. Exact numbers and data about the most frequently prescribed drugs differ enormously both between countries and between studies performed within a single country. This is also true for the kind of unlicensed drugs prescribed. In addition, studies differ in incidence figures of unlicensed and off-label prescriptions of age groups. Unlicensed and off-label prescriptions do not necessarily threaten the health of a child, but the risk of ADRs is higher, since adequate dosing schemes have often not been assessed. However, the currently available evidence consequently does not allow for definitive conclusions on the incidence of ADRs in children in the EU.

In general, the EU pharmaceutical market that consists of innovative and generic drug manufacturers is very large and highly dynamic. The challenge for the pharmaceutical industry is to develop affordable medicines tested for use in children. However, the proposed Regulation raises concerns with respect the costs of development. Will the incentives of the proposed Regulation provide sufficient turnover and profits to offset the development costs? The costs for the industry are determined by the costs of performing a paediatric evaluation. From different studies it can be concluded that a reasonable range for the costs of paediatric testing is between €1 million and €4 million. The benefits concern the financial rewards of a patent on paediatric medicines, either a six-month extension of the duration of the SPC related to marketing authorisation of new products or data protection related to products with a Paediatric Use Marketing Authorisation (PUMA). In section 3.4 an impression of the magnitude of the potential profits associated with a six-month extension of patent protection is presented. Due to limited data, no calculations could be made for a reward of 10 year of data protection for off-patent products in exchange for paediatric testing.

The cost of medicinal products for the population can be divided into individual and social costs. On the individual level, costs are related to (i) the amount of money that families spend on health care and medication and (ii) the additional individual costs associated with the health problems caused by inadequacies in paediatric medication. Since data to measure the costs for individuals are limited, only approximations of the related costs could be presented (section 3.5). From a societal perspective, the full range of costs and benefits is relevant. There are considerable gains to patients and to the community as a whole, since paediatric trials lead to a better evidence base for the paediatric use of medicines. However, there are also costs related to better medicines for children. Costs for society are related to (i) the amount of money that countries spend on health care and medication and (ii) the additional social costs associated with the health problems caused by the inadequacies in paediatric medication. The problem with these costs estimates is that data are often aggregated and not broken down into cost components (e.g. expenditure on GPs, medicines, and specialists).

If no new policies are implemented, how serious will the problem be in 2015? Throughout Europe the share of children between the ages of 0 and 19 declines both relatively and in absolute numbers. However, in 2015 there will be over 150 million children in the EU. We estimated that by 2015 the total size of the pharmaceutical market will be more than 1,000 billion dollars. Even if an increasing proportion of the market will be geared towards adults and the elderly, the paediatric population will most likely continue to be a significant market. The future costs associated with ADRs in the paediatric population as a percentage of total health care expenditure are determined to be fairly modest. However, the calculations presented in section 3.6 underestimate the true extent of the costs. Outpatient care is not included and it has been suggested that the real incidence of ADRs is considerably higher. If we assume, for the moment, that the real extent of the problem is three times as high as is shown in these figures, then the costs related to the most likely scenario would be in the range of 0.1 to 0.4% of health care expenditure. In the most expensive scenarios the costs can run as high as 2% of total spending

Similar Regulations in the US and in the field of rare diseases

In the last decade, several steps have been taken regarding medicines for paediatric use in the US. The starting point is the 1994 Paediatric Labelling Regulation, which focused on product labelling of authorised products to include permissible paediatric use. This Regulation did not stimulate the revision of labelling, because there was a need for more clinical trials, data collection and publication of information on trials in the paediatric population. In that same year the US Food and Drug Administration (FDA) implemented a Paediatric Plan to stimulate the development of paediatric data in the product development phase and after market approval. The Plan did, however, not result in a substantial increase in the number of tested medicines for paediatric use.

In 1997 a successful Regulation for stimulating the development of medicines for paediatric use was implemented. The Food and Drug Administration Modernization Act (FDAMA) introduced the possibility of obtaining six months extension of market exclusivity or patent protection if a manufacturer submitted the proposed paediatric studies together with a Written Request (the so-called Paediatric Exclusivity Provision).

By the beginning of 2003, 264 Written Requests had been evaluated by the FDA, focusing on 616 studies of which 324 were proposed paediatric study requests. This is an enormous increase in paediatric studies: between 1991 and 1997 (before the Regulation came into force) 11 out of 71 paediatric studies were completed (FDA, 2001). The FDA suggests that the provision will reduce certain types of health care expenditures, but increase others. Due to better medicines, children will recover earlier, making less use of health care services. The improved health outcomes will lead to health care cost savings. The FDA has not attempted to quantify these estimates. The health benefits will be realised when paediatric trials are completed and the medicines are used in practice. The exclusivity provision will also increase particular health care expenditures because it will delay the introduction of generics, which have a lower price than originator drugs. This will lead to a (temporary) higher average price of drugs.

In the FDA Status Report, it is estimated that over 20 years consumers are expected to pay $13.9 billion for higher priced drugs. The estimated present value of the revenue/cost increase is about $7.2 billion, or $61 million per drug (discount rate 7%). The generic sector will lose about $ 10.7 billion ($5.7 billion discounted) in new sales during a period of 20 years. On an annual basis the unrealised profits are about $ 48 million. In addition, retail pharmacies will also lose future revenues, which are estimated at $2.6 billion in 20 years. The originator drug companies will, however, gain sales due to the provision. The sales are expected to be $29.6 billion ($15.3 discounted) in 20 years. Taking the cost of production, marketing etc. into account the originator drug companies will gain about $592 million per year (FDA, 1998, p. 14-17).

Several limitations of the Paediatric Exclusivity Provision have been identified:

- Since the exclusivity applies to all products marketed, which contain the particular active substance, the provision led to an increase in medicines for which there is greatest commercial gain. These products are not necessarily focused on the greatest therapeutic need: some drug categories (e.g. old antibiotics) and age groups (especially neonates) are poorly addressed.
- The provision seemed not a big incentive to manufacturers with low sales (because it decreases the value of the exclusivity). An example is amphothericin, used for fungal infections.
- Because the exclusivity is granted at the time of submission of the studies, it has sometimes been difficult to negotiate label changes, especially when it concerned 'negative' product information.
- The provision does not address off-patent products, although several medicines (six out of the most common used medicines in children) are off-patent, these are often used unlicensed or off-label.

In 1999, the Paediatric Final Rule was implemented. This Rule requires an application for authorisation of a product containing a new active substance or for authorisation of new indications, new dosage forms, new dosing regimens, or new routes of administration to contain safety and effectiveness information on relevant paediatric age groups for the claimed indications. The Rule intends to "ensure that new drugs and biological products contain adequate paediatric labelling for the approved indications at the time of approval" (or soon after approval) (FDA, 1998: p. 66634). The Paediatric Rule is seen as complementary to the Paediatric Exclusivity Provision. Although the Rule in general is seen as successful, the Rule has been challenged in court. The FDA has set up new legislation in this respect (Paediatric Research Equity Act), which has been approved by the Senate in 2003.
The situation of medicines for paediatric use has similarities with the lack of interest in developing medicines for rare diseases ("orphan drugs"). The EU legislation for orphan medical products (2000) aims to stimulate the development of medicines for rare diseases. This Regulation includes incentives such as protocol advice, fee waivers, and access to the procedure leading to a centralised marketing authorisation and a period of market exclusivity when the product is authorised. So far, the impact of the Regulation is successful in stimulating the development of orphan medicinal products.

The nature of the impacts

The way in which pharmaceutical companies, hospitals and GPs, households and other stakeholders respond to the provisions of the proposed Regulation is not a given. Some impacts can be predicted fairly accurately in that they derive from absolute requirements laid down in the Regulation. However, most impacts depend on the preferences and choices of the main actors and on the way in which the various measures are implemented.
Some examples of the questions relating to choice and implementation are:

- How will pharmaceutical companies choose to respond to the rewards and incentives in the proposed Regulation? Are they sufficiently attractive?
- How will companies organise their paediatric investigation and where will the clinical trials take place?
- How will companies deal with the costs of paediatric testing? Will paediatric testing go at the expense of testing for use in adults?

- How will insurers (private and public), hospitals, GPs and households respond to the choice between tested and untested medicinal products for paediatric use with different prices?
- How much money will be allocated to the study fund?
- What will be the nature and quality of the scientific advice?

The effects of different provisions and the effectiveness of the Regulation (the relationship between actual and desired effects) depend on the nature of the individual provisions. Three types of provision can be identified, namely:

1. Requirements
2. Rewards and incentives
3. Support measures

Each type elicits a different kind of response, carries its own risks and uncertainties, and therefore has a different impact. The link between the type of provision, the identity of the stakeholder, and the nature of the impact is key to understanding the effects and effectiveness of the proposed Regulation.

Requirements

The immediate impact of requirements is determined by four issues:

- *The (legal) definition of compliance*: Some requirements are very straightforward. The main requirements cannot be circumvented: without submitting the results from studies carried out according to an agreed paediatric investigation plan or presenting a waiver or deferral, a marketing authorisation application cannot be granted. Beyond the obvious is a grey area where the Commission, EMEA, and the pharmaceutical industry will try to define compliance to suit their own interests. For example, what does it mean to place a product on the market: will a single pill suffice? However, the revised pharmaceutical legislation does put an obligation on the industry to continuously supply pharmaceuticals.
- *Costs of compliance*: Requirements generally impose costs upon those who have to meet them. In the case of the proposed Regulation, examples of the costs of compliance are:
    - How much will clinical trials cost if children are included?
    - How much does it cost to design an investigation plan?
    - How much will it cost to adjust labels, to comply with post-marketing requirements, or to place the product on the market within one year?
- *Costs of monitoring and enforcement*: Even when a requirement is offset by a reward, the authority that imposes the requirement has to check if those who have to meet the requirement do so and if they do it adequately. Monitoring and enforcement cost money. The main requirements of the Regulation (submitting the results from studies carried out according to an agreed paediatric investigation plan when applying for a marketing authorisation for some products) allows for centralised monitoring: companies have to apply for an authorisation, submit and discuss the plan, and report on test results. Other requirements may be more difficult to monitor (e.g. the implementation of pharmacovigilance) or to enforce (e.g. placing a product on the market). In this case, the public costs of monitoring and enforcement include the costs of setting up and managing the PB. The fines and other enforcement measures that may be written into the Regulation should reflect the costs of monitoring and enforcement.

- *Distribution of the burden*: Are the requirements in the Regulation equally burdensome for large and small companies, for companies specialised in a single product or companies that produce a wide variety of medicinal products? In addition, the burden of the requirements can vary according to the nature of the product: existing products have been tested once already (in order to receive a marketing authorisation) but new products can integrate paediatric testing into the process of clinical trials (and thus achieve an economy of scale).

