New drug application 21-045, Levonorgestrel ("Plan B", and "Preven"), ("emergency contraceptives") and their possible abortifacient effects

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TO: Ms Karen M. Templeton-Somers, and
The Joint Meeting of the Nonprescription Drugs Advisory Committee and the Advisory Committee for Reproductive Health Drugs
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: New drug application 21-045, levonorgestrel (ÒPlan BÓ, and ÒPrevenÓ)

Dear Ms Templeton-Somers and Joint Committee Members:

As a former bench research biochemist/biologist (NIH/NCI) I am sending this scientific submission for your kind consideration on Levonorgestrel (Plan B and Preven) ("emergency contraceptives"), and their possible abortifacient effects.

The major issue concerns when a new living human being begins to exist. Scientifically, there is no question whatsoever that this occurs at fertilization -- in vivo, or in vitro. By the time of implantation, the living human embryo is approximately already 5-7 days old. This is not a "religious", "prolife", or subjective "belief" or "opinion", but rather it is an objective scientific fact that has been known scientifically for over a hundred years, e.g., with the publication of Wilhelm His' (the "Father of Human Embryology"), *Anatomie menschlicher Embryonen* (Leipzig: Vogel, 1880-1885).

If "break-through" ovulation has taken place, and if fertilization has taken place, then several chemical effects due to Levonorgestrel's mechanisms of action after that point could constitute abortion.

The scientific experts who are the experts on the issue of when a human being begins to exist, and on subsequent early human development from fertilization on, are human embryologists. Although many attempt to cast even the scientific issue in "subjective" terms, it needs to be realized that in the science of human embryology these scientific experts are professionally

required to follow definitions of terms according to an *International Nomina Embryologica Committee* (INEC). This international committee meets every 3-5 years to examine, update and clarify which human embryological facts are scientifically demonstrated, accurate, and acceptable for human embryologists worldwide to employ in their own research, teaching and textbooks. In other words, these scientific definitions are not arbitrary, nor are they "relative". And among human embryologists globally there is 100% consensus on these objective scientific facts. If other scientists and physicians are not aware of these scientific facts, that is more a reflection of their lack of knowledge and/or credentials, rather than a reflection of any "confusion" on these scientific facts.

To demonstrate scientifically that normally a human being begins to exist at fertilization, please allow me to quote directly from several current human embryology textbooks (two of which are authored by members of the INEC: Moore and O'Rahilly). Note that O'Rahilly actually rejects the use of the false term "pre-embryo" in his human embryology textbook. These quotations also demonstrate scientifically that fertilization is also the beginning of the existence of a human individual, a human organism, a human embryo, normal human pregnancy, and the "embryonic period":

Keith Moore and T. V. N. Persaud, *The Developing Human: Clinically Oriented Embryology* (6th ed. only) (Philadelphia: W. B. Saunders Company, 1998): "Human development is a continuous process that begins when an oocyte (ovum) from a female is fertilized by a sperm (or spermatozoon) from a male. (p. 2); ibid.: ... but the embryo begins to develop as soon as the oocyte is fertilized. (p. 2); ibid.: Zygote: this cell results from the union of an oocyte and a sperm. A zygote is the beginning of a new human being (i.e., an embryo). (p. 2); ibid.: Human development begins at fertilization, the process during which a male gamete or sperm ... unites with a female gamete or oocyte ... to form a single cell called a zygote. This highly specialized, totipotent cell marks the beginning of each of us as a unique individual." (p. 18).
William Larsen, *Human Embryology* (New York: Churchill Livingstone, 1997): "In this text, we begin our description of the developing human with the formation and differentiation of the male and female sex cells or gametes, which will unite at fertilization to initiate the embryonic development of a new individual. ... Fertilization takes place in the oviduct ... resulting in the formation of a zygote containing a single diploid nucleus. Embryonic development is considered to begin at this point. (p. 1); ibid.: This moment of zygote formation may be taken as the beginning or zero time point of embryonic development." (p. 17).
Ronan O'Rahilly and Fabiola Muller, *Human Embryology & Teratology* (New York: Wiley-Liss, 1994): "Fertilization is an important landmark because, under ordinary circumstances, a new, genetically distinct human organism is thereby formed. (p. 5); ibid.: Fertilization is the procession of events that begins when a spermatozoon makes contact with a secondary oocyte or its investments ... (p. 19); ibid.: The zygote ... is a unicellular embryo." (p. 19); ibid.: "The ill-defined and inaccurate term pre-embryo, which includes the embryonic disc, is said either to end with the appearance of the primitive streak or ... to include neurulation. The term is not used in this book." (p. 55).

