This document represents the opinion of the Dutch Medicines for Children Research Network (MCRN) and Dutch National Centre of Excellence on Pediatric Pharmacotherapy (NKFK) and the board of the Dutch pediatric Formulary.

1. A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT

Consultation item No 1: Do you agree that the Paediatric Regulation has paved the way for paediatric development, making it an integral part of the overall product development of medicines in the European Union?

Yes, pediatric development has become an integral part of overall product development. However pediatric development seems to be an extension of adults needs instead of addressing specific pediatric needs. Especially in the area of new formulations, development has been slow.

2. **HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE.**

Consultation item No 2: Do you agree with the above assessment?

The regulation has not reduced off-label use in children. The regulation has worked well for medicines new on the market (which use has never been off-label), but due to the long deferrals granted to study children, it may take years before the effects will be seen in practice. New information on old medicines is not/poorly generated under the regulation, whilst this is essential for pediatricians. Measures to address old (off-patent) medicines are insufficient and/or insufficiently executed.

3. THE PUMA CONCEPT: A DISAPPOINTMENT

Consultation item No 3: Do you share this view? Could you give specific reasons for the disappointing uptake of the PUMA concept? Is it likely that PUMA will become more attractive in the coming years?

Yes, the PUMA concept is a disappointment. The incentive behind PUMA doesn't work.Most off-patent medicines are currently delivered on the market as generic medicines. Pharmaceutical companies of generic medicines are not well equipped for research and development.

The pediatric population in which the "PUMA' drug is used is often too small to make up for the costs of research and registration. Moreover, the small number of drugs for which a PUMA has been acquired are infrequently used drugs in children. As such they have only addressed a small medical need.

Academic networks have a track-record in doing research, but may be unaware of possibilities to register for a PUMA as a academic network. If aware of this possibility at all, they will likely have problems complying with registration requirements and costs. Data and marketing exclusivity is not an incentive for academic networks.

4. WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS. Consultation item No 4: Do you agree that, generally speaking, the paediatric obligations have no impact on timelines in adult development, as there is no evidence for delays in marketing authorisation applications for reasons of compliance with the paediatric obligation? If you feel that there is an impact, practical examples would be appreciated.

Unknown

5. MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS

Consultation item No 5: Do you have any comments on the above?

The general goal of the regulation is to address pediatric needs. There is too much emphasis on marketing authorisation to fulfil these needs. Pediatric development programs of new drugs do not necessarily solve this problem. Many drugs for which PIPs are agreed upon are developed for adult indications, e.g. antithrombolytics, antihypertensives, etc and do not present major pediatric needs. Also, it is unethical if many me-too drugs are studied in children at the same time. In the end children benefit from high quality data on the safe and effective use of medicines in children, not solely from marketing authorisation. The number of children in any given disease is relatively small, with associated inclusion problems. Research should be driven by an unmet needs agenda. This agenda has been drawn up by the field, but does not coincide with the agenda of the pharmaceutical industry.

6. THE BURDEN/REWARD RATIO — A BALANCED APPROACH?

Consultation item No 6: Do you agree with the above?

Not always, for specific indications patient population are very small. A current trend is seen that these patient groups are much smaller than the number of patients that need to be included when every company needs to study his own me-too drug. This will impose a significant burden on children, which may not be warranted by the benefits to the specific patient group.

Also, smarter study design approaches, e.g. Bayesian methods, adaptive study design, modelling and simulation, should be more frequently considered, to reduce the number of children exposed when the traditional drug development paradigm of Phase 1, 2 and 3 trials is taken

7. ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION

Consultation item No 7: Do you agree that Articles 45/46 have proved to be an efficient and successful tool for gathering and compiling existing paediatric data and making it available to the competent authorities and subsequently, via databases, to the interested public

This indeed should be the hidden gem, but it in fact also misses the point in delivering pediatric data, usefull to the public.

Pharmaceutical companies often only forward the studies executed by the company. A search on PUBMED for additional pediatric data on the medicin is often not excuted, not by the company, nor by the CHMP.

Quite often the assessment concludes there is no evidence of efficacy/safety in the pediatric age group, while extensive academic data may be available suggesting otherwise. Considering the selection bias mentioned above, the validity of this conclusion can be doubted.

If the assessment leads to the addition of pediatric data in the SmPC, data are mentioned in section 5.2 (instead of section 4.2), leaving the physician or pharmacist with no conclusion at all on dosing and not solving the off-label issue.

The Dutch Pediatric Formulary has some examples where good evidence for use in children is available, but the PAR concludes 'no evidence of efficacy and safety'. Although the level of evidence may be unsufficient for marketing authorization in children, the comment no evidence of efficacy and safety is not helpful to the prescribing pediatrician, since most products will be used anyway.

A European pediatric formulary may be helpful in disseminating knowledge derived from art45/46 procedure on pediatric use of medicines, when there is not enough evidence for pediatric MA.

8. LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED

Consultation item No 8: Do you agree that healthcare professionals may not always be as receptive to new scientific information on the use of particular products in children as might be expected? Do you agree that this problem has to be addressed primarily at national level? How could healthcare professionals be more interested and engage in paediatric clinical research?

No, we do not agree. The accessibility and presentation of information is key. The online Dutch pediatric Formulary provides evidence-based information on the use of medicines by children and is used over 4000 times/day by unique users. Professionals need a clear consolidated advise on dosage, safety aspects and daily practice. As they will not themselves search for (new) evidence, review available data and make a final conclusion, they need a translation from available evidence to daily practice.

Paediatricians are in general aware of the off-label status of most medicines, but this will not influence prescribing, as they often have no choice at all.

A European formulary would be a solution for other counties without a national pediatric formulary.

The Pediatric Regulation will not on a short term reduce off-label prescribing, but in fact can provide scientific evidence on the use of off-label medicines and in doing so guarantee responsible off-label prescribing .

We do agree that healthcare professionals could be more interested in pediatric clinical research. Historically, pediatricians do not have long-standing experience with clinical drug trials in children, as they were just not done. Although they might be interested to do research, they do not have the experience to understand what it means to participate in a clinical drug trial, including PDCO/EMA and GCP requirements. Hence, when approached by companies to participate a gap in expectations becomes evident and hampers much needed collaboration.
Moreover, as many current pediatric industry-initiated protocols balance towards more burden than benefit to the individual child, many pediatricians are reluctant to let their patients participate. This may not have been a major issue for oncology phase I/II trials,

where a potential benefit may be life-saving, for other less critical drugs, this may be a major issue for study feasibility. This roadblock may be overcome by smarter study designs and early involvement of real doctors, who see patients on a daily basis.

9. CLINICAL TRIALS WITH CHILDREN: NO SPECIFIC PROBLEMS DETECTED

Consultation item No 9: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above description?

Design of clinical trials often do not comply with daily practice in terms of standard treatment of care, measurement of outcome parameters, burden to the patients.
Also, see the above comments at 7 and 8.

10. UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS

Consultation item No 10: Do you have any comments on this point?

With a workload of the PEDCO which is already high, it seems reasonable to have a two step program in which a preliminary program can be submitted and a full review on the PIP is only executed when feasible. Especially since many products are not highly essential in solving pediatric needs.

11. SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED

Consultation item No 11: Do you agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise in the European Union?

A network of existing European networks has been established, facilitated by the pediatric regulation. It is not yet clear to what extent this network has contributed to clinical trials and expertise in Europe.