Rewards and incentives

An incentive bestows a benefit in order to draw out desirable behaviour. It is never awarded automatically but is conditional upon the right behaviour. A reward, on the other hand, is granted automatically upon compliance with requirements and serves to compensate parties for the costs of compliance. Three issues are involved:

- *Administrative costs for government*: The relevant regulatory and other government agencies have to put in place the infrastructures to dispense the incentives and rewards, which raises the costs of administration.
- *Attractiveness of rewards and incentives*: Where requirements and voluntary actions are compensated for by rewards and incentives, pharmaceutical companies can weigh costs against benefits. In the proposed Regulation the main requirements are rewarded with a six-month extension of the SPC for originator drugs. In this case the balance between costs and benefits is not a matter of choice (the requirement must be met; the reward will be given) but of satisfaction: will companies complain or rebel when they find the reward insufficient?. The ten-year period of data exclusivity is a true incentive for conducting studies and obtaining a marketing authorisation on an off-patent medicine.
- *Externalities*: The cost and benefits to two of the main parties to the Regulation – that is government and industry – do not exhaust the consequences. There will be costs (largely financial) and possible benefits (improved health care) to children, plus additional and sometimes subtle effects on care providers, adult patients, and insurers. Some of these externalities can be large in magnitude.

Support measures

The proposed support measures involve the creation and public sharing of knowledge on paediatric testing and the existing medicines for use in children, and the establishment of the Medicines Investigation for the Children of Europe, a study programme for research into paediatric medicines.

The impact of this group of measures is equal to the balance between:

- *Costs*: The expenditure involved in setting up and managing the infrastructure needed to create and exchange information as well as the funds allocated to the study programme.
- *Benefits*: All support measures are available without charge, which means that the public funds are not counterbalanced by revenues. The benefits will therefore accrue to the pharmaceutical industry (most particularly, SMEs and research institutes) and society at large.

Four types of impact

Four types of impact will be considered in the analysis:

- *Economic impacts*, such as the direct costs of implementation, indirect costs such as price increases for consumers, and the effects on the competitive strength of the pharmaceutical industry.
- *Social impacts*, such as distributional issues (by social group, region, company size, and industrial sector), the quality of life of children and their parents or guardians, and the equal treatment of manufacturers, patients and other parties.
- *Environmental impacts*, such as resource use in the pharmaceutical industry.
- *Sustainability* impacts that relate to the ability of future generations to attain the same quality of life and in this case health and health care as the current generation.

An assessment of each individual provision of the Regulation

Method

The Extended Impact Assessment involves a structured analysis based on six key questions:

1. Who is affected and what responses is the policy expected to elicit?
   The analysis began with an inventory of stakeholders and an analysis of their preferences and incentives. Four main groups are affected by the proposed Regulation, namely pharmaceutical companies, government, health care professionals (including doctors and pharmacists) and children and their parents or guardians.[22] The stakeholder analysis provides us with an understanding of their behaviour.
   Which impacts are likely to occur?
2. The first step in the impact assessment concerns an exploration of the consequences that each individual provision of the Regulation may theoretically have. For each provision, we have constructed a matrix of levels of aggregation (operationalisation, short-term effects, long-term effects, and risks) against types of stakeholder in order to indicate to what extent the provision can results in one or more of the four types of impact. Our interviews with stakeholders provide a more detailed understanding of their response to each provision.
3. Where will the costs accumulate and benefits accrue?
4. The third question is basically an extension of the second question in that it asks which stakeholders will win and which will lose in each individual article of the proposed Regulation. Which stakeholders, industrial sectors, regions, social groups or policy areas will benefit from the proposed policy and who will have to pay? In some instances the Regulation itself will identify who has to pay or who will benefit. For example, pharmaceutical companies will have to pay for the paediatric investigation (which is why they will be provided with an incentive) and children will benefit from the improvements in paediatric medication. Other costs and benefits may be hidden. For example, will SMEs and large (multinational) pharmaceutical companies benefit to an equal extent?

[22] The impacts on research institutions (academic or private) will be discussed as part of the analysis of the impact on the pharmaceutical industry. Insurance companies and reimbursement systems will be dealt with as part of our analysis of children and their parents or guardians.

Will patients in countries with different systems of health care and health insurance benefit to the same extent?

1. *How large is the impact of each policy?*
   Based on questions 1, 2 and 3 and the results of Task 2 (Measuring the current and future effects without policy change) we will summarise the impact of each element of the Regulation. The assessment of the extent of the impact involves a three-tiered approach:

   - A **qualitative** description of the extent of the impact, with a distinction among stakeholders, social groups, regions, sectors, and external impacts (*based on the analysis in steps 1, 2 and 3*)
   - **Quantitative** estimates of selected indicators (e.g. numbers of patients treated, number of deaths avoided, number of patent applications, number of companies involved) (*based on the information on and analysis of the current and future extent of the problem*)
   - A **monetary valuation** of the quantitative impacts, distinguishing costs and benefits and paying separate attention to the costs of compliance with requirements (*to the extent that the data allow such a valuation*)

   The three approaches will be combined into an integrated assessment of the costs and benefits of each policy in the form of a multi-criteria assessment that combines the qualitative and quantitative assessments.
2. *When will the effects occur: in the short term and/or in the long term?*
   Is the particular measure one that will be effective immediately, one that can be implemented easily and will be up and running in a matter of months? Or will it take a longer period – perhaps several years – to mature? Will the impact be incidental (felt only in the rush just after the regulation has been adopted, to dissipate thereafter) or will the impact be structural?
3. *What are the risks and uncertainties?*

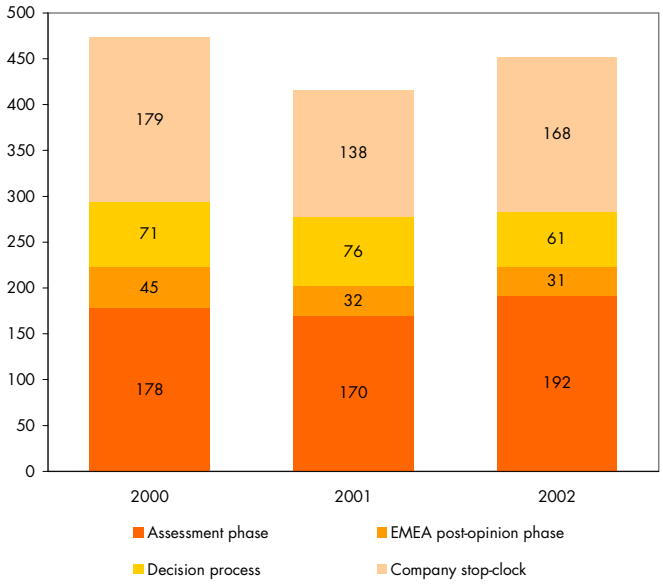
The risks and uncertainties depend to some extent on the nature of each particular instrument: is it an incentive or a support measure or is it a requirement?

- *Incentive*: Will it be effective, targeting the right triggers in stakeholder behaviour and sufficiently attractive to entice them? Will it elicit the right kind of response?
- *Requirements*: What is the risk of non-compliance and how can the regulation ensure or enforce compliance? How high are the costs of compliance and enforcement?

The guidelines on extended impact assessments call for a phased analysis of impacts. The EIA is conducted on three levels of aggregation, on the basis of the following three questions:

- What does the Regulation require the stakeholders to do? (*operationalisation*)
- What will be the short-term effects of these actions? (*short-term effects*)
- How do the provisions of the Regulation contribute towards its overall objectives and what will be the long-term impacts – desirable or otherwise – of the Regulation as is? (*long-term effects*)

Figure 4.1
Average number of days for centralised procedures, 2000-2002



Source: EMEA, Eighth Annual Report 2002, p.13

The analysis will be supplemented with a risk analysis to identify areas where the Regulation may be less effective or incomplete.
In the end we will have a analysis for each element of the proposed Regulation, detailing the nature of its impacts distinguished by stakeholder; a distinction between four different types of impact; an assessment of risks and uncertainties, effectiveness and appropriateness; and a conclusion on the question whether or not the proposed Regulation will be effective to achieve its general objectives.[23]

Impact of core requirements

The three core requirements of the proposed Regulation concern the paediatric investigation plan, the marketing authorisation requirement for new products, and the marketing authorisation for authorised medicinal products.

Operationalisation Pharmaceutical companies have to develop and carry out studies according to an agreed paediatric investigation plan for every new medicinal product and for every new indication, new pharmaceutical form and new route of administration of existing medicinal products in order to supply the data determining the conditions in which the medicinal product may be authorised for use in children, unless there is a waiver. The PB has to evaluate paediatric investigation plans and EMEA or national competent authorities have to decide on a marketing authorisation. Health care professionals and researchers can provide scientific input. Children need to be enrolled to do the studies, and parents need to give their consent.

[23] The cost estimates in the impact assessment have been made on the basis of available data, some of which has been provided by the pharmaceutical industry. The reader is consequently advised to consider the estimates as indications rather than precise measurements. Where values were recorded in dollars we have worked with the original information (in dollars), but when euros were required we have converted the amounts by means of the OECD's set of purchasing power parities for the year 2002 ($1 is €0.892).

Short-term effects The workload of EMEA will rise considerably, resulting in a demand for specialists in paediatric research, higher costs, and possibly a longer assessment period. The field of paediatric pharmacology is, however, fairly small, which can result in a bottleneck in evaluation. In 2002 an application through the centralised procedure took 452 days to complete. There is a legal limit to the assessment phase (210 days), but this only covers part of the process (Figure 4.1.). Although no precise estimate can be given, it is quite likely that the particular expertise required for a paediatric investigation will either increase the number of experts involved (an effect in person-days) or lengthen the process by a considerable number of days.

Box 4.1
Impact on the budget of EMEA

The budget of the PB and the additional funds needed by EMEA have yet to be determined. However, EMEA projects that its workload will increase from c. 60 applications per year at present to as many as 200 in the period immediately after the Regulation has entered into force, to stabilise at 100 to 150 procedures per year thereafter. Assuming constant costs per application, EMEA's budget would have to increase by *67% to 150%.* The 2003 budget amounted to €78 million (all expenses included) and EMEA employed a total of 287 people (EMEA *Budget for 2003*). In the worst-case scenario EMEA's budget would have to increase to *between €130 and €195 million* only to cope with the increase in marketing authorisation applications. The impact of EU enlargement has not yet been factored in, but if the ten new countries are added to the EMEA's jurisdiction, the workload will increase even further. On the other hand, part of EMEA's costs will be fixed, so that the marginal increase in costs will most likely be lower.

Bottom-line: A maximum increase in EMEA's budget of €130-€195 million per year.

Disclaimer: EMEA has not had the opportunity to comment on these estimates!

The increased workload would necessitate an expansion of the number of EMEA employees (e.g. scientific administrators and managers) and associated experts in the network (e.g. pharmacists and paediatricians). One observation by EMEA is particularly relevant, namely that three years after the introduction of the orphan drug regulation procedural issues are still under revision.
The requirement to submit the results from studies carried out according to a paediatric investigation plan may result in the rise of a market for specialised services and the employment of experts in developing of paediatric investigation plans. Designing clinical trials for children will become less problematic with the increase in expertise, which leaves funding as the main obstacle. The plan and the associated clinical trials will raise the costs involved in applying for a marketing authorisation by between €1 million and €7 million per drug for Phase III clinical trials in children.

Box 4.2
The total costs of additional paediatric testing

The average paediatric testing costs between €1 and €7 million, for an average of €4 million. If the anticipated increase in EMEA's workload (according to its own projections) is an indication of the marginal increase in the number of tests that will be conducted, then the total annual costs of additional paediatric testing can be estimated at €560 million in the first year, falling to between €160 and €360 million in later years.

