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MEMORANDUM

Date: August 30, 2010

From: Robert M. Nelson, M.D., Ph.D.  
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Through: Dianne Murphy, M.D., Director  
Office of Pediatric Therapeutics, Office of the Commissioner, FDA

To: Kristina C. Borrer, Ph.D.  
Director, Division of Compliance Oversight  
Office for Human Research Protections, DHHS

Re: Allegations concerning research activities conducted by Dr. Maria New at Weill Cornell Medical College (WCMC) and Mount Sinai School of Medicine (MSSM)

On February 3, 2010, a “Letter of Concern from Bioethicists” was sent to report suspected regulatory and ethics violations by Dr. Maria New in the use of dexamethasone during pregnancy for the purpose of preventing genital virilization associated with congenital adrenal hyperplasia in females. Copies of this letter were submitted to the FDA Office of Pediatric Therapeutics, the Office for Human Research Protections, and universities where Dr. New has held or holds appointments.

Dexamethasone treatment must be initiated in the 6th to 7th week of gestation, before sexual differentiation of genitalia occurs. Treatment is discontinued once the fetus is identified as being unaffected or male by chorionic villus sampling, usually performed at 10-12 weeks of gestation. If the fetus is female and affected (i.e., “at risk”), dexamethasone is continued until birth. For this indication, dexamethasone is administered at a very low dose of 20 micrograms/kg/day of pre-pregnancy weight in 3 divided doses.

The submitted letter contained the following allegations:

1. Research on the use of dexamethasone for the prevention of virilization in “at risk” fetuses was conducted by Dr. New without appropriate IRB oversight.
2. Dr. New has publicly promoted dexamethasone as safe and effective for this use, when dexamethasone has not been approved for this indication by the FDA.

In addition to the above allegations, the letter outlined three major concerns about the risk/benefit profile of administering dexamethasone:

3. Prenatal dexamethasone treatment results in detrimental changes to the brains of children who are exposed, including problems with working memory, verbal processing, and anxiety;

4. Animal studies have also indicated reason to be concerned about prenatal dexamethasone's effect on fetal brains;
5. Genital virilization is only a cosmetic issue for which alternative postnatal treatments exist.

#### Review Process:

In response to the Letter of Concern, the Office of Pediatric Therapeutics (OPT) spoke with representatives from a number of offices within the Center for Drug Evaluation and Research, including the Division of Scientific Investigation, the Pediatric and Maternal Health Staff and the Division of Reproductive and Urologic Products in the Office of New Drugs, and the Division of Drug Marketing, Advertising, and Communications. In addition, the HHS Office for Human Research Protections (OHRP) requested investigations by the universities identified by the Letter of Concern. The results of these investigations have been reviewed by OPT, and discussed with OHRP. The findings of this investigation are summarized below.

#### Summary Findings:

The available evidence indicates that:

1. Dr. New's research was (specifically, three studies at WCMC between 1985 and 2004) and continues to be conducted (specifically, one study at MSSM) under appropriate IRB oversight, based on the available documentation.
2. Existing data are insufficient to draw conclusions regarding the risk/benefit claims made in the Letter of Concern. Dexamethasone appears to reduce virilization of affected females without causing fetal malformations. High-dose dexamethasone has known adverse effects on growth and development in animals, but similar effects at low doses have not been proven. Further prospective studies are required to determine whether prenatal treatment with dexamethasone should be routinely recommended. We discuss this issue in more depth below.
3. Dr. New received an IND exemption from FDA in 1996 under 21 CFR 312.2(b) for the administration of dexamethasone during pregnancy for the purpose of preventing virilization in females with congenital adrenal hyperplasia.
4. The current administration of dexamethasone to pregnant women in order to prevent genital virilization in "at risk" females does not constitute a "clinical investigation" as the drug is being prescribed based on the clinical judgment of the women's personal physicians who are then referring the women for follow-up in Dr. New's IRB-approved research protocol.
5. The use of dexamethasone for the prevention of genital virilization in "at risk" females has not been approved by the FDA. Dexamethasone is thus being used for this "off label" as part of the clinical practice of medicine. Dexamethasone has not been found to be safe and effective for this indication by FDA.
6. FDA regulations that prohibit the promotion of "off label" use of medications apply to a sponsor, and not to physicians using the medication as part of the practice of medicine.

Discussion of the Safety of using Dexamethasone during Pregnancy:

We now summarize our assessment of the safety issues posed by this treatment in children. One study assessed the frequency and etiology of white-matter changes and temporal lobe atrophy demonstrable on MRI in a group of children and young adults with congenital adrenal hyperplasia (Nass, 1997). The authors noted that exposure to excess glucocorticoids in the process of treatment for congenital adrenal hyperplasia was a theoretically appealing explanation for these MRI findings. However, there is no clear dose-response relationship between the glucocorticoids and the MRI findings, and no correlation between MRI findings and neurological examinations.

Data on memory and processing in children who were treated prenatally with dexamethasone for CAH are small, conflicting, and difficult to interpret. Different methods of assessment were used with children at different age groups, and some studies have focused on parental perception rather than student performance. In general, no differences were observed between dexamethasone-treated children and controls in parental ratings of cognitive or motor development or school performance (Meyer-Bahlburg, 2004). Although an increase in social anxiety was observed in the CAH-unaffected dexamethasone-treated group when children rated themselves, parental ratings did not concur. Visuospatial working memory was mildly poorer in the dexamethasone-treated group, but the difference was not statistically significant (Hirvikoski, 2007). Dexamethasone-treated individuals also had poorer verbal working memory and perception of school performance than controls (Hirvikoski, 2007). However, the authors were later unable to reproduce these findings, and on further analysis concluded that they were due to a small sample size (Hirvikoski, 2008).

A number of studies of dexamethasone administration have been conducted in animals, including rats, rabbits, and primates. While adverse effects ranging from impaired memory to an exaggerated cortisol response to mild stress have been found, the animal models have been designed to imitate either the treatment of premature infants or have used very high doses of dexamethasone (Lajic, 2008). The NOAEL has not been determined, and there are few animal data using lower doses of dexamethasone that would be consistent with the prenatal indication in CAH. One study in fetal sheep suggested that early exogenous dexamethasone directly increases fetal adrenal activation but not anterior pituitary function (Braun, 2009).

Girls with CAH in its more severe forms present with a persistent urogenital sinus, in which the urethra and vagina fail to separate into separate channels. Surgical reconstruction to separate the urinary and reproductive tracts in childhood is necessary to prevent urinary incontinence and infections leading to renal damage as well as to allow normal urination and future sexual function (Diamond et al. 2010). Even uncomplicated clitoromegaly may require surgery to correct, which poses medical risks to the child.

The observational nature and small sample size of the whole body of literature pertaining to dexamethasone in this setting significantly weaken inferences about the benefits and harms of treatment. Dexamethasone seems to be associated with reduction in virilization of affected females without significant maternal or fetal adverse effects (Fernández-Balsells, 2010). There are no data on long term follow-up of physical and metabolic outcomes in children exposed to

dexamethasone. High-dose dexamethasone has known adverse effects on growth and development in animals, but similar effects at low doses have not been proven. Further prospective studies are required to determine whether prenatal treatment with dexamethasone should be routinely recommended.

### References

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