**Republic of the Philippines
FOOD AND DRUG ADMINISTRATION
Civic Drive, Filinvest Corporate City
Alabang, Muntinlupa City**

**IN RE: APPLICATION FOR RE-CERTIFICATION/
RE-EVALUATION OF CONTROLLE
(Registration No. DR-XY19742)
(Applicant: Pascual Labs)**

**ALLIANCE FOR THE FAMILY
FOUNDATION PHILIPPINES, INC.
(ALFI),
Oppositor.**

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OPPOSITION TO APPLICATION FOR RE-CERTIFICATION/RE-EVALUATION

ALLIANCE FOR THE FAMILY FOUNDATION PHILIPPINES, INC. (ALFI), represented by its President and Legal Counsel, Atty. Maria Concepcion S. Noche, respectfully submits the following Opposition to the Application for Re-Certification/Re-Evaluation of CONTROLLE filed by Pascual Labs, and states, that:

1. ALFI adopts ***in toto*** the allegations and arguments in its Preliminary Opposition to the Applications for Re-Certification/Re-Evaluation filed with the Food and Drug Administration (FDA) on October 08, 2014 (hereafter, "Preliminary Opposition"), together with all the supporting and reference materials annexed thereto as Volumes 1 and 2. It was referred to the Center for Drug Regulation and Research (CDRR) with Reference/Tracking No. 20141008142055.

2. The Preliminary Opposition was a general opposition to the contraceptive drugs/devices previously registered with the FDA including those subject of the applications for re-certification/re-evaluation recently filed with the FDA.

3. The instant Opposition refers to each individual contraceptive drug/device previously registered with the FDA including those subject of the applications for re-certification/re-evaluation recently filed with the FDA.

4. In summary, we reiterate the relevant findings and conclusions of the Supreme Court in its Decision in the consolidated cases of *Imbong, etc. vs. Hon. Ochoa, Jr., etc. (G.R. No. 204819, 204934, 204957, 204988, 205003, 205043, 205138, 205478, 205491, 205720, 206355, 207111, 207172, 207563)* (the "RH Law Decision", for brevity) as follows:

a. RH LAW PROHIBITS ABORTION AND ABORTIFACIENTS.

b. RH LAW MANDATES THAT PROTECTION OF THE FERTILIZED OVUM MUST BE **FROM FERTILIZATION ALL THE WAY UNTIL IT REACHES AND IMPLANTS IN THE UTERUS.**

c. AS DEFINED UNDER SECTION 4(A) OF THE RH LAW, AN **ABORTIFACIENT** IS ANY DRUG OR DEVICE THAT EITHER:

(a) **INDUCES ABORTION**; OR

(b) **INDUCES THE DESTRUCTION OF A FETUS** INSIDE THE MOTHER'S WOMB; OR

(c) **INDUCES THE PREVENTION** OF THE FERTILIZED OVUM **TO REACH AND BE**

IMPLANTED IN THE MOTHER'S WOMB.

d. THIS RH LAW DEFINITION OF ABORTIFACIENT PROTECTS THE FERTILIZED OVUM **FROM FERTILIZATION UNTIL IT REACHES AND IMPLANTS IN THE UTERUS**.

e. CONTRACEPTIVES TO BE INCLUDED IN THE PHILIPPINE NATIONAL DRUG FORMULARY SYSTEM (PNDFS) AND THE ESSENTIAL DRUGS LIST (EDL) ARE THOSE THAT **DO NOT HAVE THE PRIMARY AS WELL AS THE SECONDARY ACTION OF CAUSING ABORTION OR THE DESTRUCTION OF A FETUS IN THE UTERUS OR THE PREVENTION OF THE FERTILIZED OVUM TO REACH AND BE IMPLANTED IN THE UTERUS.**

f. ADDITIONALLY, RH LAW MANDATES THAT CONTRACEPTIVES MUST BE **SAFE AND POSE NO RISKS TO THE FILIPINO PEOPLE'S HEALTH.**

g. TO ENSURE THAT ALL CONTRACEPTIVE DRUGS AND DEVICES THAT ARE MADE AVAILABLE TO THE PUBLIC ARE **NON-ABORTIFACIENT AND SAFE**, THE SUPREME COURT INSTITUTED THE FOLLOWING **SAFEGUARDS:**

