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To:

Donald D. Ashley
Office of Compliance, Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 5270, Silver Spring, MD 20993-0002

Janice Weiner
Center for Drug Evaluation and Research, Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6270, Silver Spring, MD 20993-0002

Gail Bormel
Office of Compliance, Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 5184, Silver Spring, MD 20993-0002

Stephen Ripley
Center for Biologics Evaluation and Research, Food and Drug Administration 10903 New Hampshire Ave., Bldg. 71, Rm. 7268, Silver Spring, MD 20993-0002

Dear FDA Representatives:

I am a consumer and advocate that comes to you with great concern about my and my community's access to fertility biologics such as hCG and FSH. I represent over 38,000 men and women who have joined my educational sites ExcelMale.com and Facebooks Women's Health and HRT groups. I am also a long-term HIV survivor, activist, and author of four health books that educate consumers to increase their self-advocacy and health literacy about hormone treatment access.

As you are well aware, under the Biologics Price Competition and Innovation Act of 2009 (BPCIA) - Protein-based drug products like hCG, FSH, and hMG that had previously been approved as "drugs" will now be considered Biologics and will fall under the jurisdiction of the FDA's Center for Biologics Evaluation and Research (CBER). The Drug Quality Security Act (DQSA), previously gave an exemption for not having the need to file and hold a New Drug Application (NDA) for "drugs" that were filed as drugs under DQSA under section 505. Biologics must now be approved and licensed (with a Biologics License Application -BLA) under section 351. DQSA gives no exemptions under section 351. In order to lawfully enter a Biologic product into US commercial distribution, even if the product is an old generic hCG, hMG or FSH that was previously exempted, the seller must hold a BLA for that product. By the plain letter of the statutory law, this would preclude all compounding or production by 503B or 503A without a BLA. Developing a BLA is a costly and long process that is required for new research products that are considered for FDA approval. Having old urinary based gonadotropins be required to go through this process as a new biologic is counterproductive and presents barriers to access to patients who have been using these products for years to improve

their quality of life and their chances to procreate.

Compounders have been compounding urine-derived hCG, FSH, and hMG and increasing patient access to these medications for nearly 50 years. Specifically, Outsourcing Facilities have supplied HCG and Hyaluronidase so that clinicians may treat patients and come March 23, 2020 nothing in these drugs will change. For example, hCG will still be the same drug that it was in 1973 when it was approved by the FDA. It is my belief that patients should not suffer due to access issues as a result of a purely regulatory change. If FDA does not clarify that these old medications will be regulated as "drugs" for purposes of Section 503A and Section 503B of the Federal Food, Drug, and Cosmetic (FD&C) Act, significant disruptions to patient access and patient care may arise.

FDA can offer enforcement discretion to allow the continued compounding of certain transition biologics like Insulin, hCG, FSH, and hMG. However, at this time FDA has not offered any information regarding their enforcement intentions. The due date is fast approaching and the community just found out about this potential access disruption issue.

To protect patient access to these medications and resolved the current confusion, I request that the FDA immediately clarify that approved NDAs for biological products that have been compounded for many years continue to be regulated as "drugs" for purposes of compounding pursuant to Section 503A and Section 503B of the Federal Food, Drug, and Cosmetic ("FD&C") Act. This includes but is not limited to the following products: insulin, human chorionic gonadotropin (HCG), follicle-stimulating hormone (FSH), and human menopausal hormone (hMG).

I have written a brief background of what issues surrounding access to affordable hCG, FSH (and HMG) are in the following section.

Thank you so much for your consideration in this matter.

In health,

Nelson Vergel
Consumer and Advocate

BACKGROUND:

What are Gonadotropins? LH, FSH, hCG, and hMG.

The gonadotropins are peptide hormones that regulate ovarian and testicular function and are essential for normal growth, sexual development, and reproduction.

The human gonadotropins include follicle-stimulating hormone (FSH) and luteinizing hormone (LH) which are made in the pituitary, and chorionic gonadotropin (hCG) which is made by the placenta through pregnancy.

They are under the control of gonadotropin-releasing hormone (GnRH), a decapeptide produced in the hypothalamus

FSH is essential for sexual maturation and reproduction in both men and women. It is involved in ovulation and sperm production.

LH is essential to activate Leydig cells in the testicles to produce testosterone.

hCG is an analog of LH that has been used to improve fertility in men and women. It's extracted from pregnant women's urine or made by recombinant DNA process.

The first hMG (FSH + LH) was approved in the United States in 1970, for follicular development in women. It remained the mainstay of fertility treatment for almost 20 years.

