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November 15, 2000

Docket Number 97N-0289
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD, 20852

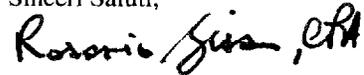
Re: My letter to the Honorable Jane E. Henney, FDA's Commissioner, dated November 15, 2000.

To whom it may concern:

Please find enclosed my letter to the Honorable Jane E. Henney, FDA's Commissioner, dated November 15, 2000, relating to the FDA/NICHED's Conference, Clinical Pharmacology during Pregnancy: Addressing clinical needs through science, to be held December 4-5, 2000, which, in part, emphasizes the 'labeling' changes in Drug Use-in-Pregnancy. This letter complements the ones to the Docket Number 97N-0289 of May 19, 1999, July 30, 2000 and September 24, 2000. I trust that this information is helpful to the Center for Drug Evaluation and Research.

Thank you for your attention. Indeed, *"every unborn's well-being is a sacred trust!"*

Sinceri Saluti,



Rosario Zisa, C.P.A.

RZ/

cc: Dianne L. Kennedy, RPh, MPH, Project Manager, Pregnancy Labeling Task Force

Enclosure

Docket Number 97N-0289 FDA/CDER November 15 2000

97N-0289

sup 2
see C6

Rosario Zisa, C.P.A.
Prospect Park, N.J., 07508-2234
(973) 942-4821

November 15, 2000

Via Certified Mail/R.R.R.

The Honorable Jane E. Henney, Commissioner
The Food and Drug Administration
Room 14-71, Parklawn Building
5600 Fishers Lane
Rockville, Maryland, 20857

Re: a) FDA/NICHD's Conference, Clinical Pharmacology during Pregnancy:
Addressing clinical needs through science, to be held December 4-5, 2000,

b) and, the *conventional wisdom* approach to prenatal obstetric analgesics, in the
context of *normal* pregnancy labor and delivery.

Dear Dr. Henney:

Pursuant to The Food and Drug Administration (FDA) and the National Institute for Child Health and Human Development (NICHD) Conference, Clinical Pharmacology during Pregnancy: Addressing clinical needs through science, to be held December 4-5, 2000, I'm very delighted to know that you--personally--will participate in this very important conference. It is my understanding that based on the conference's agenda that, in general, "the focus of the meeting will be drug therapeutics during the second and third trimester of pregnancy." In that context, I'm hopeful that, as you prepare your agenda for this very important conference, you will also address the seemingly innocuous clinical pharmacology, as the Pregnancy is about to cross the *finish line*. Or, in other words, the role of prenatal obstetric analgesics in *normal* pregnancy, labor and delivery, a subject matter which I brought to your attention on several occasions. Now, if I may, I would like to present to you some additional relevant data.

I'm aware that you alone cannot address the myriad of issues that must be addressed in the conference; therefore, you and the Agency, in part, must also rely on the expertise of your invited experts. While each and everyone of your staff and experts appear to have impeccable clinical and/or pharmaceutical credentials, for the issue that I'm particularly interested, i.e., once again . . . pharmacology in the arena of *prenatal obstetric analgesics*, in *normal* pregnancy, labor and delivery, I believe that one of your invited guests could be the ideal expert to help you sort out this critical issue. I am alluding at Michael L. Greene, M.D., FACOG, who happens to be a *regular* at the FDA's conferences, who also *Chairs the FDA's Advisory Committee on Reproductive and Neurologic Drugs*. Based upon my research, I believe that Dr. Greene appears to be a very eloquent and passionate physician when it relates to the welfare of the mother and the unborn. And, if I may, I would like to substantiate my claim, by sharing with you a *defining* passage from the doctor's arsenal, which he presented at a recent FDA Public Hearing, about the utilization of the Over-The-Counter Drugs in Pregnancy, or Part 15, of June 28, 2000. Dr. Greene eloquently stated that: "*The American College of Obstetricians and Gynecologists urges the FDA to make a rigorous assessment of reproductive toxicity safety in its broadest sense a routine and mandatory requirement for drugs being considered for over-the-counter sale. The burden of proof of safety must be high. American women expect the FDA to protect them and their fetuses from risks due to over-the-counter drugs. We trust that you will not let them down. Thank you.*"

