

FEB 17 2011

James P. Reichmann  


Re: Docket No. FDA-2008-P-0358

Dear Mr. Reichmann:

This letter responds to your citizen petition (Petition) received on June 18, 2008. In the Petition, you state that the use of terbutaline sulfate by pregnant women poses risks to the fetus, neonate, and mother and that the long-term use of terbutaline sulfate for the treatment of preterm labor is not efficacious. You request that the Food and Drug Administration (FDA or Agency) take the following actions:

- Reclassify the pregnancy risk category for terbutaline sulfate from pregnancy risk category B to pregnancy risk category C, D, or X;
- Require manufacturers to revise their labeling to reflect the change in pregnancy risk category;
- Notify obstetricians of the reclassification of the drug, the labeling change, and the recommendation of the National Asthma Education and Prevention Program;
- Issue a “Dear Colleague” letter regarding continuous subcutaneous terbutaline pump therapy (CSQT), alerting health care professionals that it has not been demonstrated to be effective and is potentially dangerous to both the mother and the fetus;
- Require all providers of the “terbutaline pump” to report all past and future maternal deaths associated with use of the “terbutaline pump” to FDA. Additionally, require long-term follow-up of adverse events in exposed offspring of treated women.

We have carefully considered your Petition. For the reasons described in detail below, your Petition is granted in part and denied in part. We have notified the NDA and ANDA holders of terbutaline sulfate products that based on animal studies, the drug is being reclassified from pregnancy risk category B to pregnancy risk category C, and that the labeling must be revised to include this new safety information. We have also notified the NDA and ANDA holders that the risks of using terbutaline sulfate for prolonged or

maintenance tocolysis (beyond 48-72 hours) must be described in the labeling of the product, and we believe that the risks should be included in a boxed warning and a contraindication for prolonged or maintenance tocolysis. We grant your request to notify obstetricians of the labeling changes. We deny your request to inform obstetricians of the National Asthma Education and Prevention Program's recommendation regarding the use of terbutaline during pregnancy. We also deny your request to issue a Dear Colleague letter, as we will be notifying health care professionals and the public that we are requiring the labeling changes above. We grant in part and deny in part your request that we require all providers of the "terbutaline pump" to report all past and future maternal deaths associated with use of the "terbutaline pump" to FDA. We deny your request to require long-term follow-up of adverse events in the offspring of women exposed during pregnancy to terbutaline delivered through infusion pumps.

## **I. BACKGROUND**

### **A. Terbutaline Sulfate**

#### *1. Indications and Off-Label Use*

Terbutaline sulfate is a beta-2 adrenergic agonist (also known as a beta-mimetic) that is available in both oral tablet and injectable formulations. Currently approved and marketed oral and injectable terbutaline sulfate drug products include 2.5 mg and 5 mg oral tablets (ANDA 07-5877, manufactured by Impax Labs, and ANDA 07-7152, manufactured by Lannett) and 1 mg/ml injectable (ANDA 07-6770, manufactured by Bedford; ANDA 07-6853, manufactured by Teva Parenteral Medicines, Inc.; ANDA 07-6887, manufactured by APP Pharmaceuticals; ANDA 07-8151, manufactured by Akorn; and ANDA 07-8630, manufactured by Hikma Farmaceutica). The oral and injectable formulations of terbutaline sulfate were originally marketed as Brethine, NDA 18-571 and NDA 17-849 (the current NDA holder for both NDAs is Lehigh Valley Technologies, Inc.), and as Bricanyl, NDA 17-466 and NDA 17-618 (the current NDA holder is Sanofi-Aventis). Both of the NDA holders have discontinued marketing the terbutaline drug products, and approval of the Bricanyl products was withdrawn in 2007 at the sponsor's request.<sup>1</sup>

The labeled indication of terbutaline sulfate is "for the prevention and reversal of bronchospasm in patients 12 years of age and older with asthma and reversible bronchospasm associated with bronchitis and emphysema." Current asthma guidelines recommend inhaled short-acting beta-2 agonists as the drugs of choice for treatment of acute asthma symptoms with oral beta-2 agonists such as terbutaline reserved for the few patients who are unable to use inhaled medication.<sup>2</sup> Terbutaline for injection has no

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<sup>1</sup> 72 FR 62858, 62859 (Nov. 7, 2007).

<sup>2</sup> Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention, 2007; National Asthma Education and Prevention Program (NAEPP), Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, National Heart Lung and Blood Institute (NHLBI), 2007.

proven benefit over inhaled beta-2 agonists; however, because it is given systemically by injection, when used, it is generally reserved for treatment of acute asthma symptoms in an emergency (emergency department) or inpatient hospital setting.<sup>3</sup> With respect to the use of terbutaline for tocolysis (i.e., to arrest preterm uterine contractions), the Precautions section of the current labeling for both the oral and injectable formulations states:

Terbutaline sulfate has not been approved and should not be used for tocolysis. Serious adverse reactions may occur after administration of terbutaline sulfate to women in labor. In the mother, these include increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration.

