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

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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.

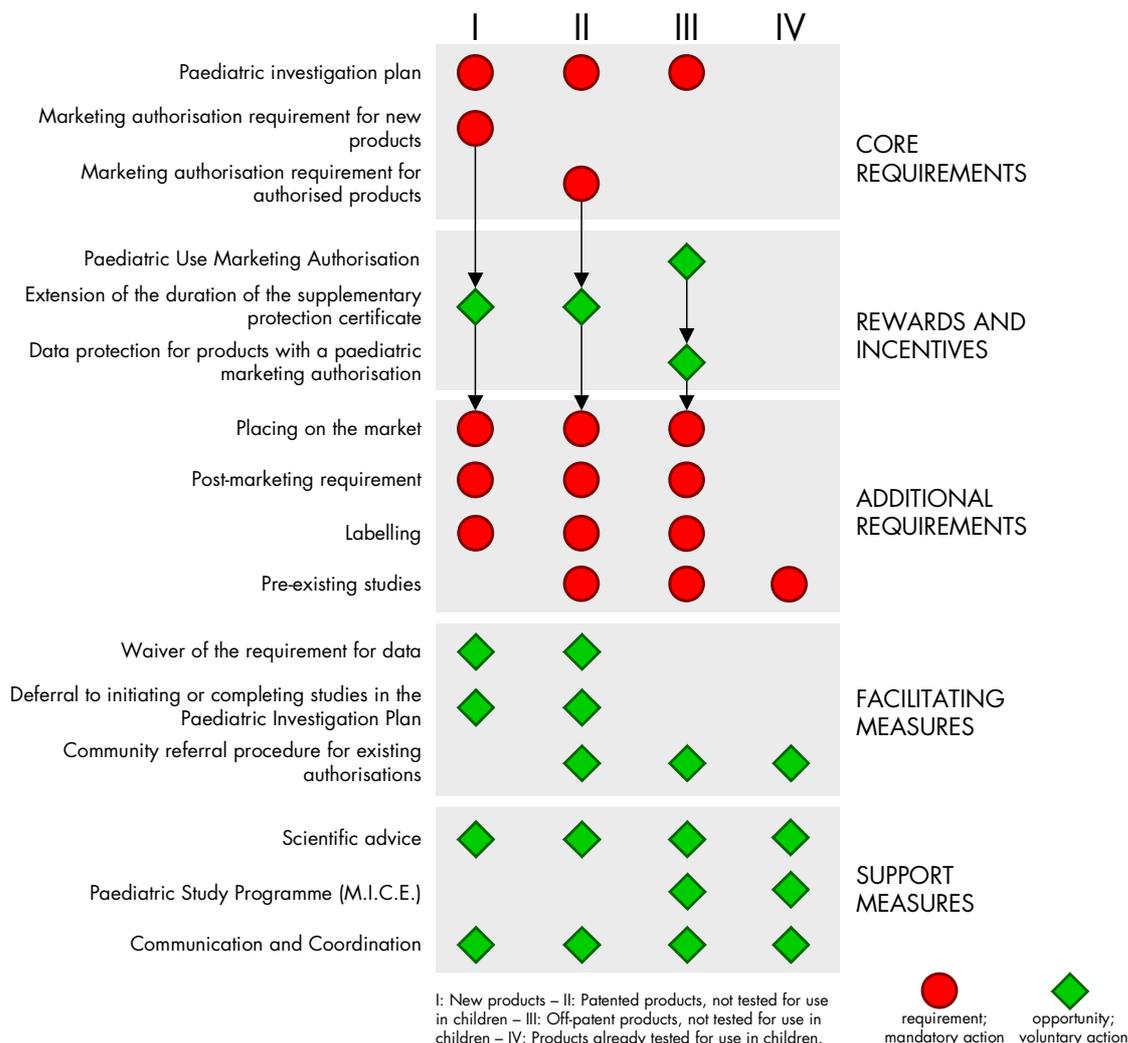
The Regulation

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 (EMA) 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-authorized 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 to 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