DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring MD 20993

RECEIVED
JUN 21 2010
OFFICE OF THE SECRETARY

June 16, 2010

Mr. George H. Sheldon
Secretary, Florida Department of Children and Families
1317 Winewood Boulevard
Tallahassee, Florida 32399-0700

Dear Mr. Sheldon:

This letter is in response to your letters dated May 18, 2010, to Commissioner Hamburg and Secretary Sebelius related to Gabriel Myers' tragic death from an apparent suicide while being treated with a combination of medications. My colleagues and I at the Food and Drug Administration (FDA) were saddened to hear about this incident, and we share your concern that all children, especially those within the foster care system, are appropriately protected and treated. I would like to address in more detail the concerns raised in your letters and your request for information about the enrollment of foster children from the State of Florida in FDA-regulated clinical trials.

As noted in your letters, the Gabriel Myers Work Group Report on Psychotropic Medication includes a recommendation (R19) that: "The Legislature should preclude any participation by children in State care in clinical trials relating to the development of new psychotropic medications." In your letter to Secretary Sebelius, you "strongly encourage the Food and Drug Administration to formally forbid the use of foster children and other children in the custody of any State child welfare system from being used in any clinical trials that are being conducted to develop new psychotropic medications or to evaluate the suitability of adult psychotropic medications for children."

Although the State of Florida may decide to prohibit the enrollment of children who are in the State's custody in clinical trials of psychotropic medications, FDA does not agree that a blanket prohibition of the enrollment of foster children and other children in the custody of any State welfare system in such trials is necessarily in their best interest. Such a policy fails to account for the potentially greater risks associated with the off-label use of psychotropic medication and the potential benefits subjects participating in appropriately regulated research may receive through early access to promising new therapies. FDA's regulations (which I describe below) provide important safeguards for children, including wards of a State, who are enrolled in clinical research.

Historically, many medical products have not been tested for use in children. In the absence of adequate directions for use in pediatric populations, physicians must use their best judgment, in

the practice of medicine, to prescribe these products for their patients. The use of medications that lack evidence in support of appropriate pediatric dosing, safety and effectiveness may, in fact, increase the risk of adverse effects and undermine the possibility of therapeutic benefit. Indeed, in part because of these concerns, Congress has enacted (and recently reauthorized) two legislative provisions, the Pediatric Research Equity Act (PREA) (21 U.S.C. § 355c) and the Best Pharmaceuticals for Children Act (BPCA) (21 U.S.C. § 355a), that address the need for development of clinical data on the safe and effective use of FDA-regulated drugs in children.

FDA agrees with the American Academy of Pediatrics that "it is morally imperative, therefore, to formally study drugs in children so that they can enjoy appropriate access to existing and new therapeutic agents."[1] For more than a decade, FDA has been actively involved in initiatives aimed at improving medical product research in children (including under the legislative mandates provided by PREA and BPCA), in order to help ensure that clinicians have the necessary information to use therapeutic agents safely and effectively in pediatric populations. Through this effort, we have come to learn that the assumption, based on adult studies, that a product would be shown to be safe and effective in children has not always been correct.[2] Thus, FDA strongly supports inclusion of children in research, provided that the research is conducted in an ethical and scientifically sound manner. We firmly believe that children must be protected from exploitation and exposure to unnecessary risks related to inclusion in clinical research.

FDA's regulations provide a framework to help ensure that children who participate in research, including those who may be wards of a State, are involved in ways that protect the children's rights and welfare. Most significantly, FDA regulations at 21 C.F.R. part 50 Subpart D, "Additional Safeguards for Children in Clinical Research" (Subpart D) set forth the responsibilities of institutional review boards (IRBs) that review FDA-regulated clinical investigations involving children as subjects, and require that IRBs make a series of determinations, based on the degree of risk posed by the research and who will benefit from it (i.e., direct benefit to the individual subjects in the trial, or generalizable knowledge about the child's disorder or condition),[3] prior to approving clinical investigations involving children as subjects.[4] In other words, these regulations restrict the types of investigations in which children

---

[1] Shaddy RE, Denne SC; and the Committee on Drugs and Committee on Pediatric Research, American Academy of Pediatrics. "Clinical report--guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations." Pediatrics. 2010 Apr; 125(4): 850-60.

[2] For instances where the labeling of drug products has been revised as a result of studies in pediatric populations, please see
http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf

[3] Subpart D sets out four categories of clinical investigations involving children as subjects: clinical investigations not involving greater than minimal risk (21 C.F.R. § 50.51); clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects (21 C.F.R. § 50.52); clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition (21 C.F.R. § 50.53); or clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (21 C.F.R. § 50.54). See also 21 C.F.R. §§ 56.109(h) and 56.111(c).

[4] The Department of Health and Human Services also has regulations, virtually identical to those of FDA, governing the inclusion of children in research conducted, supported, or otherwise subject to regulation under those provisions. See 45 C.F.R. part 46 Subpart D, "Additional Protections for Children Involved as Subjects in Research."

can be enrolled. In addition to the permission of a child's parent or legal guardian, the regulations applicable to pediatric research also require that the assent of each child be obtained, as appropriate (that is, when it is the judgment of the IRB that the child is capable of providing agreement to be enrolled, based in part on the age, maturity, and psychological state of the child).