[i] FDA MUST TEST AND EVALUATE **ALL CONTRACEPTIVE DRUGS AND DEVICES IN ACCORDANCE WITH THE CONSTITUTIONAL YARDSTICKS AND STANDARDS THAT THE SUPREME COURT HAS LAID DOWN IN THE RH LAW DECISION ([a] to [g] above).**

[ii] BASED ON ITS EVALUATION AND TESTING, **FDA MUST APPROVE AND CERTIFY** ONLY CONTRACEPTIVE DRUGS AND DEVICES THAT ARE **SAFE AND NON-ABORTIFACIENT. FDA MUST FURTHER CERTIFY THAT THEY CANNOT BE USED AS ABORTIFACIENT OR THAT THEY CANNOT ACT AS ABORTIVE (NOT THAT THEY WILL NOT BE USED AS**

ABORTIFACIENT); OTHERWISE, THEY CANNOT BE PROCURED BY THE GOVERNMENT (THROUGH THE DOH), OR DISTRIBUTED, SOLD OR OTHERWISE MADE AVAILABLE TO THE PUBLIC.

[iii] THOSE THAT HAVE BEEN DULY APPROVED AND DULY CERTIFIED BY THE FDA MUST BE PROCURED FROM, SOLD, DISTRIBUTED, OR DISPENSED BY, **A DULY LICENSED PHARMACEUTICAL COMPANY AND A DULY LICENSED DRUG STORE, UPON THE PRESCRIPTION OF A QUALIFIED MEDICAL PRACTITIONER.**

h. Recognizing the gravity of the consequences of distributing or making available to the public contraceptive drugs and devices, the Supreme Court issued a **WARNING**, thus:

> **"A HEAVY RESPONSIBILITY AND BURDEN ARE ASSUMED BY THE GOVERNMENT IN SUPPLYING CONTRACEPTIVE DRUGS AND DEVICES, FOR IT MAY BE HELD ACCOUNTABLE FOR ANY INJURY, ILLNESS OR LOSS OF LIFE RESULTING FROM OR INCIDENTAL TO THEIR USE."**

i. Therefore, it behooves the FDA to observe and follow strictly, faithfully and conscientiously the RH Decision. The price for non-compliance is stiff and high—the LIFE and HEALTH OF THE FILIPINO PUBLIC—and the consequences thereof may be final, irretrievable and irreversible. And the Government and its responsible officials, employees and agents shall be put to task for the consequences.

5. In light of and within the context of the discussion in the Preliminary Opposition on the mechanisms of action and adverse effects of contraceptive drugs and devices, citing learned treatises, reference medical books and additional available scientific and technical information from various credible sources, we scrutinize all the different hormonal

contraceptives, IUDs and injectables sold in the Philippine market that have been approved by and registered with the FDA.

6. We focus on that part of the definition of Abortifacient under Section 4(a) of the RH Law which says: "induces xxx xxx the prevention of the fertilized ovum to reach and be implanted in the mother's womb" to determine whether or not a certain contraceptive drug or device is an Abortifacient. We likewise note the adverse effects, if any, of each brand.

7. We have summarized the various pieces of relevant information in a Table (Volume 1 of Preliminary Opposition) which include the mechanisms of action and the adverse effects, and the corresponding sources of information. We have listed all the Philippine FDA-registered contraceptives that are sold in the Philippine market by indicating their brand names as appearing in the FDA websites, old and new. We then group them into two (2) main groups: (1) the combined oral contraceptives, and (2) the progestin-only contraceptives. We further subdivide each group into the different formulations or generic names based on the active ingredients of each brand name. And then, based on the various sources of information, we make a conclusion whether each brand of hormonal contraceptive, IUD or injectable is Abortifacient according to the definition in Section 4(a) of the RH Law, or whether it is Safe based on the adverse effects.