We note that terbutaline is used “off-label” (i.e., for a use or in a manner not consistent with the FDA-approved labeling for the product) in both tablet and injectable formulations to treat preterm contractions and other complications in pregnancy, including in a triage setting where a woman presents with possible preterm labor. Terbutaline is sometimes used to stabilize a patient for 48 hours or so in the face of imminent preterm delivery.<sup>4</sup> This is typically done to effect transport to a facility with a tertiary care nursery or to allow for antenatal administration of steroids to hasten fetal lung development. Terbutaline is also used in an inpatient setting to treat uterine hyperstimulation,<sup>5</sup> particularly where fetal compromise ensues, and to relax the uterus in the case of uterine inversion.<sup>6</sup> Finally, the drug is sometimes given prophylactically to facilitate attempted external version of a breech or transverse fetus.<sup>7</sup>

In 1993, FDA’s Fertility and Maternal Health Drugs Advisory Committee reviewed and discussed available literature on the safety and effectiveness of terbutaline for tocolysis.

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<sup>3</sup> National Asthma Education and Prevention Program (NAEPP), Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, NHLBI, 2007: 384-86.

<sup>4</sup> Haas DM et al. Tocolytic therapy: a meta-analysis and decision analysis. *Obstet Gynecol.* 2009 Mar; 113 (3): 585-94.

<sup>5</sup> Pacheco LD et al. Management of uterine hyperstimulation with concomitant use of oxytocin and terbutaline. *Am J Perinatol.* 2006; 23L 377-80; Egarter CH, Husslein PW, Rayburn WF. Uterine hyperstimulation after low-dose prostaglandin E2 therapy: tocolytic treatment in 181 cases. *Am J Obstet Gynecol.* 1990; 163: 794-6.

<sup>6</sup> Wendel PJ, Cox SM. Emergent obstetric management of uterine inversion. *Obstet Gynecol Clin North Am.* 1995; 22:261-74; Kovacs BW, DeVore GR. Management of acute and subacute puerperal uterine inversion with terbutaline sulfate. *Am J Obstet Gynecol.* 1984; 150:784-6.

<sup>7</sup> Collaris R, Tan PC. Oral nifedipine vs. subcutaneous terbutaline tocolysis for external cephalic version: a double-blind randomized trial. *BJOG* 2009 Jan; 116(1): 74-80; El-Sayed YY et al. Randomized comparison of intravenous nitroglycerin and subcutaneous terbutaline for external cephalic version under tocolysis. *Am J Obstet Gynecol.* 2004; 191: 2051-5; Fernandez CO et al. A randomized placebo-controlled evaluation of terbutaline for external cephalic version. *Obstet Gynecol.* 1997; 90: 775-9.

Pursuant to a recommendation by the committee, FDA encouraged sponsors to apply for approval of intravenous terbutaline for the acute treatment of preterm labor under limited circumstances. No such application has been approved.

In addition to the above in-hospital uses, ongoing oral or injectable subcutaneous (SQ) dosing on an outpatient basis has been used following acute treatment of preterm contractions for prolonged or maintenance tocolysis.<sup>8</sup> In some cases, as described in your Petition, this is done through use of an infusion pump used to deliver terbutaline provided by a home health care agency, and the treatment can last for many weeks.

The use of prolonged or maintenance tocolysis is generally discouraged by the American Congress of Obstetricians and Gynecologists (ACOG), based on the association's conclusions that such use is not effective in prolonging pregnancy or improving neonatal outcome.<sup>9</sup>

2. *Current Labeling Regarding Use During Pregnancy and Labor and Delivery*

The current labeling for both the oral and injectable terbutaline sulfate products states the following in the Pregnancy and Use in Labor and Delivery sections:

Teratogenic Effects; Pregnancy Category B

A reproduction study in Sprague-Dawley rats revealed terbutaline sulfate was not teratogenic when administered orally at doses up to 50 mg/kg (approximately 810 times the maximum recommended daily sc dose for adults on a mg/m<sup>2</sup> basis). A reproduction study in New Zealand white rabbits revealed terbutaline sulfate was not teratogenic when administered orally at doses up to 50 mg/kg (approximately 1,600 times the maximum recommended daily sc dose for adults on a mg/m<sup>2</sup> basis).

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, terbutaline sulfate injection should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

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<sup>8</sup> American Congress of Obstetricians and Gynecologists. Management of preterm labor. Practice Bulletin # 43, May 2003, reaffirmed 2008. See also Nanda K et al. Terbutaline pump maintenance therapy after threatened preterm labor for preventing preterm birth. Cochrane Database Syst Rev 2002 (4): CD003933.

<sup>9</sup> Id.

### Use In Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of terbutaline sulfate injection for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Terbutaline crosses the placenta. After single dose IV administration of terbutaline to 22 women in late pregnancy who were delivered by elective Cesarean section due to clinical reasons, umbilical blood levels of terbutaline were found to range from 11% to 48% of the maternal blood levels.