FDA's regulations specifically address the inclusion of children who are wards of a State or any other agency, institution, or entity. The regulations permit the inclusion of such children under any of the four categories of research under Subpart D, but the regulations state (21 C.F.R. § 50.56(a)) that such children can be included in clinical investigations approved under 21 C.F.R. §§ 50.53 and 50.54[5] only if the clinical investigations are (1) related to their status as wards; or (2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. This regulation is intended to prevent undue reliance on this particularly vulnerable population of children as subjects in research. Furthermore, if a clinical investigation is approved under 21 C.F.R. § 50.56(a), the IRB must require appointment of an advocate who meets certain conditions for each child who is a ward.[6]

Additionally, FDA regulations (21 C.F.R. § 56.111(b)) require that, in order to approve research for which some or all of the subjects (specifically including children) are likely to be vulnerable to coercion or undue influence, an IRB must determine that additional safeguards have been included in the clinical investigation to protect the rights and welfare of these subjects. Further, the regulations contain specific requirements for the membership of the IRB that reviews the research. Specifically, 21 C.F.R. § 56.107(a) requires each IRB that regularly reviews research involving a vulnerable category of subjects, such as children, to give consideration to including one or more individuals who are knowledgeable about and experienced in working with those subjects.

FDA believes that compliance with these regulations (i.e., special determinations related to the degree of risk and potential benefits to children of participating in the trial, appointment of an advocate for children who are wards enrolled in selected research, review of the studies by an IRB supplemented by pediatric expertise as appropriate, obtaining permission from the child's parent or legal guardian, obtaining each child's assent where appropriate) provides additional protections both for children generally and for wards who participate in FDA-regulated clinical trials.

In your letter to Commissioner Hamburg, you also made the following request: "To ensure the safety of those children in State care, I would ask the Food and Drug Administration to determine if any Florida foster children may have been used in the past in clinical trials. I would be particularly interested in information relating to the use of foster children in the clinical investigations conducted by Dr. Punjwani and for which he was issued a warning letter from the

---

[5] 21 C.F.R. § 50.53 addresses clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but that are likely to yield generalizable knowledge about the subject's disorder or condition, and 21 C.F.R. § 50.54 addresses clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

[6] 21 C.F.R. § 50.56(b).

FDA on February 4, 2010. Staff of this Department will be available to assist you in determining if any children used in these trials or investigative procedures are in fact within State care."

We are unable to answer your question as to whether any foster children in Florida may have been involved in past clinical trials regulated by FDA. Data and information received by the agency in an application or other submission generally are coded with identifiers, rather than subject names. Furthermore, a subject's status as a ward would not be submitted to the agency, nor does FDA maintain a database of individual clinical trial subjects.

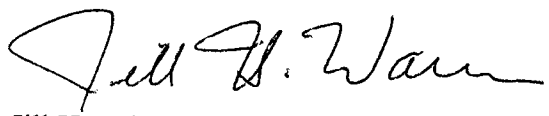
During inspections of clinical investigator sites, FDA's inspectors typically review informed consent documents to verify that informed consent was properly obtained from the subjects in compliance with all applicable regulations, including Subpart D when the clinical investigation involves children as subjects. In the case of the inspection that led to the FDA Warning Letter to Dr. Sohail S. Punjwani, all of the informed consent documents reviewed by FDA inspectors appear to have been signed by a parent. Thus, no foster children, including Gabriel Myers, appear to have been enrolled in the investigations conducted by Dr. Punjwani that were cited in FDA's February 4, 2010, Warning Letter to him.

We commend the State of Florida for undertaking a careful and extensive investigation and analysis of the circumstances surrounding Gabriel Myers' death. We note that the report of the Gabriel Myers Work Group identified a number of procedural deficiencies and recommendations that, when implemented, should better protect foster children.

Although the State of Florida is considering specifically precluding enrollment of children who are wards of the State in clinical trials of psychotropic medications, as stated above, FDA does not agree that a blanket prohibition of the enrollment of foster children and other children in the custody of any State welfare system in such trials is necessarily in their best interest. Such a policy fails to account for the potentially greater risks associated with the off-label use of psychotropic medication and the potential benefits subjects participating in appropriately regulated research may receive through early access to promising new therapies.

In summary, FDA does not believe that a child who is a ward of the State should be precluded from participating in a clinical trial for which that child is otherwise eligible. FDA recognizes that children, and particularly wards of a State, require special protections, but we believe that FDA's regulations provide such protections for FDA-regulated clinical trials. We respectfully encourage you to re-visit the question of whether children who are in the custody of the State of Florida should be permitted to enroll in certain clinical trials.

Sincerely,



Jill Hartzler Warner, J.D.
Acting Associate Commissioner for Special Medical Programs

cc: Secretary Sebelius

DEPARTMENT OF
PUBLIC HEALTH S
Food and Drug Administratio
10903 New Hampshire Avenue
WO32 - 5129
Silver Spring MD 20993-0002
Official Business
Penalty for Private Use, $300

FIRST CLASS

$ 01.05°

Mr. George H. Sheldon
Secretary
Florida Department of Children and Families
1317 Winewood Boulevard
Tallahassee, Florida 32399-0700