8. ***On The Abortifacient Nature Of Combination Hormonal Contraceptives. ---*** We have grouped the brand names based on their active ingredients or generic names.

Shown below are the different generic groups with excerpts from the prescribing information and other technical write-ups which all point to the reduced likelihood of implantation of the fertilized ovum.

Keeping in mind the definition of Abortifacient in the RH Law, the pieces of information which specifically cite the effect on the uterine lining of each generic type (based on active ingredients) of each brand of hormonal contraceptive, as well as IUD and injectable, are summarized below. For easy access

and review, the internet links where these pieces of information can readily be verified are provided immediately after the generic name for each group.

9. For the **Combined Oral Contraceptives (COCs)**, the generic groups are as follows:

(a) Ethinyl estradiol and levonorgestrel
http://www.drugs.com/mtm/ethinyl-estradiol-and-levonorgestrel.html

Ethinyl estradiol and levonorgestrel are forms of estrogen and progesterone, which are both female hormones involved in conception. ***Ethinyl estradiol and levonorgestrel are used together in this product as an emergency contraceptive (EC) to prevent pregnancy after contraceptive failure or unprotected intercourse.*** Ethinyl estradiol and levonorgestrel prevent ovulation (the release of an egg from an ovary), disrupt fertilization (joining of the egg and sperm), ***and inhibit implantation (attachment of a fertilized egg to the uterus)***.

(b) Ethinyl estradiol and desogestrel
http://www.drugs.com/mtm/apri.html

Ethinyl estradiol and desogestrel is a combination drug that contains female hormones that prevent ovulation (the release of an egg from an ovary). ***This medication also causes changes in*** *your cervical mucus and* ***uterine lining, making it*** *harder for sperm to reach the uterus and* ***harder for a fertilized egg to attach to the uterus.***

(c) Drospirenone and ethinyl estradiol
http://www.drugs.com/mtm/drospirenone-and-ethinyl-estradiol.html

Drospirenone and ethinyl estradiol prevent ovulation (the release of an egg from an ovary) and also cause **changes in** your cervical and ***uterine lining, making it*** *harder for sperm to reach the uterus and* ***harder for a fertilized egg to attach to the uterus.***

(d) Ethinyl estradiol and norgestrel
http://www.drugs.com/cdi/norgestrel-ethinyl-estradiol.html

Norgestrel/ethinyl estradiol is a combination birth control pill. It works by preventing ovulation, altering the cervical mucus, and ***changing the lining of the uterus*.**

(e) Estradiol valerate and dienogest
http://www.drugs.com/cdi/estradiol-valerate-dienogest.html

Estradiol valerate and dienogest is a combination birth control pill. It works by preventing ovulation. It may also change cervical mucus to prevent the sperm from reaching the egg and ***change the lining of the uterus to prevent a fertilized egg from implanting in the uterus.***

***(f) Gestodene and ethinyl estradiol*.**
http://www.mims.com/USA/drug/info/gestodene%20%2b%20ethinylestradiol/gestodene%20%2b%20ethinylestradiol?type=full&mtype=generic

The MIMS US website provides the following information: "Gestodene is a progestogen while ethinylestradiol is a synthetic oestrogen. Used together, they inhibit ovulation by suppressing the mid-cycle surge of luteinising hormone which causes changes in the cervical mucus, thus forming a barrier to sperm, ***and making the endometrium unreceptive to implantation."***

(g) Cypreterone acetate and ethinyl estradiol
http://www.mims.com.ph/PHILIPPINES/drug/info/Cybelle/?type=full