Bottom-line: An increase in the costs of Phase III clinical trials in drug development of €160-€360 million after the first year.

The number of clinical trials in children will increase. In addition, it may lengthen the entire drug development process. The industry will probably develop ways to organise paediatric testing parallel with testing in adults. More importantly, deferrals will provide relief. They will allow the adult version to be marketed before the paediatric version has been authorised. Time-to-market will therefore most likely not significantly be affected.

Paediatric investigations can be difficult. Some of the barriers to paediatric testing are parental consent (especially when both parents have to give their consent), its heavy administrative burden, and the requirement to differentiate between age groups within the paediatric population, which makes the recruitment process more difficult and raises the costs. On the other hand, for some diseases clinical trials provide patients with the only opportunity to receive treatment and patients are attracted by the high quality of care. The problem of recruitment depends very much on the disease in question, but the only reason consistent across all drugs for enrolling children is that they are fewer in number.[24]

Smaller companies may find it more difficult to compete in product development or will have to charge a higher price for their products in a competitive market. The costs of clinical trials will increase as paediatric testing is added, thus raising development costs. On the other hand, the costs of paediatric testing are relatively modest (probably between €1 and 4 million, with an upper margin of €20 million for major sellers). This can, in turn, result in an increase in the revenues of companies involved in Phase III paediatric research. Small companies can also opt for a partnership with other (larger) firms that have the capacity to perform paediatric studies.

Box 4.3
Impact of paediatric testing on the costs of drug development

In 2000 European pharmaceutical companies spent $17 billion (€15.2 billion) on R&D. American data suggest that Phase III clinical trials account for c. 15% of total drug development costs. This translates to $2,550 million (€2,274 million) for European manufacturers. Assuming that the estimated costs paediatric testing are accurate, they would involve an increase in expenditure on Phase III clinical trials of *25%* in the first year and *between 7% and 16%* in the following years. Total expenditure on drug development would rise by almost *4%* in the first year and *between 1% and 2.5%* in subsequent years.

Bottom-line: An increase in total European expenditure on drug development of 1%-2.5% after the first year.

[24] The MHRA UK expects that if the incentive is right, many of the barriers to recruitment will dissolve.

The PB needs to contain or gather the appropriate expertise to be able to assess draft paediatric investigation plans and the studies subsequently conducted. National regulatory agencies will also need more expertise. The composition of the PB is critical in this regard. It must contain adequate expertise but not be dominated by any single interest or stakeholder group.
Products that professionals already use will become available in tested form, which will make them aware of emerging opportunities for improvements in medicinal treatment of children.
If the marginal costs of testing are passed on to consumers, households will be faced with higher drug costs and higher insurance premiums, depending on national reimbursement systems.

Box 4.4
Impact on consumer expenditure and industry costs

The total retail value of European pharmaceutical consumption (in the EU-15 and the NAS) is about €166 billion, while from an industrial perspective (turnover in producer prices) market size is $88 billion (€78.5 billion). From both perspectives the burden of paediatric testing is relatively light. If the costs are carried forward directly, consumers (or their insurers) would be confronted with an increase in costs of *0.1% to 0.3%*, while for industry the costs amount to *between 0.2% and 0.7%* of turnover.

Bottom-line: The costs of paediatric testing add 0.1%-0.3% to consumer expenditure and 0.2%-0.7% to industrial costs.

Long-term effects The requirement to submit the results of studies performed according to an agreed paediatric investigation plan will encourage the rise of standardised methods and procedures for paediatric testing, matching the requirements of the PB. Once the Regulation is established, it will result in higher and more homogeneous quality of paediatric testing –certified by the PB– throughout Europe. The safety of clinical trials in children will be controlled and certified.
The costs of paediatric medication and paediatric health care may increase as the costs of testing are carried forward. The impact on the revenues and profits of pharmaceutical companies will depend on the price elasticity of paediatric medicines and on the willingness-to-pay of households and the willingness-to-reimburse of insurance companies. However, the costs of paediatric testing do not appear to be excessive. Health care professionals appear willing – and may even feel obliged – to switch to tested medicines regardless of the costs. National governments may decide (and are already discussing the possibility) to negotiate or enforce price reductions.
An increasing proportion of the available medicinal products will be tested for use in children. From the time of entry into force of the proposed Regulation, the currently available patent-protected products that are not tested and will not be tested for use in children will be caught by the requirement relating to applications for new indications, new pharmaceutical forms and new routes of administration. It will take approximately between 10 and 15 years before the last patent expires (Figure 4.2.). However, after the patent expires generic drug manufacturers can enter the market without having to perform paediatric tests. The proposed Regulation does not impose a requirement after the expiry of the patent, but intends to attract manufacturers of off-patent drugs by means of an incentive. The effect on the availability of paediatrically tested generic medicines will consequently be more modest (Figure 4.3.).
The markets for patented and off-patent products overlap: producers of patented products can keep the brand name of a drug after its patent expires. They can then produce a generic version of

Figure 4.2
The long-term change in the supply of patent-protected medicinal products under the proposed Regulation

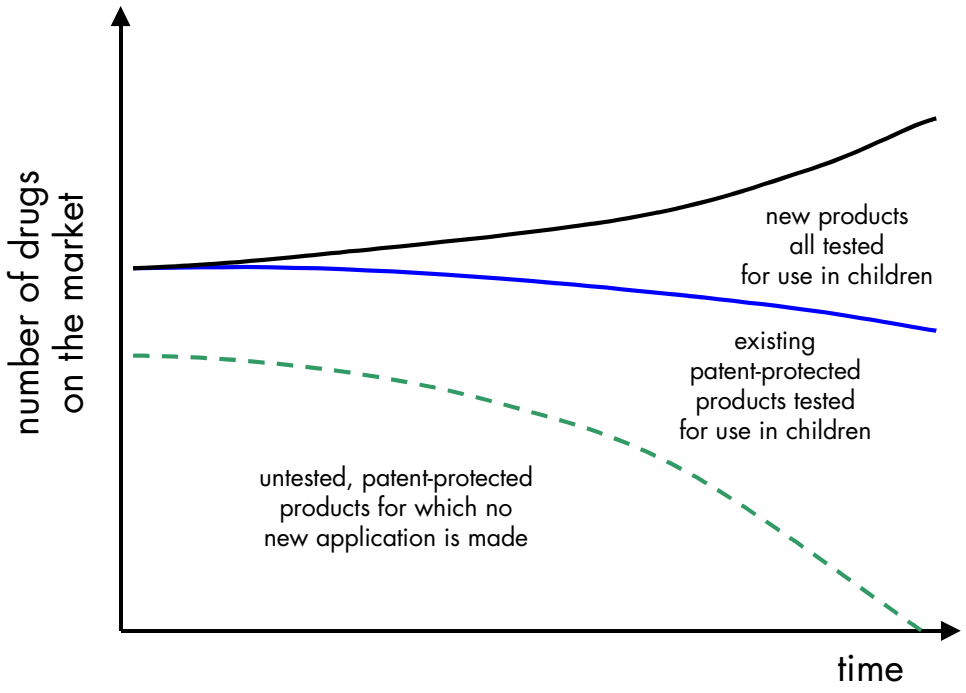
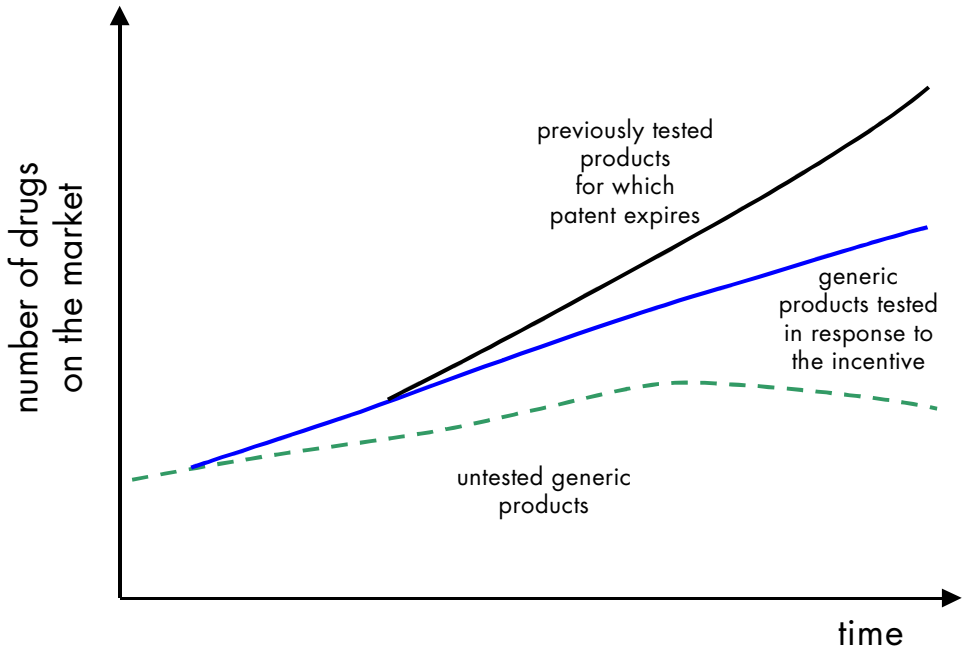


Figure 4.3.
The long-term change in the supply of generic medicinal products under the proposed Regulation



their medicine and apply for a PUMA. Companies can use their brand image to maintain market share, possibly increase it by lowering prices, and thus use the PUMA as an after-patent competitive instrument. Yet, sales do not necessarily have to increase.

The supply of licensed medicines for use in children will increase, resulting in better treatment, a higher quality of life, and lower health care costs. As such, this provision is crucial to attain the higher objectives of the proposed Regulation.

The expected increase in the supply of licensed medicines for use in children will allow health care professionals to provide better treatment, reduce the incidence of ADRs, and lower the chance of liability suits. Liability is a major issue (more in some countries, such as the UK, than in others), although it is recognised that it is not as big an issue in Europe as it is in the US.[25] It will also give them the opportunity to reduce prescribing of off-label and unlicensed products. Children are provided with a wider range of new and existing products tested for use in children, improving the quality of their treatment and raising the quality of their lives.

Box 4.5
Social savings through improvements in medicinal treatment

In Chapter 3 we constructed cost scenarios for the effects of off-label and unlicensed prescription on health care costs. In the most likely scenario – based on assumption closest to the literature– the total costs for the entire EU-15 of an additional two-day stay in hospital related to ADR would amount to *between $11 and $40 million (€10-36 million)*. In the upper range of our estimates –where ADRs occur more frequently, children have to stay in hospital for an additional three days, and more children are hospitalized annually– the costs would rise to *between $157 and $283 million (€140-252 million)*. These could be considered social savings, if off-label and unlicensed prescription were made unnecessary as a result of the proposed Regulation.

Bottom-line: The social savings of a complete eradication of off-label and unlicensed prescription are between €10-€36 million and €140-€252 million depending on assumptions. This excludes the value of improvements in the quality of life and the value of lives saved, both of which can be seen as considerably more valuable.