### **B. Previous FDA Actions Regarding the use of Terbutaline Sulfate for Prolonged or Maintenance Tocolysis**

FDA previously received three citizen petitions regarding the use of infusion pumps used to deliver terbutaline for prolonged or maintenance tocolysis. In 1996, the National Women's Health Network submitted a petition requesting that FDA enjoin Matria Healthcare, a home health care agency, from marketing and distributing SQ infusion pumps used to administer terbutaline for use in the management of preterm labor.<sup>10</sup> The petition also asked FDA to require Matria to send a letter informing physicians that there is no scientific evidence that tocolytics administered by SQ infusion pumps prolong pregnancy, and that tocolytics have been associated with maternal mortality and morbidity. FDA responded to the petition in November 1997, granting it in part and denying it in part.<sup>11</sup> Specifically, FDA found, after reviewing the literature, that:

... the documented value of tocolytics for managing preterm labor is limited to short-term, intravenous (not subcutaneous) use, i.e., prolongation of pregnancy by 48-72 hours. Moreover, there is no conclusive evidence that the use of subcutaneous terbutaline produces consistent benefits in gestational age at delivery, birthweight, neonatal morbidity, or perinatal morbidity.<sup>12</sup>

Agreeing with the petitioner, the Agency concluded that:

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<sup>10</sup> This citizen petition was originally assigned docket number 96P-0258/CP1. The number was changed to FDA-1996-P-0153 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

<sup>11</sup> Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, and Dr. D. Bruce Burlington, Director, Center for Devices and Radiological Health, FDA, to Cynthia Pearson, Executive Director, National Women's Health Network re: Docket No. 96P-0258/CP1 (November 7, 1997)(National Woman's Health Network CP Response).

<sup>12</sup> National Women's Health Network CP Response at 2.

... there is insufficient scientific support for a claim that use of terbutaline administered by continuous, subcutaneous infusion pump results in improved treatment outcomes.<sup>13</sup>

In addition, FDA noted that while the overall rate of adverse events associated with infusion pumps used to deliver terbutaline was difficult to estimate, it appeared that SQ terbutaline was associated with adverse events and at least one reported maternal death.<sup>14</sup>

Based on the lack of demonstrated effectiveness and the adverse events associated with the use of SQ terbutaline for prolonged or maintenance tocolysis, FDA granted the petitioner's request that the medical community be notified of the concerns associated with such use.<sup>15</sup> A Dear Colleague letter was sent by FDA in November 1997 advising professional organizations involved with obstetrical care that:

It is clear that the demonstrated value of tocolytics in general is limited to an initial, brief period of treatment, probably no more than 48-72 hours. No benefit from prolonged treatment has been documented. In addition, the safety of long-term subcutaneous administration of terbutaline sulfate, especially on an outpatient basis, has not been adequately addressed.

In 1998, FDA received two citizen petitions requesting that FDA reevaluate the position it took in the 1997 Dear Colleague letter. The first of these petitions was submitted on March 4, 1998, by Ms. Sherokee Ilse on behalf of the Coalition for Positive Outcomes in Pregnancy (Coalition for Positive Outcomes in Pregnancy Petition).<sup>16</sup> The second was submitted on April 7, 1998, by Dr. Fung Lam on behalf of the Terbutaline Strategy Group (Terbutaline Strategy Group Petition).<sup>17</sup>

The Coalition for Positive Outcomes in Pregnancy Petition requested, among other things, that FDA (1) meet with the petitioner and her scientific advisors to discuss the published literature on the use of SQ terbutaline, (2) hold in abeyance the policy stated in the November 1997 Dear Colleague letter, and (3) take no additional action to prohibit physicians' use of terbutaline in any form.

The Terbutaline Strategy Group Petition requested that FDA acknowledge SQ terbutaline as a drug for professional use in the treatment of preterm labor, and reevaluate the position the Agency took in the November 1997 Dear Colleague letter. The petition also

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<sup>13</sup> National Women's Health Network CP Response at 3.

<sup>14</sup> National Women's Health Network CP Response at 4-5.

<sup>15</sup> National Women's Health Network CP Response at 7.

<sup>16</sup> This petition was originally assigned docket no. 98P-0150/CP1. The number was changed to FDA-1998-P-0256 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

<sup>17</sup> This petition was originally assigned docket no. 98P-0218/CP1. The number was changed to FDA-1998-P-1291 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

requested that FDA (1) notify the organizations who received the Dear Colleague letter that the use of terbutaline in managing preterm labor is as safe and effective as ritodrine, and the deaths of patients receiving terbutaline were not due to the drug; (2) ask manufacturers of terbutaline sulfate to remove package insert statements about the use of terbutaline in managing preterm labor, and to submit data to the Agency to obtain approval for the use of terbutaline for this indication; and (3) expedite the review of any pending applications for approval of drugs for tocolysis.

On October 19, 1999, FDA responded in two separate letters to the Coalition for Positive Outcomes in Pregnancy Petition and the Terbutaline Strategy Group Petition.<sup>18</sup> In the responses to these petitions, FDA reaffirmed its position stated in the November 1997 Dear Colleague letter that there is no evidence of the effectiveness of prolonged treatment with SQ terbutaline to manage preterm labor and that there are significant safety concerns associated with unmonitored, long-term administration of the drug (i.e., beyond 48-72 hours).

### **C. Regulations on Warnings in Prescription Drug Labeling; Postapproval Studies and Trials**

#### *1. Contraindications, Warnings and Precautions, and Boxed Warnings*

FDA regulations state that the WARNINGS AND PRECAUTIONS section of prescription drug and biological product labeling (including the product's package insert) must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur (21 CFR 201.57(c)(6)(i); see also 21 CFR 201.80(e) and (f)). Labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association of the hazard with the product (Id.). For products described in § 201.56 (21 CFR 201.56), a summary of the most clinically significant warnings and precautions information must be included in the HIGHLIGHTS OF PRESCRIBING INFORMATION (HIGHLIGHTS) for the product (21 CFR 201.57(a)(10)).