The MIMS Philippines website provides the following information on cyproterone and ethinyl estradiol, in its full information on "Cybelle", a brand of hormonal contraceptives which has these as its active ingredients. In the section "Mechanism of Action", the following words were found: "Cybelle also acts like an oral contraceptive, by preventing the release of eggs, thickening the mucus in the neck of the womb

to stop sperm passing through and ***making the lining of the womb unsuitable for an egg to grow on."***

(h) Norethisterone and ethinyl estradiol
http://www.mims.com/Philippines/drug/info/Micropil/Micropil-Micropil%20Plus?type=full

The MIMS Philippines website in the full prescribing information on Micropil and Micropil Plus, brands of norethisterone and ethinyl estradiol, in the Mechanism of Action section, states the following: "Although the primary mechanism of action is inhibition of ovulation, alterations in the genital tract including changes in the cervical mucus (which increase the difficulty of sperm penetration) and ***development of poor endometrial lining (which reduces the likelihood of implantation)*** may also contribute to contraceptive effectiveness.

(i) Ethinyl Estradiol + Levonorgestrel
http://www.drugs.com/cdi/levonorgestrel-ethinyl-estradiol.html
+ Ferrous Fumarate
http://www.idruginfo.com/?cat=drug&s=Femme&ingredient=Ethinyl%20Estradiol/Iron%20(Ferrous%20Fumarate)/Levonorgestrel

Levonorgestrel/ethinyl estradiol is a progesterone and estrogen combination birth control pill. It works by preventing ovulation, thickening the mucus in the cervix, and ***changing the lining of the uterus.***

Iron (ferrous fumarate) is for transport of oxygen to tissue and in cellular oxidation mechanism. It is used in preventing and treating iron-deficiency anemia.

(j) Etonogestrel + Ethinylestradiol
http://www.drugs.com/search.php?searchterm=ethinyl+estradiol%2Fetonogestrel

Ethinyl estradiol and etonogestrel contains female hormones that prevent ovulation (the release of an egg from an

ovary). This medication also causes ***changes in your*** *cervical mucus and* ***uterine lining, making it*** *harder for sperm to reach the uterus and* ***harder for a fertilized egg to attach to the uterus.***

(k) Norelgestromin + Ethinyl Estradiol 6mg/600mcg Transdermal Patch
http://www.drugs.com/mtm/ethinyl-estradiol-and-norelgestromin-transdermal.html

Ethinyl estradiol and norelgestromin contains a combination of female hormones that prevent ovulation (the release of an egg from an ovary). This medicine also **causes *changes in*** *your cervical mucus and* ***uterine lining, making it*** *harder for sperm to reach the uterus and* ***harder for a fertilized egg to attach to the uterus.***

(l) Norethisterone Enanthate + Estradiol Valerate
Guo-wei, S. (1994). Pharmacodynamic effects of once-a-month combined injectable contraceptives. *Contraception*, 371.

The combination has a ***suppressive effect on the endometrium.***

(m) Norethisterone + Ethinyl Estradiol + Ferrous Fumarate
Note: Norethindrone (also known as Norethisterone)
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6230

http://www.drugs.com/mtm/ethinyl-estradiol-and-norethindrone.html
http://www.drugs.com/pro/norethindrone-ethinyl-eestradiol-and-ferrous-fumarate.html

Ethinyl estradiol and norethindrone is a combination drug that contains female hormones that prevent ovulation (the release of an egg from an ovary). This medication also ***causes changes in*** *your cervical mucus and* ***uterine lining, making it*** *harder for sperm to reach the uterus and* ***harder for a fertilized egg to attach to the uterus.***

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include ***changes in*** *the cervical mucus (which increase the difficulty of sperm entry into the uterus) and* ***the endometrium (which reduce the likelihood of implantation).***

Ferrous fumarate is an iron supplement.