A defining characteristic of the Regulation is, however, that it targets the production of paediatric medicines (*supply*) rather than the way in which they are used (*demand*). Unlicensed and off-label medicines can still be prescribed. Health care professionals are expected to favour tested products over untested products. If the Regulation is successful, an increasing proportion of the available medicines will be tested and prescribing practices will automatically shift in the desired direction. However, if incentives are insufficient or the Regulation is incomplete, the basic problem will persist.

In this context it is important to understand that the proposed Regulation is only half of the solution to the lack of medicines tested for use in children. Demand (prescription) and supply (production) cannot be handled in a single regulation. The Commission cannot force health care professionals only to use tested products but it can work to make certain that their supply has been ensured. The proposed Regulation will consequently present a challenge to policy makers in the health care domain. There is an opportunity here for those responsible for the delivery of health care in the Member States to use formularies and reimbursement mechanisms to swing demand towards tested, authorised products.

[25] Liability always lies with the prescriber and not with the insurance company or reimbursement system.

Risks and uncertainties Excessive demands by the PB may delay the marketing of new paediatric medicines. The legal limits to the assessment process may prevent such delays from getting out of hand and deferrals make sure the timely availability of medicines for use in adults.
SMEs may not have an adequate infrastructure and resources to successfully apply, while other companies will develop their own centres of expertise.
Paediatric testing will not considerably raise the costs of product development. For most products the costs of paediatric testing will be manageable. The industry may, however, translate not only the costs involved in paediatric testing but also the risks of Phase III trials in children (medical risks to the test subjects as well as the financial risks of potential failure) and raise the price of its medicinal products more than is warranted by the costs of testing.[26] In the absence of reliable and detailed industrial data on the costs of paediatric testing, the industry is essentially free to charge any price it wants. The impact on consumer prices may well exceed the actual increase in costs.

Box 4.6
Impact on the affordability of medicines

If pharmaceutical producers apply a risk premium to the costs of paediatric testing, the effect on consumers (or their insurers) will be slightly larger than was estimated in the above. The increase in costs would then translate into a price rise of *0.1% to 0.4%*. Paediatric testing is consequently unlikely to reduce the affordability of medicinal products, although this could be different for specific individual drugs.

Bottom-line: On aggregate paediatric testing will increase the price of individual medicines by less than 0.5%.

The requirements may lead to more research in the most profitable areas of research rather than into the development of drugs that are most needed among the paediatric population. Companies and research institutes may be given an incentive to cut corners in paediatric testing, especially for orphan products (with few test subjects and a small market) and in the event that few parents and children consent to testing. However, the PB can issue waivers specifically to prevent medicines being investigated in children when it is unlikely to bring therapeutic benefits to children. In addition, the proposed paediatric study programme can be targeted on medicines that may not be profitable.
There is a risk that companies will become reluctant to develop new indications, new pharmaceutical forms and new routes of administration in small markets and for products with low sales. However, the costs of paediatric testing are manageable and will be adequately compensated for by the six-month extension of the SPC.
Authorised but untested products that do not change will not be paediatrically tested and will continue to be used. If the adult formulation of an untested drug is cheaper than the tested paediatric version of an alternative drug, health care professionals may still prefer the cheaper adult version.
The costs of developing a new indication, new pharmaceutical form or new route of administration are lower than the costs of developing a new drug, but the reward is the same. The industry may be drawn towards the second requirement, that is, find ways to adjust existing authorised products first, and focus on new products later. This is what happened in the US. This

[26] In their 1991 estimate DiMasi et al. adjusted the total costs of clinical trials upwards by c. 120% (Love, 1997).

may have the effect of stimulating innovation for already authorised patented products as companies may develop new indications specifically to benefit from the SPC extension.
If the industry responds favourably to the incentives and complies fully and rapidly with the main requirements, the first period of entry into force of Regulation may result in severe backlog of applications and assessments. The PB and EMEA may not be able to cope with a considerable increase in the demand for evaluation and quality control. Other risks materialise when the PB and CPMP disagree on the plan and when the industry learns how to write a successful paediatric investigation plan but the actual work deviates from the plan. However, there are provisions in the legislation for modifying the paediatric investigation plan, should difficulties arise or companies receive subsequent scientific advice that is contrary to what has been agreed in the PB.
Health care professionals are not obliged to prescribe tested products only and can continue to use off-label and unlicensed prescriptions. It will take at least 10 years and possibly as long as 15 years before the last untested patented products with a benefit for children have either disappeared or have been tested for use in children. Again, full success depends on consideration by those responsible for the delivery of health care selectively including medicines authorised for use in children on formularies and reimbursement lists (Thorsen and Mäkelä, 1999).

Impact of rewards and incentives

The reward for companies that comply with the core requirements consists of a six-month extension of the duration of the SPC. The voluntary type of marketing authorisation (the PUMA or Paediatric Use Marketing Authorisation) has an incentive attached (10 years of data protection for products with a paediatric marketing authorisation) for products with a PUMA.

Operationalisation Manufacturers of off-patent medicines can apply for a PUMA for drugs designed for use in the paediatric population. The application for a marketing authorisation has to be accompanied by the results of clinical tests in children. The PB will assess the draft paediatric investigation plans; the CPMP or the national competent authorities will assess the results of these plans, consulting the PB if they wish. Health care professionals cooperate in the conduct of Randomised Clinical Trials (RCTs). Children need to be enrolled to do the studies, and parents need to give their consent.
In order to be granted the extension of the duration of the SPC pharmaceutical companies must comply with the two main requirements relating to the inclusion of the results of a paediatric study in a marketing authority application for new or existing (patented) products. Product information, which is part of the marketing authorisation, will include information about whether or not a company has submitted studies in accordance with a paediatric investigation plan (i.e. to extend the SPC). Companies can use this information as the basis of a request on national patent offices to extend the SPC.

Short-term effects The reward for patented products that submit the results of a paediatric investigation plan as part of their marketing authorisation application will probably attract a lot of interest. The Commission hopes that the PUMA and its accompanying incentive will also be attractive for the development of off-patent medicines for paediatric use. The current infrastructure is already able to deal with such applications, but EMEA and national competent authorities will have to hire paediatric experts or outsource their evaluations. The PUMA will only be accessible to products with a therapeutic benefit for children that are effective and safe. No incentive can be given without a marketing authorisation for paediatric use.

Long-term effects More off-patent products, that are not required (currently or under the proposed Regulation) to perform tests, will be tested for use in children. The PUMA gives companies the opportunity to buy market access and capture a niche (i.e. exclusive part) of the paediatric market. A PUMA is expected to be more attractive for SMEs rather than for the big players in the pharmaceutical sector.

The incentive for off-patent medicines and the rewards for patented medicines are fundamentally different. The incentive for the PUMA will only be awarded to medicines for paediatric indications, whereas the reward for originator drugs is granted for all uses, regardless whether or not the paediatric studies yield positive or even conclusive results. The number of extensions awarded will consequently exceed the number of drugs newly licensed for children.

Box 4.7
The value of a six-month extension of the SPC

We have used the available information to estimate the value of a six-month extension of the SPC per drug (1) and for total drug production (2).

(1) Profits associated with the turnover required to recover the costs of drug development during a drug's patent life while maintaining current levels of profitability and R&D intensity.

Whereas the costs of Phase III paediatric testing amount to an estimated €1 to 4 million, the lower range of estimated profits associated with the six-month extension vary between *$0.9 and $10.2 million (€0.8-9.1 million).*[27] The data refer to the development of medicines for use in adults. When taking into account to possibility of applying for an SPC, the increase in market size when the paediatric market becomes more accessible (tested products will be superior), and the potential economies of scale inherent in EU enlargement, profits will have to be adjusted upwards. However, we do not precisely know the number of drugs in the market and the calculation depends on too many assumptions.

(2) The turnover and profits associated with the products for which the patent expires.

We have used an alternative approach to indicate the extent of the benefit.

- Off-patent products account for 13% of the global pharmaceutical market. Assuming that the same percentage applies to Europe, the size of the market for generic products can be estimated at $11.4 billion (€10.2 billion) and that of patented products at $76.6 billion (€68.3 billion).
- The patent life of a drug is 20 years. This means that on average every year 5% (1/20th) of all patented products becomes available for off-patent production with an annual turnover value of $3.83 billion (€3.42 billion) at original (patent-protected) prices.
- The value of a six-month extension of the SPC amounts to 5% of $76.6 billion (€68.3 billion) divided by two, or *$1.92 billion (€1.71 billion)* of turnover per year. Assuming a profit margin of between 10% and 25%, the value of six-month extension is *between $192 and $480 million (€171-€428 million)* for the entire pharmaceutical industry.

[27] See table 3.10. for the calculations. The lower estimate of $0.9 million assumes $200 million (€178 million) development costs, 71 months time-to-market, while the upper estimate of $10.2 million assumes $800 million (€713

(Box 4.7 continued)

However, after a patent expires companies will continue to sell their branded product and may even apply for the paediatric use marketing authorisation for off-patent products. Real gains will consequently be lower. On the other hand, companies invest in paediatric testing well before they reap the financial benefits of a six-month extension of the SPC. If, on average, they test five years before patent expiry, the discounted value of the total costs of paediatric testing of €160-€360 million will be €132-€296 million; for a ten-year period these values will amount to €108-€243 million.[28] These are the kinds of value that the industry will use to assess its investments.

Bottom-line: The value of a six-month extension of the SPC more than offsets the costs of paediatric testing. Under current conditions the pharmaceutical industry will be able to recover the costs of testing and make a profit on the SPC extension of between €63 million and €205 million (profits minus the discounted costs of testing over a ten-year period).

The incentive is aimed at currently existing off-patent medicines that have yet to be tested for use in children. For those products, the incentive is most likely relatively weak. Companies have to do clinical trials in children in order to qualify for the incentive; bioequivalence and bioavailability tests will not suffice. In return they will receive 10 years of data protection.

The incentive will most likely be less valuable to manufacturers of off-patent medicines than the reward for their competitors given that (i) data protection extends only to paediatric use –while the extension of the SPC also applies to adult use–, (ii) the incentive derives its economic value from a highly specific and generally small niche in the medicinal market, and (iii) it does not involve market exclusivity and competitors can consequently compete for the same market niche. The advantage will go to the first mover. New entrants into the market will have to perform their own tests and the PB may decide not to allow trials when there is no clear therapeutic or clinical value added or if double testing can become a problem. The PUMA will not necessarily result in higher sales. The authorisation applies to products already on the market that will now be tested for use in children. Health care professionals can either switch to the tested medicine or use an off-label alternative in a proper way by applying the information gathered as a result of paediatric testing.

Box 4.8
Impact on the revenues, profits and market share of generic drug manufacturers

We assume that every year 5% (1/20th) of all patented products becomes available for off-patent production with an annual turnover value of $3.83 billion (€3.42 billion) at original (patent-protected) prices. In principle, the proposed Regulation may make this portion of the market unavailable for generic drug manufacturers for an additional six months. However, many products will be excluded from the reward associated with the requirement as a result of waivers. In addition, the size of the paediatric market is estimated at only 15% of the total pharmaceutical market.

million) development costs, 71 months time-to-market. Both only take into account the real patent life of 20 years. The EGA estimates the social costs at €50 million per drug per year for the entire EU.

[28] At the official discount rate of 4%.