Under § 201.57(c)(1), a boxed warning (sometimes referred to as a black box warning) may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury (see also § 201.80(e)). A boxed warning must contain, in uppercase letters, a heading that includes the word "WARNING" and conveys the general focus of information in the box. A boxed warning briefly explains the risk and refers to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section (§ 201.57(c)(1)). A summary of a boxed warning (with the heading WARNING and other words identifying the subject of the warning) must be

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<sup>18</sup> Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Sherokee Ilse, Coalition for Positive Outcomes in Pregnancy re: Docket No. 98P-0150/CP1 (October 19, 1999); Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Fung Lam, M.D., Terbutaline Strategy Group re: Docket No. 98P-0218/CP1 (October 19, 1999).

included in the HIGHLIGHTS in a box and in bold type (21 CFR 201.56(d)(1) and 201.57(a)(4)).

FDA's draft guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format (Warnings Guidance)*<sup>19</sup> states on page 9 that a boxed warning ordinarily is used to highlight one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug, or
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation), or
- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted.

The Warnings Guidance (at 9) also states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.

## 2. *Pregnancy Categories*

FDA regulations state that if a drug is absorbed systemically, the *Pregnancy* subsection of drug product labeling must address the teratogenic effects of the drug by inclusion of the appropriate pregnancy category, as well as the relevant required statements for that category (21 CFR 201.57(c)(9)(i) and 201.80(f)(6)(i)). The regulations specify the following criteria used to designate the appropriate category:<sup>20</sup>

- **Pregnancy Category A:** “adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy

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<sup>19</sup> The draft guidance is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf>. The draft guidance, when finalized, will represent FDA's current thinking on the topic.

<sup>20</sup> FDA has issued a proposed rule to amend its regulations concerning the requirements for pregnancy and lactation information in prescription drug and biological product labeling. See 73 FR 30831 (May 29, 2008). We note that the proposed rule, if finalized, would remove the pregnancy categories from prescription drug and biological product labeling.

(and there is no evidence of risk in later trimesters)” (21 CFR 201.57(c)(9)(i)(A)(1) and 201.80(f)(6)(i)(a)).

- Pregnancy Category B: “animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women” or “animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)” (21 CFR 201.57(c)(9)(i)(A)(2) and 201.80(f)(6)(i)(b)).
- Pregnancy Category C: “animal reproduction studies have shown an adverse effect on the fetus, ... there are no adequate and well-controlled studies in humans, and ... the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks” or “there are no animal reproduction studies and no adequate and well-controlled studies in humans” (21 CFR 201.57(c)(9)(i)(A)(3) and 201.80(f)(6)(i)(c)).
- Pregnancy Category D: “there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective)” (21 CFR 201.57(c)(9)(i)(A)(4) and 201.80(f)(6)(i)(d)).
- Pregnancy Category X: “studies in animals or humans have demonstrated fetal abnormalities or ... there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available)” (21 CFR 201.57(c)(9)(i)(A)(5) and 201.80(f)(6)(i)(e)).

### 3. *Labeling Changes Based on “New Safety Information”*

Title IX, Subtitle A, section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the Federal Food, Drug, and Cosmetic Act (the Act) to authorize FDA to require holders of approved drug and biological product applications to make safety labeling changes for an approved drug based on new safety information that becomes available after the approval of the drug (section 505(o)(4) of the Act (21 U.S.C. 355(o)(4))). As defined in section 505-1(b)(3), new safety information is information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has

become aware of (that may be based on a new analysis of existing information) since the drug was approved.

4. *Postapproval Studies or Trials*

Title IX, Subtitle A, section 901 of FDAAA authorizes FDA to require postapproval studies or clinical trials of a drug to assess a known serious risk related to the use of the drug involved, to assess signals of serious risk related to the use of the drug, or to identify an unexpected serious risk when available data indicate the potential for a serious risk (section 505(o)(3) of the Act (21 U.S.C. 355(o)(3))).<sup>21</sup>

**II. DISCUSSION**

**A. Terbutaline Sulfate Pregnancy Risk Category**

1. *Pregnancy Risk Category C*

In the Petition, you state that animal studies demonstrate that terbutaline is a developmental neurotoxicant to fetal and neonatal rats. In support of this statement, you cite numerous scientific articles (Petition at 1-2). You state further that based on this information, FDA is required to change the pregnancy risk category for terbutaline sulfate from category B to pregnancy risk category C, D, or X, and that manufacturers must update the package inserts to reflect this change. Further, based on your review of the literature, which you cite in the Petition, you state that there is evidence that terbutaline is “closely associated” with autism in children born to mothers who received terbutaline while pregnant (Petition at 2).

We grant your request to change the pregnancy risk category of terbutaline sulfate to category C, based on new nonclinical teratogenic findings.

The current terbutaline labeling designates the drug as pregnancy risk category B. As stated above, the regulations specify that pregnancy category B be designated when “animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women” or “animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)” (21 CFR 201.57(c)(9)(i)(A)(2) and 201.80(f)(6)(i)(b)).

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<sup>21</sup> See also FDA’s draft guidance for industry on *Postmarketing Studies and Clinical Trials – Implementation of Section 505(o) of the Federal Food, Drug, and Cosmetic Act*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>. The draft guidance, when finalized, will represent FDA’s current thinking on the topic.

