

Public Consultation on the Paediatric Medicines Regulation

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Part II – CONSULTATION ITEMS

1.1 More medicines for children

Consultation item No 1: Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?

We agree that a specific legislation is necessary especially in rare paediatric diseases such as cancer that do not constitute an attractive commercial market and therefore are of low interest to drug companies. In Sweden around half of the drugs given to children have not been tested in a clinical trial in children and are therefore administered "off-label". As we understand, the situation is the same in the rest of Europe.

The SIOP strategic cancer plan (Journal of Cancer Policy, 8 (2016) 17-32) conclude that there is still poor access to new paediatric drugs in Europe despite the EU Paediatric Medicine Regulation, and access of children and adolescents with cancer to innovative therapies remains insufficient and slow.

The 10 year-report to the commission from the European Medicines Agency conclude that the Regulation has had a positive impact on paediatric drug development in general, but that the Regulation has had a very limited benefit for children with cancer. Only 2 new drugs specific to paediatric oncology (Votubia and Unituxin) have been approved through a Paediatric Investigation Plan. Over 60% of 89 potentially valuable anticancer drugs granted a waiver and only between 9-15% of all oncology agents have on-going paediatric studies (European Journal of Cancer, 62, 2016, 124-131).

In Sweden, both health care providers and patients/families bear witness on the difficulties in accessing new drugs and not being able to participate in clinical trials. In the 2017 issue of "Childhood Cancer Report" (in press) published by the Swedish Childhood Cancer Foundation we highlight these difficulties and the frustration and anger this causes.

Our opinion is that although the Paediatric Medicines Regulation from 2007 is an important step forward and a positive force of change, the present Regulation needs to be revised in order to better develop evidence-based medicines for paediatric cancers.

1.2 Mirroring paediatric needs

Consultation item No 2: Do you have any comments on the above? To what extent and in which therapeutic areas has the Regulation contributed to the availability of important new treatment options?

Development of medicines for rare diseases such as childhood cancer is unprofitable and therefore ignored by the drug companies. Childhood cancers make up less than 1 percent of all cancer diagnosed each year (American Cancer Society, <https://www.cancer.org/cancer/cancer-in-children/key-statistics.html>) and the market is too small to interest the drug companies to invest in costly research and development.

Although an improvement for paediatric diseases in general, the present Regulation does not mirror paediatric needs in the specific area of childhood cancer. New drug development is slow and lagging behind adult treatments, and only few compounds are designed specifically for children. The Regulation needs to take into account that cancer in adult and children differs, and that it is extremely important to consider the molecular profile of the cancer when decision of developing a new drug for paediatric cancer patients are being made. In the present Regulation the development of paediatric cancer drugs is dependent on the development of adult drugs. For cancer diseases that afflict children but are very rare in adults, there are no effective incentives for companies to develop new drugs. This is not acceptable.

1.3 Availability of paediatric medicines in the EU

Consultation item No 3: In your experience, has the number of new paediatric medicines available in Member States substantially increased? Have existing treatments been replaced by new licensed treatments?

There has been no significant increase in paediatric medicines for cancer (see sections 1.1 and 1.2).

The major reason for lost opportunities to increase the number of new paediatric medicines is the failure to recognise the mechanism of action when establishing a Paediatric Investigation Plan. In the present regulation a waiver or deferral is allowed if the adult illness doesn't exist in children. It is important to recognize that a mechanism of action is not limited to certain diseases but can in fact be relevant in very different diseases.

1.4 Reasonable costs

Consultation item No 4: Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?

We don't have any comments on this specific question. We do however think that stakeholders might need to consider alternatives to the current model of financing drug development and that it might be necessary to share costs and in exchange get at lower price of the final drug. In addition, drug companies need to share information and collaborate with academic researchers and others that are willing to take on the development of a paediatric cancer drug.

1.5 Functioning reward system

Consultation item No 5: Do you agree that the reward system generally functions well and that early, strategic planning will usually ensure that a company receives a reward?

The reward system does not function well, since it has obviously not resulted in a better situation with new drugs for paediatric cancer patients. PIPs are either waived or significantly delayed.

The reward system might work better if offered sooner and combined with drug development in collaboration with academic groups. Importantly, rewards need to be uncoupled to the development of drugs for adult cancers, to avoid the risk of cancellation of the corresponding PIP if the drug fails to show positive results in adult cancer despite scientific evidence for positive effects in paediatric cancer.

1.6 The orphan reward

Consultation item No 6: How do you judge the importance of the orphan reward compared to the SPC reward?

The reward has not been attractive enough to have an impact on the development of new medicines for childhood cancer patients.

1.7 Improved implementation

Consultation item No 7: Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?