(Box 4.8 continued)

If we assume a paediatric market share of 15% and an additional 10% for the increase in the development of paediatric medicines, the market value at patent-protected prices that is denied to generic drug manufacturers for six months amounts to $479 million (€428 million).

Generic manufacturers generally offer their products at prices between 20% and 80% below those of the original patented product. Depending on the price cut, the maximum potential six-month loss of revenues of generic drug manufacturers can be estimated at between $96 million (€86 million) and $383 million (€342 million).

Profitability is lower among generic drug manufacturers than among originator drug companies. Assuming a profit margin of between 5% and 15%, the maximum potential six-month loss of profit amounts to between €4 million (5% of €86 million) and €51 million (15% of €342 million).

This amount can be considered the cost of adjusting to new market conditions resulting from a six-month delay of market access for a small selection of products. However, it is not incurred overnight:

- The generic drug manufacturers have already been informed of the fact that the new Regulation is approaching.
- The legislative process will take (at least) two years to complete.
- When the proposed Regulation enters into force, some provisions will be delayed by an additional one or two years.
- When patents are granted the information they protect becomes public. In addition, an SPC is requested and granted early in a product's patent life and the same will happen with the six-month extensions to the SPC.

In short, by the time the Regulation enters into force, generic drug manufacturers will have had several years to adjust to new market conditions and they will not be faced with a sudden six-month market blockade. In the future, they will be given several years advance notice of extensions to the SPC. The cost of adjusting to new market conditions will therefore be absorbed by the industry over a period of 2 to 5 years.

These costs represent a decline in annual market opportunities (and therefore impact on competitiveness). In addition, not all off-patent products are produced by generic drug manufacturers, so the estimated loss represents a maximum. And it will be a one-time cost: after the transitional period generic manufacturers will simply continue with business as usual even though they will have lost part of their market share.

Bottom-line: The producers of generic medicines will incur a one-time loss of revenue of between €86 million and €342 million or between €4 million and €51 million in profits, which represents the cost of adjusting to new market conditions during the transitional period of 2 to 5 years. After that period business will be as usual, although producers of generic medicines will have lost some of their market share.

Originator drug companies will have more time to economically exploit a patent while on a higher level of aggregation there will occur a change in the relative competitive strength of innovative pharmaceutical companies compared to producers of generics. The entry into the

market of generic drugs will be delayed. The US Paediatric Exclusivity Provision has generated the same effect.

In short, originator drug companies stand to gain substantially more than generic drug companies, resulting in a shift in their competitive position in the market in the favour of the former and an increase in the average price of medicines for use in children *and* adults (due to a rise in the share of patented as opposed to generic versions). There does not appear to be a valid reason for a longer extension of 8 or 12 months. Europe's competitive strength vis-à-vis the US does not only depend on this particular provision of the Regulation.

A clear indication of the lack of balance between the two groups of manufacturers can be derived from their respective position papers. The EFPIA paper basically reflects the current text of the proposed Regulation (although it suggest granting manufacturers of off-patent medicines market exclusivity rather than data exclusivity), whereas the EGA has repeatedly and vehemently voiced its opposition to the Regulation.

Households will be faced with higher average costs of medicinal products as the availability of generic drugs is delayed. In the long run insurance companies and households will be faced with higher reimbursement costs of medicinal prescription (due to increased testing and especially as a result of the delay of generic medicines). On the other hand, a premium may be reduced because fewer medicines are needed (more precise dosing and a lower incidence of ADRs).

Box 4.9
The impact on social costs

Based on the information and assumption used to estimate the loss of revenues for generic manufactures, we can estimate the impact of the six-month extension of the SPC on the expenditure of households and health insurers. The six-month extension of the SPC entails that consumers pay €428 million where they could be paying between €86 million and €342 million. The difference amounts to between 0.01% and 0.04% of total European health care expenditure and to between 0.06% and 0.25% of annual European pharmaceutical expenditure.

Bottom-line: The shift in market share from off-patent medicines towards patented medicines will increase European pharmaceutical expenditure by 0.06%-0.25% and total health care expenditure by 0.01%-0.04%.

Risks and uncertainties Regarding the PUMA, the current system of marketing authorisation already allows for the application of a paediatric marketing authorisation, but because of the marginal profits to be made and issues to do with brand names this has not proven to be an incentive to industry. If the incentive is insufficient or untenable, the measure will be ineffective. As it stands, the incentive for off-patent paediatric medicines may be insufficient to attract European drug manufacturers.

The 10-year period of data protection is a provision of the pharmaceutical legislation that tells regulatory authorities and other competent authorities not to license generic drugs to other companies than the one that owns the data that is protected. The data may have to be made publicly available, but only the applicant can use the data. This creates the danger of double testing: different companies can perform the same tests on children in order to gain market access, whereas double testing is considered unethical. The PB, however, will have the power to prevent such testing with regard to PUMAs.

Moreover, there may arise a legal disagreement over the definition of a "medicinal product". In the current text of the Regulation the extension of the SPC will be awarded only once per medicinal product. This leaves room for differences in the interpretation of the term product: the industry may decide that each new formulation, route of administration, indication, or dosage constitutes a new product and entitles the company to an SPC extension of the relevant patent. This would create a highly diffuse situation in which a single active substance would ultimately arrive on the market for generics in a variety of different forms. The Regulation needs to be unambiguous.

An implication of the core provisions of the proposed Regulation – the requirements, rewards and incentives – is that to a considerable extent the pharmaceutical industry determines which medicinal products become available for use in children. In general, the pharmaceutical industry prefers to invest in large markets (e.g. blockbuster drugs). Focussing the Study Programme towards niche markets may offset this. The PUMA may draw R&D funds into the most profitable areas of research rather than into the development of drugs that are most needed among the paediatric population. If the proposed Regulation draws large companies towards the development of (more profitable) originator drugs and SMEs towards (less profitable) off-patent drugs, the Regulation may widen the gap between large and small companies.

When the mutual recognition procedure is used, the extension will only be given if the product is authorised in all EU member states. This may prove difficult, especially when the NAS join the EU. On the other hand, this may act as a stimulus to shift to the centralised procedure.

Impact of additional requirements

The additional requirements describe the conditions under which the incentives and rewards are awarded. They concern labelling, placing on the market, post-marketing requirements, and pre-existing studies.

Operationalisation Pharmaceutical companies have to adjust the labels of their medicines (which involves a small cost). After a marketing authorisation has been granted for a medicines tested for use in children, the company has to ensure that the product is placed on the market within 12 months. Companies will, in selected cases, have to submit a plan on how to ensure follow-up and efficacy and to monitor ADRs related to the use of the medicinal product in the paediatric indication. If the submission of the results of paediatric testing was deferred, the marketing authorisation holder has report annually to the PB to provide an update on the progress with the realisation of the paediatric investigation plan. In the case of pre-existing studies, companies must submit the results of completed paediatric studies to the competent authorities within a year of the entry into force of the Regulation.

CPMP or a national competent authority decides when a risk management programme should be set up and specific post-marketing studies should be performed. For deferred studies, the PB needs to inform CPMP or competent national authorities if the marketing authorisation holder does not comply with the agreed paediatric investigation plan. The authorities need to assess the results of pre-existing studies and update the summary of product characteristics and the patient information leaflet. In general, government authorities must monitor and enforce compliance with the additional requirements.

The operationalisation of the post-marketing requirement needs a more systematic registration of ADRs. Health care professionals (doctors, nurses, pharmacists, coroners, dentists, and others) are expected to report ADRs either on a compulsory or voluntary basis. They can support government monitoring and provide feedback on labelling practices. Health care professionals must make sure that they acquire the most recent scientific insights. It has been suggested that health care professional be paid for their contribution, both as a reward for the considerable effort involved and as an incentive to attract experts.

Children may be enrolled in specific follow-up programmes and – depending on the system – parents and children may report ADRs directly (most likely on a voluntary basis).

Short-term effects New and existing drugs tested in children and authorised will be made available within a year. Health care professionals will gain better knowledge on ADRs and, as a result, children will receive safer treatment. If companies comply adequately, the additional requirements will generate considerable benefits to the European paediatric population and prevent the misallocation of resources at comparatively low marginal costs to pharmaceutical companies and government authorities. Both can build on currently existing (mandatory) systems.

Pharmaceutical companies will have to pay fixed costs to design plans for follow-up and progress reporting and variable costs to maintain pharmacovigilance and write annual reports. The level of costs is unknown. It is, however, already a requirement and it is safe to assume that pharmaceutical companies will have acquired the necessary expertise to adapt efficiently to the requirements of the new Regulation. Government agencies will, however, be faced with an increased workload and a need for more experts as follow-up plans have to be assessed and compliance has to be monitored and enforced. The same applies to the requirement concerning pre-existing studies. The government has to set up and finance a system of monitoring (e.g. a database of existing studies) and check if applicants have already performed studies.

Long-term effects Pharmaceutical companies will be encouraged to improve their marketing processes in order to comply with the requirement to place products on the market within 12 months. In the US this requirement did not work very well. It remains to be seen if the European industry can succeed.

Proper labelling of tested paediatric drugs will create a sharper definition of paediatric and other segments of the market for off-patent drugs. The higher objectives of the proposed Regulation are served by a clear distinction in the market between tested paediatric medicines and untested medicines for use in adults and by the gradual eradication of unlicensed and off-label prescription. Health care professionals benefit from increased transparency in the choice between tested and untested off-patent medicines: it will be easier to see whether a drug is tested for use in children or not. Increased transparency in the choice between tested and untested off-patent over-the-counter drugs (OTC-drugs) will also benefit children and their parents. Better recognition and more transparent choice do not automatically translate into a change in prescription practices: health care professionals and households remain autonomous in their choice between tested and untested alternatives.

The post-marketing requirement will force companies to develop an improved understanding of the safety, efficacy and quality of their paediatric medicines, which may result in the development of better medicines for children. Children can be treated more effectively and there will most likely be fewer cases of adverse drug reaction (ADR) or suboptimal treatment. The impact of this requirement can only really be ascertained at a later date, because the long-term effects of a drug in children cannot necessarily be assessed until much later in a child's development.

Risks and uncertainties There exists the possibility of a perverse effect on the choice of health care professionals when a comparison is made between a tested medicine (labelled) and an untested originator drug (unlabelled) when the latter has a greater therapeutic benefit but is not required by the Regulation to be tested for use in children. The same effect may occur when parents or others buy OTC-drugs and compare tested medicines (labelled) with untested drugs (unlabelled). This is a risk that will eventually dissipate as untested patented products disappear through attrition, but this will take between 10 and 15 years.

Deferral may become a very long-term affair and post-marketing reporting may become a formality. E.g. in the UK, as in other Member States, physicians report suspected ADRs only rarely. CPMP and the national authorities may not have sufficient expertise and the

implementation of a post-marketing system may be complicated. The reporting of ADRs is currently inadequate (mainly serious ADRs seem to be reported) and it may be impossible to improve reporting sufficiently to support the Regulation. Where pre-existing studies are concerned, it will be a challenge to acquire data on negative trials.

Impact of facilitating measures

Three measures have been included to make it easier for companies to fulfil the requirements of the proposed Regulation, especially in the early period of its existence. They concern the waiver of the requirement for data, deferral to initiating or completing studies in the paediatric investigation plan, and the Community referral procedure for existing authorisations.