10. ***On The Abortifacient Nature Of Progestin-Only Hormonal Contraceptives. ---*** Progestin-only hormonal contraceptives also affect the uterine lining. Goodman & Gilman's *The Pharmacological Basis of Therapeutics (12 ed.)*, a pharmacology textbook used worldwide, in its chapter entitled *"Contraception and Pharmacotherapy of Obstetrical and Gynecological Disorders"*, states as follows:

> "**Progestin-Only Contraceptives.** Progestin-only minipills contain derivatives of 17α-alkyl-19-nortestosterone but do not contain an estrogen. Although they do inhibit ovulation to some degree, their efficacy also reflects changes in the cervical mucus that inhibit fertilization and ***endometrial changes that inhibit implantation.***"[1]

MedlinePlus, mentioned earlier as a public service of the U. S. National Library of Medicine and the National Institutes of Health, states that:

> "Progestin is a female hormone. It works by preventing the release of eggs from the ovaries (ovulation) and ***changing*** the cervical mucus and ***the lining of the uterus."*** http://www.nlm.nih.gov/medlineplus/druginfo/meds/a602008.html

Medline Plus also explicitly states the following about the effect of progestin-only contraceptives on the uterine lining:

> "The progesterone in birth control pills creates a thick cervical mucus, making it difficult for sperm to reach the uterus. ***It also impedes an egg from***

[1] Brunton. L.L., Chabner, B. A., & Knollmann, B. C. (Eds.). (2010), p. 1836. Mcgraw-Hill. Medical Publishing Division.

attaching itself to the uterine lining (endometrium) because of changes in the cellular structure of the lining.”
http://www.nlm.nih.gov/medlineplus/ency/presentations/100108_6.htm
Update Date: 2/26/2012

11. The **Progestin-Only** generic groups are:

(a) Medroxyprogesterone acetate
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020246s036lbl.pdf

The US FDA website in the full prescribing information on the mechanism of action of Depo-provera, a brand of medroxyprogesterone acetate, states that this drug “inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and ***results in endometrial thinning.*** These actions produce its contraceptive effect.”

(b) Lynestrenol
http://www.mims.com.ph/PHILIPPINES/drug/info/Daphne/?type=full

The MIMS Philippines website provides the following information on Lynestrenol, in its full information on “Daphne”, a brand of hormonal contraceptives which has Lynestrenol as its active ingredient: “Daphne stops ovulation, ***thins the lining of the uterus*** and thickens the cervical mucus. In combination, these actions prevent pregnancy.”

(c) Desogestrel
http://www.netdoctor.co.uk/sex-and-relationships/medicines/cerazette.html

The netdoctor.co.uk, a leading health website in the United Kingdom, provides the following information: “Desogestrel works as a contraceptive primarily by preventing the release of an egg from the ovary (ovulation). It also acts by increasing the thickness of the natural mucus at the neck of

the womb, making it more difficult for sperm to cross from the vagina into the womb. By preventing sperm entering the womb, successful fertilisation of any eggs that are released is less likely. ***Desogestrel also acts to change the quality of the womb lining (endometrium). This prevents the successful implantation of any fertilised eggs onto the wall of the womb, thereby preventing pregnancy."***

(d) Norethisterone
http://www.mims.com/PHILIPPINES/Home/GatewaySubscription/?generic=norethisterone

Norethisterone has typical effects of a progestogen and ***converts the endometrium from the proliferative to the secretory phase*** **(which is a thin, devasculating lining, physiologically unreceptive to receiving and sustaining a human embryo).**

(e) Lynestrenol
http://www.medicineindia.org/pharmacology-for-generic/2758/lynestrenol

As a synthetic oral progestogen, Lynestrenol has similar effects as that of the natural progesterone hormone. It has a ***strong progestational effect on the uterine endometrium by transforming the proliferative endometrium into a secretory one***.