[Addendum: O'Rahilly and Muller 2001:
The term 'pre-embryo' is not used here for the following reasons: (1) it is ill-defined because it is said to end with the appearance of the primitive streak or to include neurulation; (2) it is inaccurate because purely embryonic cells can already be distinguished after a few days, as can also the embryonic (not pre-embryonic!) disc; (3) it is unjustified because the accepted meaning of the word embryo includes all of the first 8 weeks; (4) it is equivocal because it may convey the erroneous idea that a new human organism is formed at only some considerable time after fertilization; and (5) it was introduced in 1986 'largely for public policy reasons' (Biggers). ... Just as postnatal age begins at birth, <u>prenatal age begins at fertilization</u>." (p. 88) (Note: O'Rahilly is one of the originators of *The Carnegie Stages of Early Human Embryological Development*, and has sat on the international *Nomina Embryologica Committee* for decades -- DNI).

Bruce Carlson, *Human Embryology and Developmental Biology* (St. Louis, MO: Mosby, 1994): "Human pregnancy begins with the fusion of an egg and a sperm." (p. 3); " ... finally, the fertilized egg, now properly called an embryo, must make its way into the uterus ...." (p. 3).
Carlson (1994), p. 407: "After the eighth week of pregnancy the period of organogenesis (embryonic period) is largely completed and the fetal period begins." O'Rahilly and Muller (1994), p. 55: "The embryonic period proper ... occupies the first 8 postovulatory weeks ... The fetal period extends from 8 weeks to birth ... ."; Moore and Persaud (1998), p. 6: "The embryonic period extends to the end of the eighth week ... After the embryonic period, the developing human is called a fetus. During the fetal period (ninth week to birth) ... ."

It is also an objective scientific fact that the use of many "contraceptives" can be abortifacient, including the "morning-after pill", or "emergency contraception", as stated by Moore (a member of the INEC):

(Keith Moore and T.V.N. Persaud, *The Developing Human: Clinically Oriented Embryology* (6th ed. -- use this edition only)(Philadelphia: W.B. Saunders Company, 1998), pp. 45, 58, 59, 532)
-- "Inhibition of Implantation: The administration of relatively large doses of estrogens ("morning-after pills") for several days, beginning shortly after unprotected sexual intercourse, usually does not prevent fertilization but often prevents implantation of the blastocyst. Diethylstilbestrol, given daily in high dosage for 5 to 6 days, may also accelerate passage of the dividing zygote along the uterine tube (Kalant et al., 1990. Normally, the endometrium progresses to the secretory phase of the menstrual cycle as the zygote forms, undergoes cleavage, and enters the uterus. The large amount of estrogen disturbs the normal balance between estrogen and progesterone that is necessary for preparation of the endometrium for implantation of the blastocyst. Postconception administration of hormones to prevent implantation of the blastocyst is sometimes used in cases of sexual assault or leakage of a condom, but this treatment is contraindicated for routine contraceptive use. The "abortion pill" RU486 also destroys the conceptus by interrupting implantation because of interference with the hormonal environment of the implanting embryo. "An intrauterine device (IUD) inserted into the uterus through the vagina and cervix usually interferes with implantation by causing a local inflammatory reaction. Some IUDs contain progesterone that is slowly released and interferes with the development of the endometrium so that implantation does not usually occur." (p. 58)

-- [Question Chapter 2, #5 for students:]

"#5. A young woman who feared that she might be pregnant asked you about the so-called "morning after pills" (postcoital birth control pills). What would you tell her? Would termination of such an early pregnancy be considered an abortion?" (p. 45)
[Answer #5 for students:]
"Chapter 2
#5. Postcoital birth control pills ("morning after pills") may be prescribed in an emergency (e.g., following sexual abuse). Ovarian hormones (estrogen) taken in large doses within 72 hours after sexual intercourse usually prevent implantation of the blastocyst, probably by altering tubal motility, interfering with corpus luteum function, or causing abnormal changes in the endometrium. These hormones prevent implantation, not fertilization. Consequently, they should not be called contraceptive pills. Conception occurs but the blastocyst does not implant. It would be more appropriate to call them "contraimplantation pills". Because the term "abortion" refers to a premature stoppage of a pregnancy, the term "abortion" could be applied to such an early termination of pregnancy." (p. 532)

-- [Question chapter 3, #2 for students]:

"Case 3-2
A woman who was sexually assaulted during her fertile period was given large doses of estrogen twice daily for five days to interrupt a possible pregnancy.