Dr. Greene's clinical credentials can be complemented by the fact that he also *chairs* the ACOG's Committee on Obstetric Practice. As the chairman of this committee, the doctor appears to be a very enthusiastic supporter of pharmacology in the delivery room: "*While labor and delivery is undeniably a*

normal physiologic process, there is a great deal of pain for many women during this time." And the doctor continued: "I can't think of another situation where it is considered acceptable for a person to experience severe pain, amenable to safe relief, while under a physician's care. The last thing a woman needs to hear during a painful labor is that her insurance company isn't going to cover her epidural." My first reaction is that the doctor seems to be a very convincing physician, that's, . . . if Dr. Greene is alluding at a genuine clinical situation, relating to epidural: . . . consistent to safe relief; while under a physician's care.

As well, as a member of the ACOG's Committee on Obstetric Practice, Dr. Greene appears to have contributed to the AAP/AGOG's Guidelines for Perinatal Care, 4th Edition, 1997, ISBN 0-915473-35-6 [I trust that it not necessary to stress the breadth and depth by which this clinical text addresses the directives of the FDA's Drug Use-in-Pregnancy and the DEA's Controlled Substances, Act of 1970.] And, since our subject matter is pharmacology in Pregnancy, in this text there are guidelines relating to analgesics, where it is stated that a method or vehicle to achieve this objective, in part, is through the use of a class of pharmacology: **barbiturates**. Specifically, at page 105, the text stresses the use barbiturates as prenatal obstetric analgesics in the context of normal pregnancy, labor and delivery: "*Barbiturates . . . can be administered during prodromal and early labor to allow the patient to rest.*" As I have indicated before, I respectfully disagree with AAP/ACOG's unconscionable clinical assertion, because it is a documented scientific fact that barbiturates are known to create respiratory and vasomotor depression. Furthermore, as I have stated before, many clinical publications contraindicate the use of barbiturates in Pregnancy, which I would like to reiterate, for example:

| | |
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| <ul style="list-style-type: none"> ◆ <u>CURRENT's Obstetric & Gynecologic-- Diagnosis & Treatment</u>, Eighth Edition from Appleton & Lange, 1994, whereas for barbiturates used as prenatal obstetrics analgesic, it is stated that: | <ul style="list-style-type: none"> ◆ "The use of barbiturates alone for obstetric analgesia is not common practice and should be discouraged. The required dosage is dangerous to the fetus, which is extremely sensitive to central nervous system depression by these drugs. Periodic apnea and even abolition of all movements outlasts the effect of the barbiturates on the mother." |
| <ul style="list-style-type: none"> ◆ Lippincott's Seventh Edition 1994, <u>Danforth's Obstetrics and Gynecology</u>, Scott et al, barbiturates are characterized in prenatal obstetrical analgesia as follows: | <ul style="list-style-type: none"> ◆ "Barbiturates. . . Prolonged neonatal effects have been the cause of the virtual elimination of these drugs from the obstetrician's armamentarium." |
| <ul style="list-style-type: none"> ◆ As well, Lippincott's Sixth Edition 1990, <u>Danforth's Obstetrics and Gynecology</u>, Scott et al, <u>Obstetric Anesthesia and Analgesia</u>, whereas it is stated that: | <ul style="list-style-type: none"> ◆ "Barbiturates exhibit no analgesic properties. In fact, this class of drugs has an antianalgesic effect and may cause the mother to become hyperactive and disoriented. Also, severe neonatal respiratory depression may occur. Considering the lack of advantages and the possible disadvantages, barbiturates are seldom used." |
| <ul style="list-style-type: none"> ◆ PDR/Delmar's Nurse's Drug Reference 1999 Edition, relating to barbiturates in pregnancy: | <ul style="list-style-type: none"> ◆ "Importantly, barbiturates are not analgesics and therefore should not be given to clients for the purpose of ameliorating pain." |
| <ul style="list-style-type: none"> ◆ And, the observation from a very prominent medical editor, relating to barbiturates in pregnancy, at the prenatal stage: | <ul style="list-style-type: none"> ◆ "The situation that you describe is quite an extreme one in which a physician verbally prescribed a drug that is seldom used these days (Secobarbital) in a dose that would have been quite high in any setting (the average dose being 100 milligrams or less) for a patient who was pregnant and then did not follow up for a total of 11 hours." |