We agree that based on the references you submitted, the pregnancy category should be changed to category C. At the time of the original approval, reproductive toxicology studies demonstrated no adverse developmental outcomes in rabbits exposed to approximately 810 times the maximum recommended daily human SQ dose of terbutaline. However, newer published data in pregnant rats that received terbutaline at doses 24 to 48 times the recommended human dose showed abnormal brain development in exposed offspring.<sup>22</sup> Further, as discussed below, we have concluded that there are no adequate and well-controlled studies in humans, and there are situations where the use of terbutaline in pregnant women may be acceptable despite its potential risks. Thus, terbutaline meets the criteria for pregnancy category C, namely that “animal reproduction studies have shown an adverse effect on the fetus, ... there are no adequate and well-controlled studies in humans, and ... the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks” (21 CFR 201.57(c)(9)(i)(A)(3) and 201.80(f)(6)(i)(c)).

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<sup>22</sup> Slotkin TA, Oliver CA, Seidler FJ. Critical periods for the role of oxidative stress in the developmental neurotoxicity of chlorpyrifos and terbutaline, alone or in combination. *Brain Res Dev Brain Res* 2005; 157: 172-180; Aldridge JE, Meyer A, Seidler FJ, Slotkin TA. Developmental exposure to terbutaline and chlorpyrifos: pharmacotherapy of preterm labor and an environmental neurotoxicant converge on serotonergic systems in neonatal rat brain regions. *Toxicol Appl Pharmacol* 2005; 203: 132-144; Meyer A, Seidler FJ, Aldridge JE, Slotkin TA. Developmental exposure to terbutaline alters cell signaling in mature rat brain regions and augments the effects of subsequent neonatal exposure to the organophosphorus insecticide chlorpyrifos. *Toxicol Appl Pharmacol* 2005; 203: 154-166; Rhodes MC, Seidler FJ, Qiao D, Tate CA, Cousins MM, Slotkin TA. Does pharmacotherapy for preterm labor sensitize the developing brain to environmental neurotoxicants? Cellular and synaptic effects of sequential exposure to terbutaline and chlorpyrifos in neonatal rats. *Toxicol Appl Pharmacol* 2004; 195: 203-217; Kreider ML, Seidler FJ, Slotkin TA. Beta-adrenoceptor modulation of transiently overexpressed alpha 2-adrenoceptors in brain and peripheral tissues: cellular mechanisms underlying the developmental toxicity of terbutaline. *Brain Res Bull* 2004; 62: 305-314; Rhodes MC, Seidler FJ, Abdel-Rahman A, Tate CA, Nyska A, et al. Terbutaline is a developmental neurotoxicant: effects on neuroproteins and morphology in cerebellum, hippocampus, and somatosensory cortex. *J Pharmacol Exp Ther* 2004; 308: 529-537; Slotkin TA, Tate CA, Cousins MM, Seidler FJ. Beta-adrenoceptor signaling in the developing brain: sensitization or desensitization in response to terbutaline. *Brain Res Dev Brain Res* 2001; 131: 113-125; Slotkin TA, Kudlacz EM, Lappi SE, Tayyeb MI, Seidler FJ. Fetal terbutaline exposure causes selective postnatal increases in cerebellar alpha-adrenergic receptor binding. *Life Sci* 1990; 47: 2051-2057; Slotkin TA, Baker FE, Dobbins SS, Eylers JP, Lappi SE, Seidler FJ. Prenatal terbutaline exposure in the rat: selective effects on development of noradrenergic projections to cerebellum. *Brain Res Bull* 1989; 23: 263-265; Zerrate MC, Pletnikov M, Connors SL, Vargas DL, Seidler FJ, et al. Neuroinflammation and behavioral abnormalities after neonatal terbutaline treatment in rats: implications for autism. *J Pharmacol Exp Ther* 2007; 322: 16-22; Garofolo MC, Seidler FJ, Cousins MM, Tate CA, Qiao D, Slotkin TA. Developmental toxicity of terbutaline: critical periods for sex-selective effects on macromolecules and DNA synthesis in rat brain, heart, and liver. *Brain Res Bull* 2003; 59: 319-329; Slotkin TA, Seidler FJ. Developmental exposure to terbutaline and chlorpyrifos, separately or sequentially, elicits presynaptic serotonergic hyperactivity in juvenile and adolescent rats. *Brain Res Bull* 2007; 73: 301-309; Fujita H, Tanaka J, Maeda N, Sakanaka M. Adrenergic agonists suppress the proliferation of microglia through beta 2-adrenergic receptor. *Neurosci Lett* 1998; 242: 37-40; Nunez JL, Alt JJ, McCarthy MM. A novel model for prenatal brain damage. II. Long-term deficits in hippocampal cell number and hippocampal-dependent behavior following neonatal GABAA receptor activation. *Exp Neurol* 2003; 181: 270-280; Slotkin TA, Seidler FJ. Transient postnatal elevation of norepinephrine content and turnover in brain regions of rats exposed to terbutaline prenatally: evidence for autoregulation of noradrenergic development? *Res Commun Chem Pathol Pharmacol* 1992; 76: 269-278.

We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the Act. Section 505(o)(4) of the Act authorizes FDA to require holders of approved drug and biological product applications to make safety related labeling changes based upon new safety information that becomes available after approval of the drug or biological product. Accordingly, based on the new data, we are requiring the NDA and ANDA holders to revise the labeling to reflect the change in the pregnancy risk category to C.