Operationalisation Regarding the Community referral procedure, pharmaceutical companies will be gaining an opinion of the CPMP, which will lead to a Commission decision, which will direct the Member States to implement specific wording in product information. In the case of deferrals, companies have to report regularly on ongoing studies and take into account the need to avoid delaying the availability of new medicines for use in adults. The PB has to assess requests for waivers and deferrals. EMEA will maintain a list of product specific and class waivers and publish this list on its website. All requests for waivers and deferrals can be processed through existing procedures or through amendments of existing procedures.

Companies have to allocate funds to collecting current evidence (i.e. literature searches, hiring experts) to support a claim with respect to the therapeutic benefits, efficacy and safety of a drug when used in children, this in addition to the costs of clinical testing. Such costs will, however, be minor. The PB, in turn, needs to hire or contract the expertise to decide on waivers and deferrals. The accumulation of incomplete paediatric investigations needs to be monitored and eventually assessed.

Short-term effects Deferrals are not intended as a means to reduce the workload of the PB and EMEA, but they will help during the transitional period when the number of applications is expected to increase considerably. Current ongoing applications will not be affected by the proposed Regulation, but will be completed following normal procedures. Waivers will quickly help to focus the work of the PB on those products that may be of value for the medicinal treatment of children.

The Community referral procedure provides a shorter route to gain access to the markets of all EU Member States. The incentive to turn from the mutual recognition procedure to the Community referral procedure will increase the workload of the latter, although it will be compensated for by a reduction in the workload of the mutual recognition procedure.

Long-term effects Paediatric testing will only be done when necessary, that is, when it can possibly make new or existing medicines available for safe and effective use in children. The possibility of deferral allows the pharmaceutical industry to adjust to new requirements or when paediatric testing takes longer to complete, without obstructing the availability of medicines for use in adults.

Waivers will help identify medicinal products that are not fit for use in children, which acts as a support for health care professionals in their choice between different available medicinal products. They will also prevent unnecessary testing when a new paediatric medicine has no apparent therapeutic or clinical value added.

Risks and uncertainties For some medicinal products a waiver will be clearly appropriate or inappropriate. However, there will be a grey area where decisions are difficult and it is uncertain how many medicinal products inhabit this grey area. Decisions in this area are inherently hazardous, which may lead to risk-averse decision-making to the detriment of paediatric medicinal development.

Deferral may become an automatic resort when standard investigation plans are submitted but resources are not (immediately) allocated to put them into action. In the worst case, the product may never be labelled for children. No time limit has been set for the deferral of paediatric investigations and enforcement measures are limited to annual progress reports, fines and a naming and shaming policy. This is especially so, because the hurdles for taking products off the market are very high.

Health care professionals may decide to prescribe the medicine for use in children in anticipation of their eventual testing, even though the tests do not have to be conclusive or even positive.

Impact of support measures

Finally, the objectives of the proposed Regulation are reinforced by three support measures, namely the provision of free scientific advice, a number of initiatives involving communication and coordination, and the establishment of a Paediatric Study Programme or Medicines Investigation for the Children of Europe (MICE).

Operationalisation Companies can request scientific advice to support and improve paediatric testing. Pharmaceutical companies and health care professionals may submit proposals for studies on existing products to be funded by the study programme. The MICE has to be established by the authority of the Commission, the European Parliament, and the Council of the European Union. Funds will have to be allocated. One of the first tasks of the PB will be to identify research priorities. The priorities should ideally balance acute and chronic conditions. EMEA must evaluate the functioning of the programme on a regular basis. Children and their parents can become involved in the work of MICE either as patients in trials financed by the study fund or by lobbying to influence the assignment of research priorities.

In turn, the knowledge base depends crucially on the contribution of companies, academic researchers, and health care professionals. They can give input, provide feedback, and supply experts for the creation of new knowledge (e.g. for the inventory of existing medicinal products). Specific health care experts may be asked to become advisors to the PB, they may become members of the network, and they are required to provide information on all existing uses of medicinal products in paediatric indications.

EMEA and the PB have to establish a network with specific expertise in the performance of trials in the paediatric population. They can build on the existing network of 3,000 experts maintained by EMEA, although it may have to be enhanced to improve the quality of advice specific to the needs of the paediatric population. In addition, they have to put in place databases and online facilities as well as hire in-house experts. EMEA gives advice on the design and conduct of various tests and studies necessary to demonstrate the quality, safety and efficacy of the product in the paediatric population. Such advice is already available for a fee that varies between €6,000 and €70,000 depending on the nature and extent of the questions.[29]

[29] EMEA provides advice on the manufacturing process, on pre-clinical trials, and on clinical trials. The more a company asks, the higher the fee will be.

Box 4.10
The value of free scientific advice

The additional applications that EMEA expects to have to handle when the Regulation enters into force, may all accompanied by a request for free scientific advice. If that advice is valued against current fees, then the total value of this particular measure can be estimated. In the first year the expected costs would amount to *€840,000* for minor requests and *€9.8 million* for major requests. After the first year the costs would decline to *between €240,000 and €540,000* for minor requests, and *between €2.8 and €6.3 million* for major requests.

Bottom-line: Providing free scientific advice will cost EMEA anywhere between €0.25 million and €6.3 million in lost revenues.

Disclaimer: EMEA has not had the opportunity to comment on these estimates!

Short-term effects Access to knowledge about paediatric medicines, clinical trials involving children, and related issues will be improved. Pharmaceutical companies can achieve efficiency gains by obtaining prior information on the PB's assessment of the paediatric investigation plan as well as by improving the design of clinical trials. Free advice can help to contain the costs of developing a paediatric investigation plan.

The government's interests will be served by the higher average quality of submitted paediatric investigation plans and a shorter average period of assessment. Providing free scientific advice will, however, cost time (increased workload for EMEA and the PB) and public money (fixed costs for establishing a network, a database, a survey, etcetera; variable costs for maintaining and updating the instruments). Health care professionals will benefit indirectly in that better clinical trials may lead to better evidence on the use of paediatric medicines, which can in turn result in better treatment.

The inventory of existing medicinal products will help to create a good picture of the products that are currently available for the use in children and to centrally collect the information that is available on each medicine in different countries and with different stakeholders. In addition, the inventory will prevent the duplication of clinical trials in children.

Long-term effects In the long run free scientific advice, communication and coordination, and the study fund will generate economies of scale and scope in pharmaceutical R&D and paediatric testing. It is generally considered a highly valuable measure that will provide a strong stimulus to paediatric research in Europe. The inventory of existing medicines will provide companies with an overview of the market for paediatric medicinal products and help to identify opportunities (e.g. therapeutic gaps). Knowledge will spill over from large companies to SMEs that have a narrower knowledge base. SMEs are most likely to use the opportunity to acquire free advice, because they lack in-house expertise on trial designs, pre-clinical and clinical trials, and on the centralised procedures. Larger companies generally employ experts in each area, but even they may not have sufficient expertise in the area of paediatric medicines.

The period between trials, approval, and placing on the market will become shorter. Improvements in knowledge transfers may also result in more cost-effective study designs and industrial savings and will prevent the duplication of tests. In this fashion the government contributes to a more homogeneous basis to the performance of tests.

The instruments of communication and coordination create greater transparency in the market and provide support for the self-regulating behaviour of companies (which products to select) and health care professionals (which medicines to prescribe). For example, health care professionals as well as children, parents and guardians can use the inventory of existing medicinal products to

choose between medicines (prescription or OTC; tested and untested). The network of experts can create an economy of scope considering that there are relatively few experts and they are scattered across Europe.

The Study Programme can give support to off-patent drug manufacturers for the investigations needed for a paediatric marketing application. The programme can be used to strengthen pharmaceutical R&D in Europe. It will prove particularly useful for small companies, whose work is restricted by a narrow knowledge base, small markets, and a lack of access to capital. The Study Programme can support the development of medicines for rare child diseases, support paediatric testing of orphan drugs, and thus provide health care professionals with better medicinal tools. Children with a rare disease will be given a wider range of medicinal products for treatment.

Health care professionals gain quicker access to new drugs and new forms of existing medicines and improved study designs will lower the risks for children enrolled in clinical trials. Once the Study Programme begins to generate results, it will make available tested medicinal treatments for rare childhood diseases that would otherwise remain unavailable. One such area concerns neonatal medicines. Almost all neonatal medicines are currently unlicensed and parents are highly reluctant to enlist their child in a clinical trial. Under the auspices of the Commission the Study Programme could act as a trusted party.

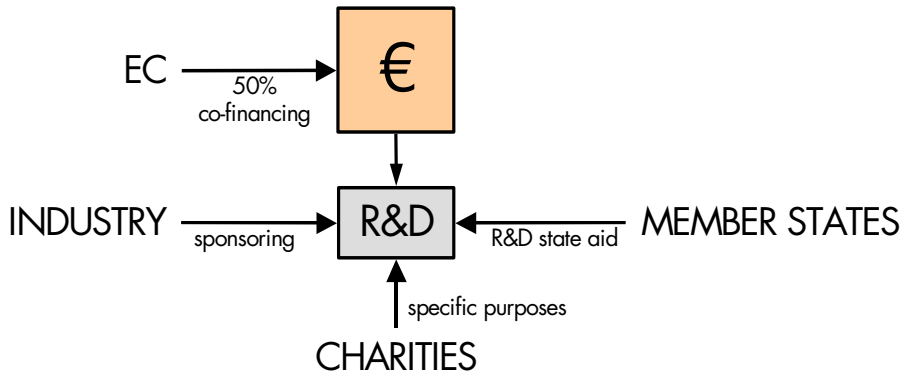
Risks and uncertainties Pharmaceutical companies as well as researchers will be reluctant to share proprietary information on medicinal R&D, testing, and marketing, particularly if such information is publicly disseminated. If the government provides free advice, it can act as a disincentive to hire experts (an effect on employment) or on the creation of knowledge within companies and institutions (an effect on the overall knowledge base). The quality of the information can also pose a problem, especially when parties with an interest in the market supply it. As a consequence of the current lack of knowledge in the field, it is uncertain whether a working group of the CPMP, which will be responsible for providing scientific advice, has sufficient expertise in the field of paediatric testing. The network of experts could function as an autonomous entity, but it would work better if a central authority (e.g. the PB or EMEA) were to act as an executive power. It seems likely that the working group will consult the PB before giving its advice on draft protocols.

Companies will become dependent on the expertise and speed of the authorities. Delays in the response to scientific questions can affect the development and marketing process. However, the advice process has fixed time frames implying that there is a maximum time within which the advice has to be agreed.[30] In addition, the benefits appear to be very real. In its annual report EMEA states: "42% of the medicinal products that received a positive opinion in 2002 had previously benefited from scientific advice, whereas 90% of applications that were withdrawn had not requested scientific advice."

The main challenge of the support measures concerns the financing of the work commissioned by the study fund. Usually, the EU can only provide support on the basis of 50% co-financing, which means that applicants for the fund need to have alternative sources of funding. It will prove particularly difficult – if not infeasible – for health professionals and academic researchers to find additional funding, especially because their work generally is not destined for the market. Three sources of matching funds can be identified (Figure 4.4.): (i) national governments (e.g. that want to strengthen their R&D capacity to work towards the objectives of the Lisbon strategy), (ii) pharmaceutical companies (e.g. as a social investment), and (iii) charities (to support

[30] The legal limit is 120 days. In 2002 it took EMEA an average of 106 days to handle requests for advice (EMEA, *Eighth Annual Report 2002*).