Likewise, the ACOG has contradictory perspectives, when it relates to barbiturates as prenatal obstetric analgesics. For your convenience, I would like to show you again the table, which presents ACOG's contradictory assertions, when compared to the claim as per the AAP/AGOG's Guidelines for Perinatal Care,

4th Edition, 1997, whereas it is stated that "*Barbiturates . . . can be administered during prodromal and early labor to allow the patient to rest.*" Please note that this data was presented to Sandra Kweder, M.D., FDA's Co-Chair, Pregnancy Labeling Task Force, where I also copied you:

| | |
|---|--|
| <ul style="list-style-type: none"> ▪ ACOG's text <u>Rosen's Management of Labor Physician's Judgement and Patient Care</u>, Second Edition, 1998, (ISBN 0-412-13811-5,) proudly 'edited' by Dr. Ralph W. Hale, the ACOG's Executive Vice President--whereas relating to "Sedation and Analgesia" it is indicated that: | <ul style="list-style-type: none"> ▪ " . . .Rarely use barbiturates for these patients." |
| <ul style="list-style-type: none"> ▪ Stanley Zinberg, M.D., MS, FACOG, ACOG's Vice President, Practices Activities, where he informed me that: | <ul style="list-style-type: none"> ▪ "You will note that it [ACOG's Educational Bulletin #231 Seizure Disorders in Pregnancy] discusses the possibility of administering anticonvulsants during labor when necessary." |
| <ul style="list-style-type: none"> ▪ Ralph W. Hale, M.D., FACOG, and ACOG's Executive Vice President, where in part he indicated to me that: | <ul style="list-style-type: none"> ▪ "The use of all barbiturates has decreased over the last 15-20 years and they are only occasionally utilized, but in appropriate cases they are indicated." |
| <ul style="list-style-type: none"> ▪ ACOG' Technical Bulletin, Number 225—July 1996, <u>Obstetric Analgesia and Anesthesia</u>: | <ul style="list-style-type: none"> ▪ Apparently none [It appears that there are no references available about the use of 'barbiturates' as prenatal obstetrical analgesics] |

Considering the foregoing contradictions relating to the use of barbiturates as prenatal obstetric analgesics, I wonder if Dr. Greene--in the name or cause of ameliorating pain in the *prenatal* stage--would support the use of barbiturates with his pharmacology's genuine enthusiasm: "*I can't think of another situation where it is considered acceptable for a person to experience severe pain, amenable to safe relief, while under a physician's care?*" Or, presented from another perspective, I would be very curious to know about the validity to sedate a patient with 200 milligrams of Seconal--a preoperative dosage, which requires prompt clinical attention--especially when the *art* of obstetrics is practiced by 'phone,' in the middle of the night, and then the physician does follow up the order at his/her convenience, say after eleven (11) hours? Indeed, I believe that Dr. Greene could help you and the Agency sort out this extreme pharmacology technique--prenatal obstetric analgesic, in the arena of *normal* pregnancy, labor and delivery. Furthermore, Dr. Greene could also help define the obstetric *protocol* for *verbal orders*, while taking into consideration the concept of the safe pain relief, while under a physician's care.