12. ***On The Abortive Mechanism Of Action Of The Five Hormonal Contraceptives Included In The Philippine National Drug Formulary.*** --- Five (5) hormonal contraceptives are listed in the Philippine National Drug Formulary (PNDF), Vol. 1, 7th Edition 2008,[2] which according to the DOH Center for Pharmaceutical Assessment and Monitoring (CEPAM) is the one currently in use. These are: (1) ethynilestradiol + levonorgestrel; (2) ethinylestradiol + desogestrel; (3) ethynilestradiol + norgestrel; (4) ethinylestradiol + norethisterone; and (5) medroxyprogesterone. **As already shown earlier, all five hormonal contraceptives listed as such in the PNDF/EDL**

[2]Pages 79-80 of the PNDF/Essential Drugs List; http://www.philhealth.gov.ph/partners/providers/pdf/PNDFvol1ed7_2008.pdf - accessed on September 29, 2013.

cause changes in the uterine lining, making it harder for the fertilized egg to implant.

Executive Order No. 49, s. 1993 directed "the mandatory use of The Philippine National Drug Formulary (PNDF) Volume 1 as basis for procurement of drug products by the government."[3]

13. After a diligent, careful, thorough and judicious reading and examination of all the reference materials, we have arrived at the well-considered conclusion that: **Every single hormonal contraceptive, IUD and injectable, whether of a "combined estrogen-progesterone formulation" or of a "progestin-only formulation", by its mechanism of action, causes changes in the uterine lining which make it harder for a fertilized egg to attach to the uterus, i.e., inhibit implantation. Such changes "induce the prevention of the fertilized ovum to reach and be implanted in the mother's womb", as stated in the definition of "abortifacient" in R. A. 10354. This then may induce "abortion or the destruction of a fetus insde the mother's womb". All hormonal contraceptives, IUDs and injectables by causing such changes, can cause the death of newly-conceived life in the womb. Therefore, all hormonal contraceptives, IUDs and injectables sold in the Philippine market and approved by and registered by the FDA are Abortifacients. Further, they also are harmful to the health of women.**

14. The summary of information on Abortifacient and Harmful Effects with reference to corresponding sources is in a Table (Volume 1of Preliminary Opposition).

15. ***On the Adverse Effects of Hormonal Contraceptives, IUDs and Injectables.*** There are glaring and disturbing findings of adverse effects. The summaries of some studies made and their respective findings and results are discussed in the Preliminary Opposition. The complete texts of the articles taken from various scientific journals accessed through the electronic resources collections of the UST Miguel de Benavides Library and the Makati Medical Center Library,

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[3]http://uhmis2.doh.gov.ph/doh_ncpam/images/publication/pndf.pdf - accessed on September 29, 2013.

as well as from various websites online are compiled and attached in Volume 2 of Preliminary Opposition.

16. For CONTROLLE, we have carved out from the Table (Volume 1 of Preliminary Opposition) and highlighted the relevant information and the corresponding sources, and we attach the same as well as the printed copies of the reference/supporting materials, all of which we make integral parts hereof.

PRAYER

Wherefore, ALFI prays that the Food and Drug Administration:

1. DENY ALL APPLICATIONS FOR RE-EVALUATION/RE-CERTIFICATION OF CONTRACEPTIVE DRUGS AND DEVICES;

2. RECALL ALL CONTRACEPTIVE DRUGS AND DEVICES IN THE PHILIPPINE MARKET AND SUBJECT ALL OF THEM TO THE REQUIRED RE-EVALUATION/RE-CERTIFICATION PROCESS PURSUANT TO THE RH LAW DECISION;

3. ENSURE THAT NO CONTRACEPTIVE DRUGS AND DEVICES ARE SOLD, DISTRIBUTED OR OTHERWISE MADE AVAILABLE UNLESS SUCH SALE OR DISTRIBUTION IS WARRANTED BY A CREDIBLE, TRANSPARENT AND JUDICIOUS RE-EVALUATION/RE-CERTIFICATION PROCESS CONDUCTED BY FDA.

Taguig City for the City of Muntinlupa, November 22, 2014.

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