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My name is Ron Portman. I have been the head of the Pediatric Center of Excellence at Bristol Myers Squibb for the last 4 years after a career as a professor of pediatric nephrology at the University of Texas in Houston. I am not a pediatric oncologist but am here to provide the perspective of a pediatrician working in the biopharmaceutical industry and to discuss the opportunities and challenges of pediatric drug development with special emphasis on drugs for pediatric cancer. The final responsibility to improve children's health should be shared in partnership by industry, regulatory agencies, health professionals and society as a whole. As a part of this coalition, I appreciate the opportunity to speak today.

As Dr. Seuss once wrote: 'Sometimes the questions are complicated and answers simple'. There are over 10,000 children diagnosed with cancer each year in the US. While remarkable progress has led to effective therapy in almost 80% of them, cancer is still the leading medical cause of death in children. Cancer, however, is a term that encompasses numerous different conditions requiring diverse treatment regimens with many cancers affecting only a few hundred children per year, thus making the performance of clinical trials very challenging and often requiring years to accomplish. Nonetheless, the simple answer is that we must find ways to treat these conditions for our children regardless of the difficulties.

I congratulate Congress for developing and enacting PREA and BPCA. These dual statutes governing pediatric research have been remarkably successful in ensuring that the medications used in children are studied and labeled appropriately and ensure that every drug entering the clinical space is considered for pediatric use. PREA assures that pediatric use must be considered and studies conducted if relevant to pediatrics. BPCA provides an incentive to encourage industry to conduct studies for uses that may be unique to children. History shows that market forces by themselves are inadequate to stimulate pediatric research, however; pediatric product development is a societal good and thus the cost should be shared by all sectors. These 2 programs allow pediatricians within companies to plan and execute comprehensive pediatric development programs knowing some costs may be recovered, even though it may be over a decade before an incentive is realized and the financial future of the drugs may be presently unknown.

In the decade prior to the enactment of these laws, 10 drugs were labeled for pediatric use while over 400 have been labeled since. These laws have also stimulated building of industry infrastructure to sustain pediatric drug development, have led to establishing

close collaborations with pediatric academia, and, in concert with the European pediatric legislation, have stimulated companies to address pediatric plans much earlier in development to shorten the gap between data being available to inform safe and effective use in adults and similar information being available for children. Pediatric development plans are now designed with the same rigor as those for adults including all components of a full drug development program. The amount of funding available and the clinical research capacity in this private-public partnership far exceeds that which would be available with public or foundation funding alone. However, in order to maximize this continued progress, a predictable regulatory environment is needed. Both BPCA and PREA are due for reauthorization and should be made permanent. The 5-year sunset of both legislations results in uncertainty for future pediatric development making it difficult for industry to invest in pediatric infrastructure and for the FDA to issue needed guidance. Given the success and continued improvement in execution of pediatric programs, there seems no logical reason to continue to allow such important legislation to sunset and endanger ongoing progress.

As new drugs for the treatment of cancer are approved, they have entered into pediatric practice through off-label use, often with academic study, but not with the same rigor as the regulatory approval processes require. We are here to focus on some of the obstacles for the development of approved drugs for pediatric cancer and suggest how legislation can help overcome them. There are several scenarios for consideration.

- First: a drug may be developed for adult patients with cancer and used for the same indication in children, e.g., imatinib and dasatinib for CML. A study for children can be required under PREA unless approved as an orphan indication for adults and thus serves a very small adult population. However, the drug is eligible for an agreed development plan with FDA under BPCA.
- Next, a drug can be developed for an adult indication and the pediatric indication may be different. An example is crizotinib which is an ALK inhibitor (anaplastic lymphoma kinase) developed for non-small cell lung carcinoma in adults. It is undergoing clinical trials for a form of lymphoma (anaplastic large cell lymphoma) in both adults and children, and neuroblastoma in children. In this case the classification of the specific cancer may be less important than either the genetic abnormality causing the cancer or the mechanism of the drug's action. In this scenario, PREA does not apply to require the pediatric research; however, a written request under BPCA could be issued requesting pediatric studies. These first two examples clearly demonstrate the excellent partnership of these two laws.
- A third example is that of a drug that fails to achieve its objective for adult cancer but has a mechanism of action which may be appropriate for a pediatric indication. Currently, only the Orphan Designation regulation, if relevant, would offer a limited incentive to continue development in a narrow pediatric-only indication; a written request cannot be issued if the drug is not approved for another use. An example of this situation in oncology is the IGF1 receptor antibodies class. One such antibody was being developed primarily for lung cancer in adult patients but has not been

successful. As a result, evaluation of potential use in pediatric sarcoma was also discontinued.

- Finally we have the possibility of a drug that could be developed for pediatric cancer alone, i.e., without an adult indication. It may not be a sound financial decision, from the perspective of the biopharmaceutical industry, to develop such drugs for extremely small populations, given the very expensive, resource and time consuming process of drug development. Thus the latter two scenarios demonstrate that legislation in addition to making BPCA and PREA permanent is needed to stimulate research for these smaller populations of children with cancer and other lower prevalence pediatric diseases. Initiatives such as the Creating Hope Act may allow development of a new form of public-private partnership to address this type of drug development.

Finally, two other considerations that impact global pediatric development programs are worthy of mention:

- First, when multiple drugs are being developed for the same condition, a process is needed to determine which drugs to assess in children when the patient populations are often so small. While the issue is being addressed, good solutions have not yet been found.
- Second is the timing of mandatory consideration of pediatric plans. EU requires pediatric plans very early in drug development when >80% of drugs are withdrawn from consideration for further development following early studies. In the US, pediatric consideration is not required until the filing of a new or supplemental new drug application. This timing, on the other hand, is too late. Even if the choice is made not to begin clinical studies in children until after approval in adults, preclinical work in preparation for pediatric studies can be performed if the pediatric plan can be agreed upon with FDA at an earlier time point. As in the original FDA pediatric rule, the appropriate timing for most drugs is in between these two regulations - at the end of phase 2. An exception is noted for therapies being developed for serious diseases like cancer, when one should consider a more simultaneous development for all age groups based upon unified mechanisms of action.

Together BPCA and PREA are fulfilling the purpose of generating a wealth of pediatric drug and research information, but additional legislation may be necessary to stimulate the development of drugs for children, independent of such development for adults. I thank you for your interest in pediatric cancer research and hope that we can work together to achieve improved therapies.