



## **FDA Briefing Document**

### **Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)**

**June 29, 2016  
Afternoon Session**

#### **DISCLAIMER STATEMENT**

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Food and Drug Administration  
Silver Spring, MD 20993

## Memorandum

Date: June 3, 2016

To: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)  
Members, Consultants, and Guests

From: Gregory Reaman, MD  
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Subject: FDA Background Package for June 29, 2016 Afternoon Session

Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC. With the recent permanent reauthorization of the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) and their associated amendments, pediatric study plans now require earlier consideration of potentially relevant new drugs for one or more distinct pediatric cancers. The subcommittee will hear about a significant unmet clinical need in pediatric oncology: addressing the nearly uniformly fatal diagnosis of Diffuse Intrinsic Pontine Glioma (DIPG) and the evaluation of the benefit:risk assessment of surgical biopsy of DIPG to molecularly characterize individual patient tumors to select appropriate molecularly-targeted drugs for therapeutic evaluation. Surgical biopsies at diagnosis and/or at relapse are becoming routine in precision medicine approaches to cancer therapy in both adults and children. Recent data confirms that the biology and molecular phenotype of DIPGs vary significantly and therapeutically actionable mutations have been identified in autopsy specimens and more recently in pre-therapy biopsy specimens. Throughout Europe, pre-therapy biopsy of suspect DIPG lesions is being performed routinely to guide targeted drug selection and therapeutic decision-making. The practice is becoming more popular at centers in the U.S. as well since the promise of precision medicine is likely no more desperately needed than in DIPG. The committee will review data on the incidence of actionable mutations in DIPG, the current adverse event rate associated with surgical interventions in the brain-stem with present day techniques and the current application of precision medicine techniques to the study and management of DIPG. The committee will be asked to consider the assessment of benefit:risk of pre-therapy surgical biopsy of DIPG for molecular analysis to select an appropriate targeted drug for therapeutic evaluation in this disease for which there is no cure and for which there are no currently approved drugs.

No specific drug or biologic products or class of products will be discussed outside of recent clinical experience to provide examples of the application of precision medicine to DIPG.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 29, 2016.



REFERENCES:

1. **Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA):**  
Title V – Pediatric Drugs and Devices (pages 47-58).  
FDASIA legislation is available at: <http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf>

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## **Pediatric Legislative Initiatives**

### Pediatric Legislative Initiatives Including the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act

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Pediatric legislation, including a combination of incentives and requirements, has significantly increased pediatric drug research and development and led to a substantial increase in products with new pediatric information in labeling.

Pediatric legislative initiatives:

- 1997 The Pediatric Exclusivity provision - created in the Food and Drug Administration Modernization Act (FDAMA)
- 2002 Best Pharmaceuticals for Children Act (BPCA) – reauthorization of the Pediatric Exclusivity provision
- 2003 The Pediatric Research Equity Act (PREA - a requirement which allows the FDA to require pediatric studies in drugs and biologics for certain applications
- 2007 Re-authorization of BPCA and PREA in the Food and Drug Administration Amendments Act (FDAAA)
- 2010 The Biologics Price Competition and Innovation Act of 2009 (BPCI) was included in the Patient Protection and Affordable Care Act – created a framework for the approval of follow-on biologics and made biologics, including follow-on biologics, eligible for Pediatric Exclusivity through amendment of section 351 of the Public Health Services Act. BPCI sunsets in March 2015
- 2012 BPCA and PREA made permanent in the Food and Drug Administration Safety and Innovation Act (FDASIA)

Each one of these pediatric milestones has expanded and improved consistency and transparency of the pediatric information available for product use. For example, FDAAA requires that study data, both positive and negative, conducted under BPCA and PREA be described in product labeling. Also, a labeling statement of the FDA's determination whether or not the studies demonstrate safety or efficacy or if the studies were inconclusive in pediatric populations must also be included. Another important milestone with the recent passage of FDASIA was the permanent reauthorization of BPCA and PREA. Other important changes to pediatric drug development were included in this legislation. One such change was the new requirement for drug developers to submit more detailed plans to perform pediatric studies earlier during drug development. Traditionally, drug developers were not required to provide plans for pediatric studies until relatively late the development of a product. New legislation under PREA requires that drug developers submit plans for pediatric drug development earlier during the development of the product (i.e., at the end of phase 2). The intent of this legislation is to promote earlier development of products for pediatric use.

The following is a brief review of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, two laws that support pediatric drug development, and recent changes to these laws under the Food and Drug Administration Safety and Innovation Act.