Figure 4.4. Potential sources of matching funds for applicants of the Paediatric Study Programme



research into a specific disease, although this possibility only really exists in a few countries, such as the UK). Another solution that was suggested by several experts was to impose a surcharge (1 or 2%) on pharmaceutical sales to finance the fund.

What will be the impact of the Regulation as a whole?

The provisions of the Regulation have been examined more or less independently. How will they work as a whole and will the proposed Regulation achieve its objectives?

Certainties

The Regulation will cost money. Industry will have to pay for complying with the requirements and applying for a PUMA. Government has to provide an infrastructure and invest time and effort in handling applications, doling out rewards and incentives, and providing scientific advice and other benefits. It will be possible to build on existing structures and procedures (e.g. for pharmacovigilance), but the level of activity will increase considerably.

The two main requirements of the proposed Regulation are inescapable. In order to obtain a marketing authorisation a paediatric investigation plan must be drafted and its results must be submitted. Waivers and deferrals prevent unnecessary testing and give the PB an instrument to avoid misuse of the Regulation. Deferrals will also prevent any delays to market for products developed for adults.

The pharmaceutical industry will be rewarded with a six-month extension of the SPC for submitting the results of tests for the use of medicines in children. This does mean that the generic equivalent of the tested medicines will arrive on the market six months later and – given that generic medicines are much cheaper – that consumers will have to pay higher average prices for medicines for paediatric and adult use.

A best-case scenario

The Commission hopes that the Regulation will achieve its main objectives. What if all predicted positive impacts that were identified in the preceding analysis come true?

- A larger proportion of medicines will be tested for use in children and medicines for children will become safer and more effective. Ten to 15 years from the Regulation's entry into force all patent-protected medicines will be tested for use in children (unless the requirement to be tested has been waived). The Study Programme will ensure that

medically indispensable but economically less interesting medicines (e.g. orphan drugs) are studied as well.

- The interplay between a number of provisions will encourage pharmaceutical R&D –in industry, academia and specialized research institutes– and improve the competitive strength of European manufacturers vis-à-vis the United States. This concerns the requirement to perform paediatric testing, the PUMA as a competitive instrument in the market for off-patent medicines, the Study Programme, the network of experts, and the support measures (free scientific advice, an inventory of available medicines, et cetera).
- The support measures will increase the amount of knowledge on performing clinical trials involving children and on the medicinal treatment of children, and will ensure the wide availability of that knowledge throughout Europe and the pharmaceutical industry. They will thus raise the quality and homogeneity of clinical trials involving children as well as shorten the assessment period.
- By changing the supply of medicinal products, the Regulation will change prescription practices. Health care professionals will reduce off-label and unlicensed prescription and switch to medicines tested for use in children, even when they are more expensive. Their incentives are not targeted directly, but they will feel obliged to provide their patients with the best possible treatment.
- Better testing, safer medicines, and the greater availability of tested medicines will improve health care for children and reduce the prevalence of ADRs and the burden of childhood disease. Improved paediatric medicines translate into shorter hospitalisation, lower medicinal consumption, lower liability costs, and lower insurance premiums. Although the extent of the reduction in costs cannot easily be determined, it will most likely more than compensate for the increase in average drug prices brought about by the delay in the marketing of generic alternatives.

Limits to the best-case scenario

In our analysis we have identified a number of potential problems and risks, some of which are more likely to occur than others. To what extent will the shortcomings and likely risks and uncertainties challenge the achievement of the best-case scenario?

- The incentive to attract generic medicines to the PUMA is relatively weak. It is unlikely to result in a sizeable increase in the number of tested generic products. The Regulation will also not capture all patent-protected products: those that have already been granted a marketing authorisation but that do not change, will not be required to be tested for use in children. The treatment of children will consequently continue to involve a considerable, albeit declining, number of untested patented and off-patented medicines.
- R&D will be drawn first of all towards the most profitable medicinal products, the largest markets, and the adjustment of existing patented products rather than the development of new products. Moreover, the industry and not government will decide on the direction of R&D. The study programme may provide solace by funding research into underrepresented areas.
- Even though the effect on prices and costs may be neutral, the industry can decide to raise prices over and above the increase in the costs of testing. At the same time health care professionals may choose to prescribe cheaper untested medicines instead of their tested alternatives.

- Operationalisation will be a major challenge for the public authorities charged with the implementation and enforcement of the Regulation. Administrative inefficiencies, backlogs, and a lack of experts and funds may make the Regulation less effective.
- The impacts of the Regulation will not be divided equally among companies of different sizes and specialisations and between the Member States of the EU. Companies that specialize in off-patent medicinal products will not gain as much as originator drug companies. The Regulation may draw large companies towards the development of (more profitable) originator drugs and SMEs towards (less profitable) off-patent drugs, thus widening the gap between large and small companies.

Economic impacts

The economic impacts of the proposed Regulation concern all stakeholders. It is also the area where trade-offs are most important. What are the costs and benefits of the proposed Regulation?

Government The operationalisation will cost the government a substantial amount of money: to finance the increased workload of EMEA (€130-195 million), the finance the Study Programme ($250 million in the US), and to provide free scientific advice (up to €6.3 million) and other facilitating and supporting measures.

Public investment is repaid:

- *in kind* through an increase in the availability of medicines tested for use in children (better treatment; a higher quality of life)
- *in money* when better treatment reduces the length and costs of paediatric health care treatment (shorter hospitalisation; fewer ADRs) and through the fees paid for marketing authorisations

Industry will also have to invest to meet the new requirements and to take advantage of the benefits, most notably the PUMA.

- The total annual costs of paediatric testing can be estimated at €560 million in the first year, falling to €160 to €360 million in later years
- The drug development process may become longer to allow for paediatric testing although time-to-market for adult medicines will not significantly be affected.

The benefits accrue both on a macro-economic and a micro-economic level:

- *Micro-economic impacts*: The pharmaceutical industry will have to invest in paediatric testing, but in return it receives a reward (for compliance with the requirement for patented products) or an incentive (for the paediatric use marketing authorisation for off-patent products).
  - Originator companies (patent holders) are rewarded with a six-month extension of the SPC, which could be worth up to €1.7 billion in turnover per six months and estimated profits of between €63 and €205 million.
  - Producers of off-patent medicines receive ten years of data protection, but its value cannot be determined. The incentive they receive does appear to be weak and may not attract much attention. Moreover, they incur a one-time loss in profits of between €4 and €51 million over a 2 to 5 year period (an *incidental* loss) and they lose part of their market share (a *structural* loss).
- *Macro-economic impacts*: The costs of testing will benefit research institutes and the services that supply the pharmaceutical industry, geared especially towards paediatric

testing or involved in a more general capacity. Increased testing will actually create value added for the European economy, unless research is outsourced to institutes outside the EU.

Consumers and health care professionals Consumers will experience a slight increase in the health care costs and the price of medicines. The worst-case estimate shows a 0.25% increase in pharmaceutical expenditure.
They are rewarded with improvements in child health care and in the safety and efficacy of medicines. Much depends on the willingness of health care professionals to prescribe medicines tested for use in children, but our estimates show that the price will not be an obstacle. The affordability of medicines will most likely remain as it is.

Social impacts

The Regulation will not result in a win-win solution. Producers of generic medicines will not benefit as much as the producers of originator drugs. Their main advantage lies in the support measures (e.g. free scientific advice). The effects will consequently also vary between Member States, given that in some countries generic medicines have captured a sizeable proportion of the market (up to 40%), whereas they are insignificant in other markets.
SMEs will be able to benefit from the economies of scale and scope inherent in the support measures: access to free advice and information on therapeutic needs (which has market value). They may find it more difficult to compete in the market for paediatric medicines when the Regulation raises the costs of drug development. They will have to find creative ways to remain competitive, while containing costs. In addition, SMEs may be concentrated in the market for off-patent medicines and as a result the gap between large and small companies may widen.
The main social impact will be that the increased availability of medicines tested for use in children –without a substantial rise in medicinal prices– will provide the opportunity to avoid preventable ADRs, raise the quality of medicinal treatment for children, and thus improve their quality of life. The proposed Regulation will therefore achieve its highest objective.

Environmental impacts

The measures proposed in the Regulation have no substantial environmental impacts. However, the development and manufacturing of medicinal products requires natural resources and generates waste. In addition, households, GPs and hospitals regularly dispose of unused medicinal products. The pharmaceutical industry currently operates in a framework of environmental regulation, both at EU and national level. As a consequence, the industry tries to minimise its impact on the environment by adopting the waste minimisation hierarchy of elimination, re-use, recycling, recovery and disposal (www.efpia.org). The minimal impact (confirmed by the interviews) prompted us to forego a detailed assessment of the environmental impacts of the individual provisions of the proposed Regulation.

Impacts on sustainability

Sustainability relates to three issues: (1) protection and renewal of the stock of natural, human, and other resources; (2) the technical efficiency with which resources are used to produce goods and services; and (3) equity within and between generations. We will only discuss the impact on sustainable development of the Regulation as a whole, because a discussion of the way in which each of the individual key provisions affects sustainability is neither feasible nor useful.

1. *Protection and renewal of stocks of resources*: The impact of the proposed Regulation is limited. The Regulation is mainly aimed at encouraging clinical trials in the paediatric

population. However, it is most unlikely that an increase in the number of trials in the paediatric population will have serious consequences for the stock of resources.

2. *Technical efficiency of resource use*: The Regulation may have an impact on the direction and potentially –albeit to a lesser extent– the speed of innovation in the pharmaceutical industry, because of the increased stringency of the requirements for bringing a product on the market. In contrast, innovation in paediatric medicines may, however, be increased.
3. *Equity within and between generations*: Equity is probably most affected by the proposed Regulation. The Regulation will impose costs and award benefits to a different extent to countries (because of differences in health care and health insurance systems), companies, and groups of people. It does not result in a win-win solution, although there do not appear to be outright losers. Few concerns were expressed with respect to intergenerational equity. Future generations of children are more likely to be enrolled in clinical trials, but in return they will be provided with better medicines, more effective and safer treatment, and a higher quality of life.

Will the Regulation achieve its higher objectives?

Our assessment indicates that the proposed Regulation will achieve its objectives. The effect on each objective will, however, vary:

- **Stimulating the development of medicines for use in children.** This objective will be achieved, albeit at a price. Producers of patented medicines will benefit substantially more than producers of off-patent products. Households, health care professionals, and insurers will be faced with slightly higher drug prices, due to a delay in the marketing of off-patent medicines and as a result of the costs of paediatric testing. Our main doubt concerns the attractiveness of the PUMA and the impact on producers of generic medicines.
- **Ensuring that such medicines are appropriately researched and authorised.** The proposed Regulation will unequivocally achieve this objective. Marketing authorisations become conditional upon agreement on a paediatric investigation plan and the performance of paediatric studies. The additional requirements and facilitating and supporting measures provide strong support for research by smoothing procedures, providing information, and ensuring availability.
- **Improving information on the use of medicines in children of different ages.** The mechanisms proposed in the Regulation will contribute to the creation of a firm knowledge base on the medicinal treatment of children and on clinical trials in children. The Regulation will introduce a potential force for standardisation, cooperation, and prioritisation. Whether this improved information directly leads to improved prescribing is beyond the scope of the proposed Regulation.
- **Achieving these aims without delaying the authorisation of medicinal products for other segments of the population**. Some of the main risks and uncertainties relate to possible delays in drug development, marketing and authorisation. The proposed Regulation provides adequate instruments to prevent most of these from materializing. Waivers single out products for which paediatric testing is deemed unnecessary. Deferrals allow the adult version of a medicine to be marketed, while testing for the use in children continues. Thus, this objective is likely to be achieved.