This product was obtained from the urine of postmenopausal women. Postmenopausal urine contains both FSH and LH in high concentrations. hMG, indeed, consists of approximately one-half FSH and LH, though intermixed with a relatively high concentration of co-purified urinary proteins.

hCG

Human chorionic gonadotropin (hCG) can be recovered from the urine of pregnant women or be produced from recombinant DNA. It acts similarly to LH, but the larger supply makes it less costly; it also has a longer half-life.

In Women: Used to induce final maturation of follicle and subsequent ovulation. Also used for luteal phase support. Typically, a single injection of 10,000 international units is used to induce ovulation.

In men: Used to treat select cases of Hypogonadotropic Hypogonadism in adult males. Typical

dosages are 500-1000IU three times weekly or 4,000IU three times weekly for 6-9 months until atrophy is reversed and the dose is reduced to 2,000IU three times weekly. These doses are starting guidelines for treatment and variable depending on individual response. In off-label use, some urologists prescribe hCG in low doses in combination with Testosterone replacement to preserve fertility.

In male children: Also used to treat prepubertal cryptorchidism, not due to anatomical obstruction. therapy is usually administered between ages 4 and 9

Produced by human placenta, a sterile product derived from the urine of pregnant females

In men, HCG mimics LH from the pituitary to stimulate Leydig cells of testes to produce testosterone. However, it is not detected as LH in blood tests.

The normal lyophilized vial contains 6,000-12,000 units HCG by compounding pharmacies (commercial products cost 3X compounding)

Used by fertility specialists to induce ovulation to harvest eggs, etc.

Testosterone replacement therapy (TRT) can dramatically decrease sperm count and fertility. The latest data show that the majority of men that add hCG to their TRT were able to remain fertile using an hCG dose of 500 IU 3 times per week. 2/3 of men responded. Age and prior testosterone exposure time were limiting factors to treatment response.

It can improve sperm production in men on TRT even with the absence of FSH.

The usual recommended dose is 350-500 IU twice per week for prevention/reversal of testicular atrophy and improvements in libido (patient self-reports collected from different private practices.)

Brand hCG access has had issues in the past due to shortages.

More information about hCG

FSH

Injectable follicle-stimulating hormone (FSH) is used to establish or restore fertility in men with hypogonadotropic hypogonadism (HH) and provides ovarian stimulation (OS) in women undergoing both in vitro fertilization (IVF) and oocyte cryopreservation (OCP).

Preparations of follicle-stimulating hormone (FSH) mainly include those derived from the urine of menopausal women, as well as recombinant preparations. The recombinant FSH preparations are more expensive. The urinary preparations are equally effective and less expensive.

Brand FSH (B-FSH) is prohibitively expensive and can be a major roadblock to couples pursuing fertility treatment.

Compounded FSH (C-FSH) is considerably more cost-effective with promising early clinical results.

A study at Baylor College of Medicine in Houston was performed to assess the clinical efficacy and cost-effectiveness of compounded FSH (C-FSH) in both men and women.
It involved a retrospective chart review that identified all men prescribed C-FSH with azo/severe oligozoospermia (<5 million sperm) and hypogonadotropic hypogonadism that did not respond to clomiphene citrate.

FSH levels, semen analysis, and pregnancy outcomes were noted and median pre/post-treatment levels were analyzed using the Wilcoxon test.

They concluded that compared to brand name FSH, compounded FSH provides unprecedented cost savings to male and female patients undergoing FSH therapy and may allow some couples to achieve parenthood who otherwise would be prohibited by cost.(Reference 1)

	B-FSH	C-FSH
Price per unit	$2.20	$0.32
Units per vial	450	1500
Price per vial	$988.38	$480.00
Price per average IVF cycle (2800 IU)	**$6,160.00**	**$896.00**
Price per average male recovery cycle (6750 IU)	**$14,850**	**$2,160**

More information about FSH

History of Gonadotropins for Fertility Use (Extracted from Reference 2)

The first hMG (FSH + LH) was approved in the United States in 1970, for follicular development in women. It remained the mainstay of fertility treatment for almost 20 years.

This product was obtained from the urine of postmenopausal women. Postmenopausal urine contains both FSH and LH in high concentrations. hMG, indeed, consists of approximately one-half FSH and LH, though intermixed with a relatively high concentration of co-purified urinary proteins. Until recently, hMG was administered exclusively by i.m. injection. Its clinical efficacy in achieving ovulation, or so-called 'controlled ovarian hyperstimulation', has been established beyond any reasonable doubt and pregnancy rates of ~11.7% per treatment cycle have been reported in the literature. In combination with intrauterine inseminations (IUI), they may approach 15%.