### **Best Pharmaceuticals for Children Act**

The intent of BPCA is to provide an incentive to drug developers to perform pediatric studies in order to improve the efficacy and safety data available for products used in children and infants. This incentive allows sponsors to qualify for an additional six months of marketing exclusivity for the entire moiety (molecule responsible for the pharmacological action of the drug), if specific studies addressing relevant pediatric indications are completed and submitted to FDA. A Written Request is a document issued by the FDA which outlines the type of studies to be conducted, study design and objectives, and the age groups to be studied. Because the pediatric exclusivity provision is voluntary, the sponsor may decline a Written Request. Thus, FDA has the ability to request that the sponsor perform pediatric studies under a Written Request that can lead to additional marketing exclusivity for the product.

This process can be initiated by either the sponsor or the FDA. A sponsor may submit a proposal to the FDA to conduct pediatric studies. If the FDA determines there is a public health need, the Agency will issue a Written Request for pediatric studies. These studies may or may not include the studies proposed by the sponsor. FDA may issue a Written Request on its own initiative when it identifies a need for pediatric data.

Of note, prior to 2010, the Written Request process only applied to drugs, and not to biological products. However, under BPCI, biological products became eligible for additional marketing exclusivity through the Written Request process. To date, no Written Requests have been issued for biologic products.

### **Pediatric Research Equity Act**

PREA works in concert with BPCA. In contrast to BPCA, which is based on incentives for drug developers to voluntarily perform needed pediatric studies, PREA requires that pediatric studies must be performed. However, this requirement only applies to the specific indications for which the sponsor is seeking approval for their product. PREA is triggered when an application or supplement is submitted for a new indication, new dosing regimen, new active ingredient, new dosage form, and/or a new route of administration. Under PREA, the FDA may require that the sponsor develop age appropriate formulations for use in required pediatric studies and that the required pediatric studies must include data to support pediatric dosing and administration. Additionally under PREA, pediatric studies of currently marketed drugs and biologics may be required if the product is used by a “substantial” number of children, if adequate pediatric labeling would provide “meaningful” therapeutic benefit compared with existing treatments for children for the claimed indication, or if the lack of “adequate” labeling poses a risk for the pediatric population.

Pediatric studies may be deferred (postponed until a later date) by the FDA in certain situations including if the application is ready for approval for use in adults before pediatric studies are complete, or when additional safety or effectiveness data needs to be collected before studying in the pediatric population. Studies may be waived in full or in part in certain situations, including when a clinical condition or disease entity does not occur in the pediatric population, when necessary studies are impossible or highly impracticable, there is evidence strongly suggesting that the product would be ineffective or unsafe in all or some pediatric age groups or the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients.

It should be noted that PREA does not apply to products granted orphan designation. PREA has limited applicability for drugs and biologics being developed for oncology as the tumors being treated in adults rarely occur in children. Therefore pediatric tumors are considered as distinct indications and are studied by a Written Request under BPCA.

### **Pediatric Study Plan (PSP)**

With passage of FDASIA in July 2012, both BPCA and PREA have been permanently reauthorized precluding the necessity of periodic (every 5 years) justification for reauthorization. Among the changes brought by this legislation is the requirement under PREA for earlier initiation of discussion of the proposed studies to be conducted in the appropriate pediatric populations. Sponsors are now required to submit an initial PSP within 60 days of the End of Phase 2 (EOP2) meeting with the FDA. The content of the PSP includes an outline of the sponsor's proposed study(ies): objectives, design, age groups evaluated, relevant endpoints, and statistical approach. Requests for deferral or waiver may be made with supporting information. Relevant information to understand the rationale for the PSP should be included to describe, as appropriate, a disease overview in the pediatric population and the product under development, potential plans and justification for the use of extrapolation of data generated in other patient populations, nonclinical data both existing and planned to support pediatric studies, plans for pediatric specific formulation when appropriate, synopsis/summary of proposed study(ies) and timelines for completion, information with respect to agreements with other Health Authorities, e.g. Pediatric Investigation Plan( PIP) for EMA. PSPs will be required for all products (drugs and biologics) that trigger PREA if an EOP2 meeting is held as of January 5, 2013.

### **Additional Provisions of Food and Drug Administration Safety and Innovation Act (FDASIA)**

In recognition of the particular need for clinically evaluated drugs in neonates, specific justification for the inclusion or exclusion of neonatal subjects in the proposed studies must be provided in the PSP. This information is to be explicitly stated in any Written Request.

Studies that are required under PREA include specific deadlines for completion. Under FDASIA, a new provision allows for an extension of the deadline for submission of these deferred studies. However, the requests for deferral must be reviewed by the Pediatric

Review Committee within FDA and recommendations regarding whether the deferral extension should be granted. For studies that have not been submitted prior to the established deadline, FDASIA has provided increased enforcement mechanisms including the public posting of non-compliance letters for overdue PREA post-marketing requirements and a process for misbranding products, if applicable.