## 2. *Pregnancy Risk Category D*

In evaluating your request to change the pregnancy risk category, we also considered whether it should be changed to category D. Based on our review of the literature, we conclude that the available human data do not support classification of the drug as pregnancy risk category D, which is designated when “[t]here is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risk” (21 CFR 201.57(c)(9)(i)(A)(4) and 201.80(f)(6)(i)(d)).

In the Petition, you cite human data published in the scientific literature that you assert suggests an association between terbutaline exposure in utero and autism.<sup>23</sup> You state that investigators at Kennedy Krieger Institute and Johns Hopkins University have begun extensive research on the link between slightly different versions of the gene (polymorphisms) that code for the beta-2 adrenergic receptor ( $\beta$ 2AR) and increase the risk for autism when combined with terbutaline exposure. You also state that the twin study by Connors et al. published in 2005 shows that prenatal exposure to terbutaline was associated with increased risk of autism (Petition at 2).

We find that the referenced human data do not warrant changing the pregnancy risk category to D. First, the data are confounded by several factors. Children born to mothers with preterm labor and delivery represent a population at higher risk for neurological compromise, whether due to prematurity itself or the underlying condition resulting in preterm labor. Preterm labor is poorly understood and may be associated with inflammation, infection, multiple gestation, uteroplacental insufficiency, and/or other factors, each of which may increase the risk for abnormal neurodevelopmental outcomes. Second, autism has highly variable clinical neurodevelopmental manifestations, and its etiology is complex and poorly understood, so it is difficult to

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<sup>23</sup> Petition at 2, citing Feldman H. Expressive language delay in a toddler. *J of Dev & Beh Ped*; 4/1/2001; Connors SL, Crowell DE, Eberhardt CG, Copeland J, Newschaffer CJ, Spence SJ, Zimmerman AW, Beta-2 adrenergic receptor activation and genetic polymorphisms in autism: data from dizygotic twins. *J Child Neurol* 2005 Nov; 20(11):876-84; Cheslack-Postava K, Fallin MD, Avramopoulos D, Connors SL, Zimmerman AW, et al.  $\beta$ <sub>2</sub>-adrenergic receptor gene variants and risk for autism in the AGRE cohort. *Mol Psychiatry*. 2007; 12: 283-91; and Kilburn, KH, Thrasher, JD, Immers, IB. Autism, terbutaline and neurological impairment. *Eur J Oncology* 2007 (according to the Petition, this last article was “in press” at the time the Petition was submitted).

draw conclusions from the data presented. Moreover, the references you cite to support the association of terbutaline with increased risk of autism have limitations: the sample sizes are small (one is a case report), they each lack key information (such as, depending on the reference, terbutaline dose, duration of exposure, route of administration, use of other medications, and family history), and the studies fail to control for important potential confounding factors between exposed or affected populations and control populations.

At the present time, it is not possible to draw conclusions regarding an association between terbutaline exposure in utero and autism, as the hypothesis that overstimulation of the  $\beta$ 2AR and the ensuing pathways results in brain alterations is based on animal models and in vivo results using other organ systems, which have shown substantial variation in response across systems. Whether this hypothesis is generalizable to the developing human fetal brain is not clear. Future work in models relevant to the developing nervous system will be needed to determine the biological relevance of current data.

Accordingly, we conclude that the available human data regarding an association between terbutaline sulfate and autism are not sufficient to conclude that there is “positive evidence of human fetal risk,” and therefore the data do not warrant changing the pregnancy risk category to D.

### 3. *Pregnancy Risk Category X*

In evaluating your Petition, we also examined whether terbutaline sulfate should be designated as pregnancy risk category X. We conclude that category X is not appropriate. Under FDA regulations, category X must be used when:

Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available) (21 CFR 201.57(c)(9)(i)(A)(5) and 201.80(f)(6)(i)(e)).

We find that category X does not apply to terbutaline sulfate. As discussed above, terbutaline sulfate is used in some obstetrical emergencies, such as uterine inversion and uterine hyperstimulation, where there is no alternative available therapy. In addition, as recommended in 1993 by FDA’s Fertility and Maternal Health Drugs Advisory Committee, SQ terbutaline has clinical utility for short-term ( $\leq$ 48-72 hours), in-hospital use for preterm labor to allow administration of steroids to accelerate fetal lung maturity and transfer of the pregnant woman to a tertiary care facility. Although other agents are available for short-term tocolysis, they may be contraindicated or poorly tolerated. For these reasons, we conclude that the risk of the use of the drug in a pregnant woman does

not clearly outweigh any possible benefit and therefore terbutaline sulfate should not be designated as category X.

**B. Contraindication and Boxed Warning Regarding Off-Label Use of SQ Terbutaline Sulfate for Prolonged or Maintenance Tocolysis**

In the Petition, you state that the American College of Obstetricians and Gynecologists (ACOG), the Agency for Healthcare Research and Quality (AHRQ), and FDA recommend against use of terbutaline for tocolysis, and that the National Asthma Education and Prevention Program recommends that pregnant women with mild, intermittent asthma should be prescribed short-acting beta-2 agonists rather than oral terbutaline (Petition at 2-3). You also state that no randomized controlled trials have demonstrated the effectiveness of long-term use of continuous SQ terbutaline, and that maternal safety with the use of continuous SQ administration of terbutaline sulfate remains questionable (Petition at 3-4). Citing five studies and case reports, you state that they, along with other information, suggest that concern regarding maternal safety is warranted.