The first alternative medication to hMG became available in the United States in 1987 in the form of human urinary FSH. Like hMG, this product was still urine-derived but was largely purified of LH (though not of co-purified proteins) and was still administered by the i.m. route. As LH absorption techniques moved from absorption by polyvalently bound antibodies to purification by immunoaffinity columns, purification standards increased further and the resulting products, though still urinary in nature, achieved a significant level of purity. In fact, highly purified urinary FSH contained at that point <0.1 IU LH and <5% of co-purified proteins.

A final step in the purification of FSH was achieved when in the mid-1990s, recombinant FSH was introduced to the market. Recombinant (r)FSH is in its amino acid sequence identical to human FSH, though carbohydrate side chain attachments cause pharmacodynamics, which does differ to some extent from human pituitary FSH.

In the United States, gonadotrophins are currently marketed by three pharmaceutical companies, with others expected to enter the fray in the near future. Urinary-based gonadotropins are also made by compounding pharmacies.

Is there a difference in safety?

Whether recombinant gonadotropins, indeed, offer an improvement in safety margins over the older urinary products is one of the most crucial questions in this analysis.

Many scientists strongly argued that: (i) a pure (i.e. recombinant) product was in principle preferable to an impure (i.e. urinary) product; (ii) human (i.e. urinary) products carried a risk of infection by slow-viruses, raising concerns; (iii) human products, since impure, carried a risk of immunogenicity and (iv) human products had repeatedly been demonstrated to be uneven in biological potency.

In over 30 years of clinical use of urinary gonadotropins, not a single case of infectious contamination has been reported. Even cases of slow viruses should, in such a time span, have

clinically become apparent (Balen, 2002).

IVF (In Vitro Fertilization) Medication Prices Rose by 50% Over the Past 5 Years (Extracted from Reference 3)

A new GoodRx analysis has found that prices for in vitro fertilization (IVF) medications have steadily climbed since 2014, contributing to the already high cost of infertility treatment. Three drugs heavily contributed to this increase: Gonal-F RFF, Menopur, and Follistim AQ.

These days, price increases come as no surprise. But the cost for these drugs can be a major burden for women looking to undergo IVF. Most of these medications aren't covered by insurance and are brand-only drugs, so they don't have cheaper generic alternatives. This means that the patients who need these medications are on the hook to pay the costs out of pocket.

How expensive is IVF?

Infertility is a common condition: 6.1 million women in the United States experience difficulty getting pregnant or staying pregnant. To treat infertility, women often turn to assisted reproductive technologies, like IVF or egg-freezing. The decision to undergo these treatments is not easy — even if you can afford them.

The average cost of IVF is about $23,000 per cycle. The out-of-pocket cost and lack of insurance coverage for IVF are hurdles that are insurmountable for some. Making up a sizable portion of that cost are the medications needed to ensure a successful course of IVF.

Some popular brand name medications used in IVF, like Follistim AQ, Gonal-F, or Cetrotide, all come with a high price tag. For example, the best GoodRx discount price for one vial of Gonal-F, an injectable medication used to induce ovulation, is $1,095 — and patients may need to take multiple injections.

But medications aren't the only cost. From start to finish, the IVF journey is filled with doctor visits, counseling, and other procedures. IVF usually doesn't work on the first try, either, and often takes 2 or 3 cycles. Because the process is so individualized and can take so many cycles, it's easy to see how costs can spiral out of control.

But even though it's not always effective, IVF is still the most successful type of fertility treatment.

How much have IVF drugs increased in price?

According to the GoodRx list price index, the list price for drugs used in IVF has increased by 50% since 2014, with some noteworthy drugs driving the increase. This rise in the list price is even higher than the overall increase for all prescription drugs since 2014, about 30%.

References:

1- Gondokusumo, J. et al. American Urological Association Conference 2019. MP07-11 ANALYSIS OF THE CLINICAL AND COST-EFFECTIVENESS OF COMPOUNDED FSH FOR MALE INFERTILITY TREATMENT. Journal of Urology Volume 199, Issue 4S

2- Gleicher, N et al. Bye-bye urinary gonadotrophins? Recombinant FSH: A real progress in ovulation induction and IVF?. Human Reproduction, Volume 18, Issue 3, March 2003, Pages 476–482.

3- Lauren Chase. IVF (In Vitro Fertilization) Medication Prices Rose by 50% Over the Past 5 Years