Difficulties in development of drugs for pediatric use in rare diseases have long been an important issue. FDASIA includes a new provision known as the Pediatric Priority Review Voucher. This program awards developers of products for a rare pediatric disease a voucher for 'priority review' of a subsequent human drug application. To qualify for this voucher program, the product and its development program must meet three requirements:

- Definition of a pediatric rare disease; a “disease that primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children and adolescents” and that meets the definition of a “rare disease or condition” set forth under the Orphan Drug Act.
- The application for the voucher “relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population” and
- The applicant “does not seek approval for an adult indication in the original rare disease product application”.

Additionally, within 18 months of the passing of FDASIA, FDA held an open public meeting on the development of new therapies for pediatric rare diseases, including cancer and has subsequently drafted a Report to Congress on the status of pediatric drug development.

The various pediatric initiatives have led to a dramatic increase in pediatric studies submitted to the FDA and resulted in new pediatric information in labeling. There have been 466 pediatric labeling changes for drugs and biologics between 1998 and October 2012. Of these, 15 labeling changes, including 4 approvals for pediatric use, were for drugs used in oncology.



## AFTERNOON SESSION

### **TOPIC: Consideration of benefit:risk of surgical biopsy for precision medicine approaches to address the unmet clinical need in the nearly uniformly fatal brain tumor, diffuse intrinsic pontine glioma (DIPG)**

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#### **I. Executive Summary**

During the afternoon session, information will be presented on the current unmet clinical need in the nearly uniformly fatal brain tumor, diffuse intrinsic pontine glioma (DIPG) which occurs predominantly in the pediatric age group. The diagnosis of DIPG is typically based on characteristic radiographic and clinical features in lieu of brain biopsy, and as a result there is limited tissue available to evaluate the molecular and cellular biology of this disease. Treatment for children with DIPG is generally based on treatment regimens for high-grade gliomas; however, recent data have demonstrated that the histology, molecular biology and pathophysiology of these tumors vary significantly. Treatment for progressive disease generally includes protocol-directed administration of investigational drugs which are not selected based on the molecular phenotype of the patient's tumor. As there are at present no approved drugs for this disease and no investigational drugs which have demonstrated sufficient activity to move forward in development, clinical investigators seek better understanding of the molecular biology of DIPG to provide potentially predictive information by evaluating the genomic signature of tumors at either diagnosis or relapse. This information can be used to appropriately select specific molecularly targeted drugs based on the genetic aberrations of an individual patient's tumor, and to analyze the pharmacodynamics and pharmacogenomics of these agents. Similar biopsy and resulting bio-marker-driven treatment selection is commonplace in clinical trials in other human solid tumors and hematological malignancies in adults and children. Over the past decade, biopsy of suspected DIPG has become standard practice throughout Europe and is a standard component of clinical trials for this disease in the European pediatric cancer clinical trials network, SIOPE, based on demonstration of the relative low morbidity with this procedure. There has also been growing interest and experience in the U.S. pediatric neuro-oncology community at multiple academic centers to promote the use of routine biopsies of suspected DIPG; however, it is still unclear whether these procedures are considered "significant risk" by regulatory authorities. The Agency, both the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiologic Health (CDRH) seek the input of panelists, including patient advocates, in assessing benefit:risk consideration given the potential for an adverse event associated with a surgical intervention in the brainstem. The Agency will consider information on the potential for risk, current surgical techniques and current adverse event rates associated with surgery, and the state of the science with respect to potential for selection of drugs for actionable mutations. The Agency will seek the input of the subcommittee, including an assessment of benefit/risk given the potential for an adverse event associated with a surgical intervention in the brainstem.

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2. Wang ZJ, Rao L, Bhambani K, et al.: Diffuse intrinsic pontine glioma biopsy: a single institution experience. *Pediatr Blood cancer*, 62:163-165, 2015
3. Grill J, Puget S, Andreiuolo : Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. *Pediatr Blood cancer*. 58:,489-491, 2012
4. MacDonald T: Diffuse intrinsic pontine glioma (DIPG): Time to biopsy again. *Pediatr. Blood Cancer*, 58:487-488,2012
5. Cage TA, Samagh SP, Meuller, et al.: Feasibility, safety, and indications for surgical biopsy of intrinsic brainstem tumors in children. *Childs Nerv Syst*,29:1313-1319, 2013
6. Minutes of the Joint Meeting of the Pediatric and Oncologic Drug Advisory Committees, U.S. FDA, Apr. 27, 2009. [www.fda.hhs](http://www.fda.hhs).

#### Discussion Items

1. Consider changes over time in the adverse event rate associated with surgical biopsy of the brainstem to obtain DIPG tissue for biology studies and more recently to select molecularly targeted drugs for therapy.
2. Consider the benefit:risk assessment of surgical biopsy of DIPG for molecular analysis of both newly diagnosed and progressive (on current therapy) tumors for the purpose of selecting an appropriate molecular phenotype-directed targeted therapeutic agent for patients with this disease.
3. Is the benefit: risk assessment favorable?