The higher objective of the Regulation –the very reason why it was drafted in the first place– is **to improve the health of the children of Europe**. The proposed Regulation provides one half of the solution. By changing the economics and legal preconditions of the production of medicines, the Commission hopes to steer consumers (health care professionals and households) towards tested and, hence, safer and more effective medicines. If the tested medicines are indeed prescribed, children will receive better treatment, involving shorter hospitalisation and lower drug consumption, and enjoy a higher quality of life. A number of risks and uncertainties remain, but the most likely ones do not substantially threaten the impact of the Regulation. Choice remains the most uncertain factor: the readiness of the industry to focus on the development of paediatric medicines, the response of generic drug manufacturers to the incentives of the PUMA, and the willingness of health care professionals to prescribe tested medicines. The final piece –regulating prescription practices– will have to be provided by policy makers in the health care domain.

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APPENDICES

Appendix A: Evaluating implementation and outcomes

Introduction

In order to evaluate both the implementation process and the outcomes of the Regulation, clear objectives need to be set and measurable indicators need to be defined. To measure the impact of the Regulation, systematic data collection needs to be planned in advance in order to start at the moment that the Regulation comes into force. Reconstituting missing data is cumbersome, expensive and might lead to unreliable data. Therefore it important to design an evaluation strategy as part of the extended impact assessment to ensure that adequate data will be available and that the most relevant questions will be asked in the evaluation. The evaluation strategy needs to specify the following:

- What types of evaluation are needed? What should be the focus of the evaluation?
- What are the appropriate indicators? What type of data needs to be collected?
- Who is responsible for carrying out the evaluation? When should evaluations be planned?

Types of evaluation

Broadly speaking, three types of evaluation of policy or regulation can be distinguished:

- *Ex-ante evaluation or structure evaluation:* This type of evaluation is aimed at assessing whether a specific policy or regulation is designed in such a way that successful implementation of that policy or regulation is possible. Important questions in this type of evaluation are, for example, whether the policy or regulation is internally consistent, and whether the policy or regulation is expected to contribute to the defined objectives.
- *Process evaluation:* This type of evaluation is aimed at gaining an insight in the implementation of a specific policy or regulation. Important questions in this type of evaluation are, for example, whether the policy or regulation was implemented as intended, and whether the resources were used efficiently.
- *Ex-post evaluation or outcome evaluation:* This type of evaluation is aimed at assessing whether a specific policy has led to the desired outcomes. Important questions in this type of evaluation are, for example, whether the objectives of the policy or regulation were reached, and whether the policy or regulation has had any unintended effects.

All three types of evaluation are important as each of the types of evaluation can generate important lessons for the future. A proper evaluation of a policy or regulation thus includes all three types of evaluation. The current extended impact assessment is a form of ex-ante evaluation. This section of the report sets out a strategy for the process and outcome evaluations of the Regulation on medicinal products for paediatric use.

Process evaluation: indicators and data needs

The process evaluation of the Regulation on medicinal products for paediatric use should focus on the question whether the Regulation is implemented in such a way that the overall objective of the Regulation can be reached, and, if not, what suggestions can be made for future implementation of the Regulation. The overall objective is "*to promote the development of medicinal products for human use in order to meet the specific therapeutic needs of the paediatric population*". In the process evaluation of the Regulation, the following data are of importance and need to be collected:

Quantitative indicators

- Number of awards of Supplementary Protection Certificates and of data exclusivity (including number of waivers and deferrals)
- Percentage of marketing authorisations granted through the different procedures (central procedure and mutual recognition procedure)
- Number of requests for free scientific advice
- Number of studies funded by the study programme
- Number of trials entered in database
- Workload for EMEA/CPMP and PB related to implementation of the Regulation (FTE's)
- Economic costs of implementing the Regulation
- Number of ADR reports
- Number of children enrolled in paediatric clinical trials

Qualitative indicators

- *Functioning of the PB:* What is the expertise available to evaluate the paediatric investigation plans and to assess requests for waivers and deferrals? To what degree has the Board been able to set research priorities?
- *Functioning of the network for the performance of clinical trials in the paediatric population:* Who are involved? What is the type and frequency of interaction? What are the main focus areas of the network? What are the achievements of the network to date?
- *Coordination between the European Commission and the EU Member States:* To what degree have member states introduced policies to complement the Regulation? Have the Member States delivered the required information to the Commission? Have they reported on any problems with the implementation of the Regulation?
- *Coordination between the PB and CPMP:* What is the type and frequency of interaction? How are responsibilities divided among these organisations? Is this division of responsibilities satisfactory?
- *Timely implementation of the Regulation:* Is the implementation of the different components of the Regulation going according to plan? For example, are products placed on the market within the specified term; is the survey on existing paediatric uses conducted within two years of the entry into force of the Regulation; did the Commission publish a list of companies that have benefited from any incentives in the Regulation on an annual basis?

Outcome evaluation: indicators and data needs

The outcome evaluation of the Regulation on medicinal products for paediatric use should focus on the degree to which the Regulation has contributed to reaching the intended objective. An evaluation of the outcomes of the Regulation is however difficult for several reasons:

- *The objective of the Regulation is not very well specified*: The objective of the Regulation is very broad and not quantified, which makes it difficult to assess the outcome of the Regulation against this objective. As the objective is defined in terms of "promoting development" and "meeting needs" and not in terms of, for example, the percentage of medicinal products tested in children, it will not be easy to assess whether the objective has been reached. In addition, it is also unclear what the specific therapeutic needs of the paediatric population are, i.e. there is currently no consensus on research priorities in the field of medicinal products for paediatric use. The latter problem may however be resolved if the PB takes on the task to define research priority that is assigned to the Board.
- *The Regulation introduces policy measures that are different in nature and purpose:* The outcome evaluation is complicated by the fact that it is not focused on measuring the outcomes of a single policy measure, but that it is aimed at measuring the outcomes of a range of policy measures that may jointly contribute to the same objective but that may also interact.
- *Missing data*: The outcome evaluation is also complicated by the fact that some of the required data are currently not available and may not be available at the moment that the Regulation becomes effective.

Here, we will try to operationalise the objective and to identify measurable indicators that will make it possible to evaluate the success of the Regulation.

- Number of granted marketing authorisations that include a paediatric investigation plan and number of granted paediatric use marketing authorisations: The granting of marketing authorisations implies that, where needed, clinical trials in the paediatric population were conducted or are planned. These trials may generate information that may support health care professionals in making treatment decisions. The number of granted marketing authorisations is thus an easy to collect but rather indirect indicator of the quality of medical treatment. Finally, it needs to be stressed that the number of granted marketing authorisations as such does not give an indication of the number of clinical trials in the paediatric population, as the requirement to do such trials may have been waived. Therefore information on waivers also needs to be collected.
- Percentage unlicensed and/or off-label prescriptions for children: A decrease in the percentage of unlicensed or off-label prescriptions does not necessarily mean that the quality of medical care for children has improved. However, there are studies showing that adverse drug reactions (ADRs) are more frequent when medicines are prescribed unlicensed or off-label (e.g. Turner et al, 1999; Choonara and Conroy, 2002), so that it is fair to assume that the percentage of unlicensed and/or off-label prescriptions for children gives an indication of the quality of medical care.
- *Prevalence of adverse drug reactions in the paediatric population:* To assess the quality of medical treatment for children, data on the prevalence of ADRs in the paediatric population are important. The interpretation of these data will however be difficult, because of interactions between policy measures proposed in the Regulation. On the one hand, the Regulation includes several measures aimed at increasing the number and

quality of clinical trials in the paediatric population. As a consequence of these measures, the objective would be a decrease in the number of registered ADRs. On the other hand, the Regulation also includes post-marketing requirements to improve the registration of ADRs in the paediatric population. As a consequence of that measure, the objective would be an increase in the number of registered ADRs.

In addition, to measuring the effect on the quality of medical treatment, the Regulation may also have other impacts that need to be evaluated. These potential impacts are discussed in Chapter 4 of this report. Examples of indicators that may be used to monitor these impacts are:

Quantitative indicators

- Size of investments of the pharmaceutical industry in R&D (including how and where the money is spent)
- Market share of different sub-sectors of the pharmaceutical industry
  - EU vs. US vs. Japan
  - Large vs. small and medium enterprises
  - Producers of innovative medicines vs. producers of generics
- Prices of medicinal products
- Percentage of expenditures on pharmaceuticals in total health expenditures

Qualitative indicators

- *Overview of clinical areas in which clinical trials are conducted:* What types of clinical trials have been conducted? How do these relate to the research priorities that will be set by the PB?
- *Shifts in training and education of health care professionals:* Has the attention for paediatric pharmacology in existing training programs increased? Were new training programs established?
- *Dissemination of generated knowledge and insights to health care professionals and other stakeholders:* How easy is it to access information? How frequently is the database with paediatric clinical trials (as proposed in the Regulation) consulted and by whom? Did the available information change the decision-making behaviour of health care professionals?
- *Differential impact of the Regulation:* Is there any evidence that different groups are affected by the regulation in different ways? Is there any evidence that the effects are different in some countries than in others (e.g. because of differences in health insurance and reimbursement systems)?

Division of responsibilities and timing of evaluations

The responsibility for the process and outcome evaluation of the Regulation lies with the European Commission. However, the Commission needs the help of a wide variety of actors in the collection of adequate data. For example, the member states should provide information on the impact of the regulation in their countries, the regulatory authorities in the member states need to report how the regulation affects their work in the field of granting marketing authorisations, health care professionals and possibly children and their parents need to report on ADRs, etc. The Commission should however take the lead in scheduling the evaluations, in conducting the evaluations (although this task may be outsourced to an external organisation), and to ensure active participation of all stakeholders in the evaluation process.

With regard to planning of the process evaluation, we believe that the implementation process should be evaluated on a regular basis. As it is most likely that possible problems will arise in the first years after the Regulation has come into force, the process evaluation should take place more frequently in these first years. Process evaluations may be planned, for example, one, two and five years after the Regulation became effective.

The planning of the outcome evaluation should follow a different schedule. Because of the nature of the Regulation, it may take a long time before some of the effects of the Regulation will be visible. Therefore, we believe that the outcomes of the Regulation should be monitored over time, for example, five, ten and fifteen years after the Regulation became effective. Although the outcome evaluation itself may only take place a couple of years after the Regulation has come into force, it is important to realise that data need to be collected at moment that the Regulation becomes effective, in order to enable an outcome evaluation at a later stage.