Similarly, while Dr. Greene participates in shaping the FDA's pharmacology directives, it would be quite interesting to know what would be his pharmacology's perspective when he wears the hat of Fellow of the ACOG? Is the doctor bound to 'practice' those FDA, and for that matter the DEA's rules, including current directives, which he might have been one of the contributors? Why would I make this observation? Because I have repeatedly presented my concerns about the validity of "barbiturates" as prenatal obstetric analgesics in the context of *normal* pregnancy, labor and delivery to the ACOG and the AAP, yet they have maintained a solemn *silence*. Explicitly, I have formally asked senior executives of the ACOG and the AAP whether:

- a) the directives of Title 21 CFR 201.57, Drug Use-in-Pregnancy, Category strong proviso: . . . to treat serious disease in pregnant women . . . and specifically ". . . if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective," and,
- b) the Drug Enforcement Agency's (DEA) Controlled Substances [Act of 1970] . . . particularly Title 21 USC 829—Prescriptions, Schedule II: . . . "verbal orders" in a "genuine emergency" situation . . . i.e., Emergency telephone orders [for limited quantities, as per USP DI, and other icons in the Health Care Industry] are authorized. . .

have any applicability, relevance or significance to the AAP/ACOG? To this writing, and after two (2) years and counting, I have still not received a reply to these serious concerns from the ACOG or AAP, and most recently, even from the FDA.

As you prepare to conclude your presentation for this conference, I trust that you would make abundantly clear--via an uncompromising Pregnancy Labeling methodology--that pharmacology in Pregnancy would be prescribed *only* and *if* in a genuine "clinical" situation, and not as *reckless parking contraptions*, just because an 'obstetrician' elects not to get out of bed in the middle of the night. This, as it appears that there is an obstetrical perception, which indicates: "Whatever the time of year, doctors don't like late-night, weekend deliveries." Or, presented from another perspective, I would like to ask you and the FDA to make a rigorous assessment of pharmacology as prenatal obstetrical analgesics in the context of *normal* pregnancy, labor and delivery in its broadest sense a routine and mandatory requirement. The burden of proof of safety must be high. American women expect the FDA to protect them and their fetuses from risks due to *reckless verbal/phone orders*, because the apparent obstetrical perspective: "Whatever the time of year, doctors don't like late-night, weekend deliveries." especially when there is involved a "*verbal order*" in the middle of the night, is not consistent to the concept of ameliorating pain safely, while under a physician's care. I trust that you will not let me or the American women, and their fetuses down. I am very well aware that the concerns that I have presented to you predicate considerations such as *conventional wisdom*, scientific and political, . . . and for the latter, the protocol by which the ACOG and the AAP view the pharmacology directives of the FDA and the DEA. However, I'm confident that you--the intellectual curious health executive--will make sure that they will be dealt with fairly, where the unborn's welfare must never be compromised! Therefore, I would like to respectfully ask you for your undivided attention!!! As I anxiously look forward to your reply, I would like to take this opportunity to sincerely thank you for your courtesies, time, and consideration. Indeed, "*every unborn's well-being is a sacred trust!!!*"

Sinceri Saluti,



Rosario Zisa, C.P.A.

RZ/

cc: Steve Berman, M.D., FAAP, AAP's President
 Ilene Corina, Director, P.U.L.S.E. of New York
 Michael F. Greene, M.D., Associate Professor of Obstetrics, Gynecology & Reproductive Biology
 Ralph W. Hale, M.D. FACOG, ACOG's Exec. VP
 W. Benson Harer, Jr., M.D. FACOG, ACOG's President
 Nikol Huff, Program Manager, Leapfrog Group
 Jennifer L. Howse, Ph.D. President, March of Dimes
 Dianne L. Kennedy, M.D., FDA's Manager, Labeling Pregnancy Task Force
 Ruth Kirschstein, M.D., Acting Director, National Institutes of Health
 Will Kubofcik, Mayor, Prospect Park, NJ
 Sandra Kweder, M.D., Co-Chair, Pregnancy Labeling Task Force
 Yvonne Maddox, Ph.D., Acting Deputy Director, National Institutes of Health
 Joe M. Sanders, M.D., FAAP, AAP's Executive Director
 David Satcher, M.D., Ph.D., U.S Surgeon General
 Donna E. Shalala, Health and Human Service Secretary
 Kenneth I. Shine, M.D., President, Institute of Medicine
 Bill Pascrell, U. S. Congress, N.J. 8th District
 William C. Richardson, Ph.D., President and CEO, W. C. Kellogg Foundation
 Robert G. Torricelli, U.S. Senate, New Jersey
 Joanne E. Turnbull, Ph.D., Executive Director, AMA's National Patient Safety Foundation,
 Janet Woodcock, M.D., Director, Center for Drug Evaluation & Research
 Stanley Zinberg, M.D., MS, FACOG, ACOG's VP, Practice Activities
 Docket Number 97N-0289, Docket Management Branch (HFA-305)

