MINUTES OF THE PEDIATRIC ADVISORY COMMITTEE

The public meeting was convened 8:30 a.m. to 5:15 p.m. on March 6, 2017

Members Present (Voting)	**Temporary Voting Members (Voting Consultants)**
Mary Cataletto, MD Avital Cnaan, PhD Peter Havens, MD, MS (phone) Erin Moore, BS (*Family-Patient Rep.)* Wael Sayaj, MD Christy Turer, MD, MHS Kelly Wade, MD, PhD, MSCE Michael G. White, MD, PhD	Premchand Anne, MD, MPH David Callahan, MD Frederick Kaskel, MD, PhD Priya Kishnani, MD (phone) Athena Zuppa, MD, MSCE
Non-Voting Members Mark Hudak, MD *(Chair)* Bridgette Jones, MD (*PHO Rep.)* Ronald Portman, MD (*Industry Rep.)*	**Designated Federal Official (DFO)** Marieann Brill, MBA, RAC, MT (ASCP)

U.S. Food and Drug Administration (FDA) Participants

Office of Pediatric Therapeutics	**CDER Divisions**	**CDER Office of Surveillance and Epidemiology(OSE)**
Robert "Skip" Nelson, MD, PhD Judith Cope, MD, MPH	Rama Dwivedi, PhD Thomas Papoian, PhD, Fortunato (Fred) Senatore, MD Patroula Smpokou, MD **CDER Division of Pediatric & Material Health (DPMH)** John Alexander, MD, MPH Ethan Hausman, MD Lily (Yeruk) Mulugeta, PharmD Jacqueline Spaulding, MD	Amy Chen, PharmD Page Crew, PharmD, MPH Kate Gelperin, MD, MPH Patty Greene, PharmD CDR S. Christopher Jones, PharmD, MPH Robert Levin, MD Kusum Mistry, PharmD Saharat Patanavanich, PharmD, BCACP Kimberly Swank, PharmD Kathy Robie-Suh, MD, PhD Peter Waldron, MD Daniel Woronow, MD

Welcome and Introductory Remarks

- Marieann Brill, MBA, RAC, MT (ASCP), Designated Federal Official, Pediatric Advisory Committee, Office of Pediatric Therapeutics, Office of Special Medical Programs, FDA
- Mark Hudak, MD, Chair of the Pediatric Advisory Committee
- Robert "Skip" Nelson, MD, PhD, Office of Pediatric Therapeutics, Office of Special Medical Programs, FDA, introduced Susan McCune, MD, the new Director of the Office of Pediatric Therapeutics.

Open Public Hearing

An opening statement was read by the Marieann Brill, DFO.
There were no public presentations and the session was closed.

Pediatric Focused Safety Review Update --Exjade (deferasirox)

This presentation provided updated information on FDA's ongoing evaluation of acute illness and adverse effects of kidney and liver injury in the pediatric population using Exjade (deferasirox). The initial mandated Pediatric Safety and Drug Utilization review was presented to the Pediatric Advisory Committee (PAC) in September 2015 and the PAC requested that FDA review any data regarding the safety of continued use of Exjade (deferasirox) in children who have fever. A follow-up of the ongoing review was presented at the September 2016 PAC meeting. For this update, Drs. Waldron and Gelperin presented FDA's further analysis of renal or hepatic events in pediatric patients with fever and/or dehydration in their review of FDA Adverse Event Reporting System (FAERS) reports, published literature and clinical trial data. FDA is continuing to evaluate measures to assure the safe use of deferasirox in children. When the review is completed FDA will work with the sponsor to determine any appropriate updates for product labeling.

Committee Discussion: Members of the committee suggested evaluating infants younger than 2 years of age, and that patient weight, an appropriate biomarker to improve the detection of acute kidney injury and long-term follow-up be added to the collected data. It was noted, however, that these data may not be available. The role of iron burden as measured by serum ferritin was discussed as a potential variable, once "excess" iron has been chelated, the drug would start to chelate "essential" iron. If feasible, the committee suggested that this additional information be added to the 5-year registry, as it is not possible to obtain it from the FAERS data. In response, it was mentioned that biomarkers had not been collected in the 5-year registry. The committee also raised the concern about detection of proximal tubular injury and long-term effects of acute kidney injury and wished to understand better the incidence of renal and hepatic injury among subjects who did not have fever or dehydration events. The committee looks forward to reviewing the results of the future data analyses.

Center for Drug Evaluation and Research (CDER) Standard Presentations

Kuvan (sapropterin dihydrocholoride) – Jacqueline Spaulding, MD

The Safety and Drug Utilization Review found no new safety signals. FDA plans to monitor for epistaxis and insomnia in all patient populations.

FDA recommended continued post-marketing safety surveillance.

- The Committee concurred with the FDA proposal to continue post-marketing safety surveillance, (Yes - 13; No - 0)

Nitropress (sodium nitroprusside) – Lily (Yeruk) Mulugeta, Pharm. D.

The Safety and Drug Utilization Review concluded that most adverse event reports came from patients who had complex underlying medical conditions. Nitroprusside exposure is associated with elevated carboxyhemoglobin levels of uncertain clinical relevance. The presentation noted that the Office of Surveillance and Epidemiology (OSE) recommends adding this information to the post-marketing adverse event section as a laboratory finding. This recommendation was not supported by the Office of New Drugs (OND) division as it is of uncertain clinical significance.