As we stated in the 1997 National Woman's Health Network Petition response, we agree that there is no documented evidence of therapeutic benefit associated with the prolonged (beyond 48-72 hours) use of terbutaline sulfate for tocolysis. In evaluating the current Petition, we reviewed the available post-1997 literature regarding effectiveness. We conclude that the post-1997 literature does not reveal any additional data that would support the effectiveness of terbutaline sulfate for preterm labor tocolysis beyond 48-72 hours.

We also agree that there are demonstrated maternal risks associated with the use of terbutaline sulfate for prolonged or maintenance tocolysis. In our review of postmarketing reports, we found three reports of maternal deaths associated with the use of an infusion pump to deliver continuous SQ terbutaline. We also found a total of 16 fatal cases reported for all terbutaline formulations and routes of administration, including oral, SQ, and intravenous (IV). In addition, we found 12 serious cardiovascular events associated with the use of terbutaline, including three reported with prolonged use of the SQ pump for tocolysis. The latest of these was reported in September 2005. The cardiovascular adverse event reports describe symptoms involving hypertension, tachycardia, cardiac arrhythmias, and pulmonary edema.

We consider these human data regarding cardiovascular events and the animal data regarding neurotoxic risks to be "new safety information" as defined in section 505-1(b)(3) of the Act. Based on this new safety information and the lack of demonstrated effectiveness with the use of terbutaline sulfate for prolonged tocolysis, we conclude that a contraindication and boxed warning are warranted regarding the use of terbutaline sulfate for prolonged or maintenance tocolysis. We have notified the NDA and ANDA holders that under 505(o)(4) of the Act, the labeling must be revised to address the new safety information associated with off-label use of injectable terbutaline for prolonged or

maintenance tocolysis in the outpatient setting.<sup>24</sup> Specifically, we have notified the NDA and ANDA holders that we believe the use of injectable terbutaline for prolonged and maintenance tocolysis must be contraindicated and a boxed warning must be added stating that injectable terbutaline is not approved and should not be used for prolonged or maintenance tocolysis, and that serious adverse reactions, including death, have occurred following use in pregnant women.

Our letters notifying the NDA and ANDA holders that we believe the labeling for terbutaline sulfate products should be modified to include a contraindication and boxed warning were issued yesterday, based on our authority with respect to safety labeling changes under section 505(o)(4) of the Act. In accordance with section 505(o)(4) of the Act, the terbutaline sulfate NDA and ANDA holders are required to submit within 30 days following notification either a supplement containing the proposed labeling changes, or notify the Agency that it does not believe labeling changes are warranted and submit a statement detailing the reasons such changes are not warranted.

If the terbutaline sulfate NDA and ANDA holders do not submit proposed safety labeling changes, or if we disagree with the language proposed or the statement setting forth the reasons why no labeling change is necessary, the Act provides strict timelines under section 505(o)(4) for discussions regarding the labeling changes. At the conclusion of these discussions, section 505(o)(4)(E) allows FDA to issue an order directing labeling changes as deemed appropriate to address the new safety information. We are awaiting the responses of the terbutaline sulfate NDA and ANDA holders, under these FDAAA procedures, to our notification that additional warnings and other revisions to product labeling are necessary. The specific language we have recommended is subject to change depending on what language the NDA and ANDA holders propose. Thus, we have not required specific labeling changes at this stage of the process under section 505(o)(4) of the Act. However, we have taken all the necessary steps required under section 505(o)(4) of the Act to pursue the necessary changes.<sup>25</sup>

**C. Requests to Notify Obstetricians of the Labeling Changes and of the National Asthma Education and Prevention Program's Position on Terbutaline Use During Pregnancy, and to Issue a Dear Colleague Letter**

You request that FDA notify obstetricians of the labeling changes and issue a Dear Colleague letter to alert health care professionals that continuous subcutaneous terbutaline pump therapy (CSQT) has not been demonstrated to be effective and is potentially dangerous to the mother and the fetus (Petition at 1).

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<sup>24</sup> Although your Petition focuses largely on continuous SQ administration of terbutaline, safety labeling changes notifications were also sent to oral terbutaline NDA and ANDA holders addressing the off-label use of oral terbutaline for tocolysis.

<sup>25</sup> The labeling for a generic drug product approved under an ANDA is required to be the same as the labeling for the reference listed drug, with certain permissible differences not relevant here (see 21 U.S.C. 355(j)(2)(A)(v), 21 CFR 314.94(a)(8)(iv); see also 21 CFR 314.127(a)(7)). Therefore, the ANDA holders will be required to make the same labeling changes as the NDA holder for all generic versions of the drug.

You also request that FDA notify obstetricians “that the National Asthma Education and Prevention Program recommends ‘Terbutaline no longer be given to women with mild or intermittent asthma while they are pregnant.’”

We grant your request that we notify obstetricians of the labeling changes. FDA has posted information on our Web site at [www.fda.gov](http://www.fda.gov) informing health care professionals and the public that we are requiring the labeling changes described above. We are also issuing a drug safety communication and a press release.