P.S. Please find enclosed my e-mail to Dr. Dianne L. Kennedy, Manager, Pregnancy Labeling Task Force, dated October 29, to follow upon my letter of September 24, where I also copied you.

To
From
P2
Date

Docket Number 97N-0289
Rosario Zisa, CPA
Letter to Dr. Janet Henney, Comm.
November 15, 2000

11-15-00



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Subj: Please . . .THIRD Request--My letter of Sept. 24
Date: Sun, 29 Oct 2000 10:50:42 PM Eastern Standard Time
From: "Rosario Zisa" <rjzisa@hotmail.com>
To: KENNEDYD@CDER.FDA.GOV
CC: JHENNEY@OC.FDA.GOV, WOODCOCKJ@CDER.FDA.GOV, KWEDER@CDER.FDA.GOV, DSatcher@OSOPHS.DHHS.GOV, joanne_turnbull@ama-assn.org, mike_flynn@torricelli.senate.gov, bill.pascrell@mail.house.gov, sarah.kan@mail.house.gov, mayor4all@aol.com, saruzisa@aol.com

Dear Dr. Kennedy:

Please, allow me (. . .this is my THIRD request) to follow upon my letter of September 24, as per your correspondence of September 14.

Once again, why would I want to pursue the concerns, which I brought to your attention? Because I'm very optimistic about Dr. Janet Woodcock's caring initiative which: ". . .encourages consumers to help prevent errors by being vigilant about their health-care . . .," as per the FDA Consumer Magazine's article, "Make No Mistake: Medical Errors Can Be Deadly Serious," Sept-Oct 2000. Furthermore, according to the same article, it is indicated that: 'For its part, the Food and Drug Administration will take a "much-enhanced" role in error prevention, says Janet Woodcock, M.D., the head of FDA's Center for Drug Evaluation and Research.' We'll be taking a much harder look at medical products--beyond just whether they're safe and effective, to how they'll be used in the real world.'

I'm confident that the FDA has a very genuine interest to help eradicate Medical Mistakes/Errors, etc. However, it is also fair to point out that this monumental undertaking "cannot" be achieved until there is a clear understanding--which must be never compromised--whereas the consumer/client/patient must be an active participant in solving this apparently complex, yet seemingly simple undertaking. Perhaps, the latter could be better said with Dr. Woodcock's words: 'Historically, people have looked for someone to blame when medical accidents happen, according to FDA's Woodcock. For victims and their relatives, she says, there may be some satisfaction in that. But from the perspective of fixing the problem, the secrecy that results keeps the medical community from learning what happened and how to correct the problem.' If I may, I would like to repeat the last sentence, because I believe that this powerful assertion is the core of my plea: "But from the perspective of fixing the problem, the secrecy that results keeps the medical community from learning what happened and how to correct the problem." Once again, as I look forward at your prompt reply, I would like to express my sincere gratitude for your courtesies, time and consideration. Indeed, "every unborn's well-being is a sacred trust!"

Sinceri Saluti,

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 From: "Rosario Zisa" <rjzisa@hotmail.com>
 To: KENNEDYD@CDER.FDA.GOV
 Cc: JHENNEY@OC.FDA.GOV, WOODCOCKJ@CDER.FDA.GOV, KWEDER@CDER.FDA.GOV, DSatcher@OSOPHS.DHHS.GOV, joanne_turnbull@ama-assn.org, mike_flynn@torricelli.senate.gov, bill.pascrell@mail.house.gov, sarah.kan@mail.house.gov, mayor4all@aol.com, saruzisa@aol.com
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