Committee discussion: The committee discussed the clinical relevance of the elevated carboxyhemoglobin levels noted in the 2005 publication of post-cardiac transplant patients in Spain, as described in the OSE FAERS review. The committee asked about finding new cases in the literature for the last decade, and was informed by FDA that there was no documentation of any additional cases of this type. There was discussion about ways in which the prevalence of elevated carboxyhemoglobin levels could be ascertained by looking at

data from the use of nitroprusside infusions in pediatric intensive care units. The PAC encouraged FDA to explore ways to obtain and evaluate such data.

FDA question to the Committee: Are available data sufficient to support labeling for elevation of carboxyhemoglobin level at this time?

- The Committee voted no: there are not sufficient data available at this time to make a labeling change. (Yes - 1; No – 12).

Additional FDA question to the committee: FDA recommends continued post-marketing safety surveillance. Does the Committee concur?

- The Committee concurred with the FDA's proposal to continue post-marketing safety surveillance. (Yes - 13; No - 0).

Pharmacogenomics (presentations and PAC discussion only)

The Role of Pharmacogenomics Data in Pediatric Therapeutics, - Robert "Skip" Nelson, MD, PhD

Pharmacogenomics in Pediatric Product Development and Labeling, - Dionna Green, MD

Summary: Pharmacogenomic information is increasingly being incorporated in FDA-approved drug labels and can facilitate tailored drug therapy for the individual patient. The majority of pharmacogenomic information in drug labeling is derived from studies in adults. Developmental differences in gene expression, drug response, and drug metabolizing capacity can result in an inability to universally assume that adult genotype-phenotype relationships apply to all pediatric age groups. The application of adult-derived pharmacogenomic information to pediatrics is particularly challenging when attempting to apply findings to the youngest patients (e.g., neonates, infants).

Case Studies in Pharmacogenetics, - Michael Pacanowski, Pharm D, MPH

Summary: The goal is to improve health with the use of diagnostic testing to identify patients at risk for outcomes that would skew the benefit/risk with drug use. Case examples illustrate that proactively characterizing and managing gene-drug interaction liabilities is feasible for outcomes and genetic factors that are common. Rare events may have a clear genetic etiology, but rarity complicates assessment of validity and utility. Prescribing recommendations balance uncertainty with the information that is needed to inform prescribers.

Analytical and Clinical Validation of Pharmacogenetic Tests, - Kellie B. Kelm, PhD

Summary: Analytical validation of pharmacogenetic tests should be robust, including assessment of accuracy, reproducibility/repeatability, appropriate DNA input, and potential interferences. Clinical validity information can come from several sources. There are analytical and clinical considerations to keep in mind for pharmacogenetic tests.

Clinical Implementation of Precision Therapeutics in Children, - J. Steven Leeder, Pharm. D., PhD.

Summary: The challenges facing clinical implementation of pharmacogenomics information in pediatrics can be addressed by (1) prospective validation of population-based genotype data for clinical application to

"individual" children, (2) characterization of all pathways of drug clearance, and (3) generating data in pediatric population in which the drug will be used. If the goal is drug response, investigate the role of ontogeny and genetic variation of drug targets. Genotype-stratified PK study designs allow for effect of genotype on dose-exposure relationship to be assessed in a relatively small cohort. Genotype-stratified PD study designs require means of controlling the dose-exposure relationship to assess exposure-response relationship.

Discussion Topic 1 (of 2): Based on your clinical experience and the information provided to you at this meeting, please discuss the role of pharmacogenomic testing in your care of patients. In this discussion, please consider the following topics: situations that merit ordering a pharmacogenomic test before prescribing a medication; challenges that may arise in obtaining and/or using this information; situations where you would request a pharmacogenomic test to explore an association with a serious adverse drug effect experienced by a patient; and the source(s) of pharmacogenomic information that you (and other pediatric practitioners) may use to inform your clinical practice.

Committee Discussion: The committee discussed the use of pharmacogenetics in infectious diseases, specifically the HIV-infected pediatric population. They mentioned how there is variability in the pediatric population, such as children with ADHD, and there is different drug penetrance. The Clinical Pharmacogenetics Implementation Consortium guideline would provide some pediatric information and could apply across the lifespan in certain populations. The committee thought it would be useful to understand better the pharmacogenomics for certain products, such as corticosteroids, warfarin for use in patients with aortic valves, biologics used to treat inflammatory bowel disease, and valproate in children <3 years of age.

Discussion Topic 2 (of 2): Discuss the specific role of product labeling to inform your use of pharmacogenomic data in your clinical pediatric practice. In this discussion, please address the location in the product label (e.g., a boxed warning, contraindication, warning and precautions, dosage and administration). As examples, please discuss the issues you would consider in deciding whether to order a POLG test prior to prescribing valproic acid or a CYP2D6 test prior to prescribing atomoxetine. Finally, please discuss how you would describe pharmacogenomics testing to you patients/parents.

Committee Discussion: The committee discussed the complexity and challenges of pharmacogenomics information in a clinical setting, such as inconsistency with product labeling, cost of genetic testing, genetic variability across the population, and ethical concerns with decision making.

Adjournment: - Mark Hudak, MD, Chair

FINAL APPROVAL:

/s/
Marieann R. Brill, MBA, RAC, MT(ASCP)
Designated Federal Officer, PAC

/s/
Mark Hudak, MD
Chairperson, PAC