We deny your request that we notify obstetricians of the National Asthma Education and Prevention Program’s (NAEPP’s) position on terbutaline use during pregnancy. We have determined that the required labeling changes, along with posting information about the required labeling changes on our Web site, are sufficient. We also believe that in most cases, a pregnant woman’s asthma would be managed by her internist or pulmonologist, who presumably would already be aware of the NAEPP’s position on the use of terbutaline during pregnancy, rather than by her obstetrician; thus, we do not believe that your requested notification is necessary. We also note that, contrary to your assertion with respect to the NAEPP’s recommendation, the NAEPP 2004 guideline states that albuterol is the preferred short-acting beta agonist for use during pregnancy because there are more safety data on its use during pregnancy.

We deny your request that we issue a Dear Colleague letter because we are using other methods to inform health care professionals and the public of the labeling changes. As discussed above, we have posted information about the labeling changes on our Web site at [www.fda.gov](http://www.fda.gov). In addition, we are issuing a drug safety communication and a press release.

**D. Reporting of Maternal Deaths and Long-Term Follow-Up of Adverse Events in Offspring of Treated Women**

In the Petition, you request that FDA require all providers of the “terbutaline pump” to report all past and future maternal deaths associated with the SQ terbutaline pump to FDA (Petition at 1). To the extent that you request that FDA require device manufacturers and user facilities to report to FDA maternal deaths that they become aware of that may have been caused or contributed to by the use of infusion pumps to deliver terbutaline, we grant that part of your request. To the extent that you request that FDA impose any obligations on device manufacturers and user facilities that are not required under the Act and FDA implementing regulations, we deny that part of your request.

Please note that FDA has not cleared or approved an infusion pump intended for use in delivering terbutaline subcutaneously for tocolysis. Continuous delivery of terbutaline by SQ infusion for tocolysis would be considered “prolonged or maintenance tocolysis,” and would not be within the cleared or approved intended use of any infusion pump.

FDA already requires device manufacturers and device user facilities to report to FDA maternal deaths that they become aware of that may have been caused or contributed to by the use of infusion pumps to deliver terbutaline. Specifically, infusion pump device manufacturers are required to submit reports to FDA within 30 calendar days after the day they become aware of information, from any source, that reasonably suggests that their infusion pump may have caused or contributed to a serious injury or death (section 519(a) of the Act and 21 CFR part 803 Subpart E).<sup>26</sup> In addition, device user facilities, including outpatient treatment facilities and hospitals, are required to submit reports to both FDA and the manufacturer of the device, if known, as soon as practicable but no more than 10 work days after the day when they become aware that a device has or may have caused or contributed to the death of a patient in their facility (section 519(b) of the Act and 21 CFR part 803 Subpart C).<sup>27</sup> Individual health care providers, such as physicians, and their patients are encouraged to voluntarily notify the manufacturer when they become aware of such events and to make reports to FDA using FDA Form 3500.<sup>28</sup>

Therefore, FDA considers its current reporting mechanisms to be appropriate to help ensure that the Agency receives information regarding maternal deaths that may have been caused or contributed to by the use of infusion pumps to deliver SQ terbutaline. Accordingly, we conclude it is neither necessary nor appropriate to impose additional reporting requirements with respect to such events.

You also request that FDA require long-term follow-up of adverse events in the offspring of women exposed during pregnancy to terbutaline delivered through infusion pumps (Petition at 1). We deny your request. Under the Act, FDA may require a sponsor to conduct postapproval studies or clinical trials of a drug to assess a known serious risk related to the use of the drug involved, to assess signals of serious risk related to the use of the drug, or to identify an unexpected serious risk when available data indicate the potential for a serious risk (section 505(o)(3) of the Act (21 U.S.C. 355(o)(3))). We agree that there is a signal of serious risk related to use of terbutaline in some clinical settings; however, based on our overall response to this petition, we conclude that a postapproval study to assess long-term adverse events in exposed offspring is not necessary at this time. Given that we are requiring that the NDA and ANDA holders revise the labeling of terbutaline sulfate to contraindicate the drug for prolonged or maintenance tocolysis, and to add a boxed warning, we expect that the use of terbutaline for

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<sup>26</sup> For additional information on mandatory reporting by manufacturers, see <http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149238.htm>.

<sup>27</sup> For additional information on mandatory reporting by user facilities, see <http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149238.htm>.

<sup>28</sup> For additional information on voluntary reporting by healthcare professionals and patients, see <http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082725.pdf>.

prolonged or maintenance tocolysis will decline, and therefore, a long-term follow-up study is not needed. Although we are not requiring a postapproval study, we will continue to monitor terbutaline, as we do all drugs, and take further action if necessary to address any safety concerns.

### **III. CONCLUSION**

Based on our review of the Petition and the scientific literature referenced therein, we grant your Petition in part and deny it in part. We grant your request to change the pregnancy risk category for terbutaline by changing the category from B to C. We have also notified the NDA and ANDA holders that the labeling must be revised to include new safety information regarding the drug and, in particular, that we believe (1) use of terbutaline for prolonged or maintenance tocolysis must be contraindicated, and (2) a boxed warning must be added to note that terbutaline is not approved and should not be used for prolonged or maintenance tocolysis, and that serious adverse reactions, including death, have occurred following use in pregnant women. We also grant your requests to inform obstetricians of the labeling changes. We deny your requests to inform obstetricians of the NAEPP's position on the use of terbutaline during pregnancy and to issue a Dear Colleague letter. We also deny your request to require long-term follow-up of adverse events in the offspring of women exposed during pregnancy to terbutaline delivered through infusion pumps.

Sincerely,

/s/

Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research