Although the Regulation has had a positive impact on attitudes and awareness, the problem that paediatric cancer patients are excluded from the development of new drugs is not solved. We have not observed any significant improvement of the implementation of the Regulation over time. The Regulation needs to be revised to force paediatric development if medically and scientifically justified.

1.8 Waivers and the "mechanism of action" principle

Consultation item No 8: Do you have any comments on the above? Can you quantify and qualify missed opportunities in specific therapeutic areas in the last ten years?

We fully agree with the conclusion of European Medicines Agency concerning the importance of the "Mechanism of Action" principle. On p56 in the 10 year-report to the commission they conclude:

"Paediatric oncology has been identified as a neglected therapeutic area as little progress has been made with new and better treatments for childhood cancers, and this was attributed in part to the difference in clinical conditions between adults and children. Cancers that concern children are biologically different from those concerning adults, and therefore any medicine's mechanism of action needs to be used to guide investigating treatments of the paediatric malignancies and to address the unmet therapeutic needs in paediatric oncology. Consequently, the development should be driven by the potential paediatric use, i.e. by the data (existing or to be generated as part of a PIP) on the mechanism of action, or on the target of the anti-cancer medicine where the anti-cancer adult indication is under development"

An example of a missed opportunity is the drug Crizotinib that was authorised in Europe for treatment of the adult cancer "non-small cell lung cancer "(NSCLC). A paediatric investigation plan was waived in 2010 on the grounds that NSCLC does not exist in children despite being known at that time that it was active at the molecular level in childhood cancer.

1.9 Deferrals

Consultation item No 9: Do you agree with the above assessment of deferrals?

To our knowledge there is no evidence that the paediatric requirements have delayed the development of adult applications.

A major concern is however the delay in drug development for paediatric oncology patients compared to that for adults. Drug development for children is often not initiated until late in the process of clinical trials. Children need to get access to high-priority drugs much earlier since cancer is a life-threatening disease. The reference to safety issues is not always justified, as neither adult trials nor mouse studies can for sure tell whether a drug will have side effects in children and is therefore not an argument to wait and prevent children from accessing the drug.

1.10 Voluntary paediatric investigation plans

Consultation item No 10: Do you have any comments on the above?

Voluntary PIPs have not had a significant impact on the development of new drugs for paediatric cancer patients. Cancer in children is a life threatening disease and development of new drugs should not depend on voluntary PIPs. The Regulation needs to be revised to force paediatric development if medically and scientifically justified.

1.11 Biosimilars

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1.12 PUMA – Paediatric-use marketing authorisation

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1.13 Scientifically valid and ethically sound – Clinical trials with children

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1.14 The question of financial sustainability

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1.15 Positive impact on paediatric research in Europe

Consultation item No 15: How do you judge the effects of the Paediatric Regulation on paediatric research?

The Regulation has had an impact on attitudes and awareness within industry and among researchers and parent organizations. This has however not been enough to make a true difference for paediatric cancer patients who still don't have access to the new drugs. Childhood cancer is still the major cause of death by disease for children in Sweden as well as in the rest of Europe.

1.16 "Mirror, mirror on the wall"- Emerging trends and the future of paediatric medicines

Consultation item No 16: Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?

The technical advances in obtaining and analysing Big Data is fast and significant, and the knowledge about what drives cancer at the molecular level is exploding. The development of future precision medicines for adults is therefore promising.

It is of utmost importance that the progress in cancer drug development also includes the paediatric cancer patients. A revision of the Regulation can make this happen as stated elsewhere in this reply to the Commissions Public Consultation.

1.17 Other issues to be considered

Consultation item No 17: Overall, does the Regulation's implementation reflect your initial understanding/expectations of this piece of legislation? If not, please explain. Are there any other issues to be considered?

We fully support the recommendations in the Position Statement¹ by SIOPE, Unite2cure and Cancer Research UK to make the following changes in the Paediatric Medicines Regulation:

- Ensure that the *obligation* to undertake a Paediatric Investigation Plan is based on how a drug works and its capacity to address an unmet medical need in children – rather than the type of disease in adults for which it is first introduced.
- Set up a mechanism to choose the best potential drugs and prioritise, among drugs developed by different companies, in relation to the real needs of children affected by rare cancers.
- Reduce delays in paediatric medicines reaching children by enabling Paediatric Investigation Plans to start no later than the start of pivotal trials in adults, if paediatric biology, preclinical and preliminary clinical data are available to better evaluate the potential therapeutic benefit in the paediatric population.
- Add provisions for more effective and flexible awards for companies undertaking early and timely Paediatric Investigation Plans and those researching therapies specifically for cancers, which only occur in children.