- -- If fertilization had occurred, what do you think would be the mechanism of action of this hormone?
- -- What do lay people call this type of medical treatment? Is this what the media refer to as the "abortion pill"? If not, explain the method of action of the hormonal treatment.
- -- How early can a pregnancy be detected?" (p. 59)

[Answer Chapter 3, #2 for students:]:
"Chapter 3-2 (p. 532)
Diethylstilbestrol (DES) appears to affect the endometrium by rendering it unprepared for implantation, a process that is regulated by a delicate balance between estrogen and progesterone. The large doses of estrogen upset this balance. Progesterone makes the endometrium grow thick and succulent so that the blastocyst may become embedded and nourished adequately. DES pills are referred to as "morning after pills" by lay people. When the media refer to the "abortion pill", they are usually referring to RU-486. This drug, developed in France, interferes with implantation of the blastocyst by blocking the production of progesterone by the corpus luteum. A pregnancy can be detected at the end of the second week after fertilization using highly sensitive pregnancy tests. Most tests depend of the presence of an early pregnancy factor (EPF) in the maternal serum. Early pregnancy can also be detected by ultrasonography."

Given these objective scientific facts, please allow me to apply them to the specific case of Levonorgestrel.

According to their drug insert, Levonorgestrel states that "is believed to act to prevent ovulation, fertilization and implantation." As also stated therein, "After a single act of unprotected intercourse the treatment fails in about 2% of women who use it within 72 hours after intercourse." This failure rate is "based on one-time use. If Levonorgestrel ... is used on more than one occasion the cumulative failure rate will be higher." Accordingly, even Gedeon Ritcher LTD-EGIP admits that pregnancies can occur even with one-time use, and with more frequency when used more that once.

It has been demonstrated above that fertilization is the beginning of the existence of a new whole living human being. The fact that these pregnancies have taken place indicates that "break-through" ovulation and fertilization have occurred -- and can occur -- and that Levonorgestrel has failed contraceptively.

Levonorgestrel also, however, can prevent this living human embryo/being from implanting in the woman's uterus (which normally takes place about 5-7 days post-fertilization). Quite obviously, as explicitly indicated by the scientific quotations above, if "break-through" ovulation and fertilization have taken place, then to prevent this new living human being from implanting would be abortifacient. Indeed, as demonstrated above, "It would be more appropriate to call them 'contraimplantation pills'. Because the term 'abortion' refers to a premature stoppage of a pregnancy, the term 'abortion' could be applied to such an early termination of pregnancy."

For these scientific reasons, I would submit that Levonorgestrel should not be allowed to be distributed, and I request that the U.S. Federal Drug Administration take the above objective scientific facts into their considerations.

For your information, I am willing to submit about 55+ xerox copies of pages from the several outstanding and current human embryo textbooks from which I quote above Ð all of which are in

concert with the international nomenclature committee. I will also attach a recent publication of mine: D. N. Irving, "When does a human being begin? 'Scientific' myths and scientific facts", International Journal of Sociology and Social Policy, 1999, 19:3/4:22-47.

In closing, I would suggest that both women and men would be precluded from giving ethically or legally valid informed consent by not being given the accurate objective scientific facts about human embryology and early human embryological development (as provided, e.g., above). It should also be considered that there are many women and men who, although they may personally condone genuine contraception, would not personally condone or desire abortion. These people have the right to know what the objective scientific facts of human embryology are so that they may make a truly informed decision as to whether or not to buy or take Levonorgestrel or any other contraceptive or "emergency contraception".

Thank you very much for your kind consideration. If there are any questions, please advise.

Sincerely,
Prof. Dr. Dianne Nutwell Irving, M.A., Ph.D.