



# Resolving the Current Injectable Estrogen Shortage: A Public Health Imperative

# RESOLVING THE CURRENT INJECTABLE ESTROGEN SHORTAGE: A PUBLIC HEALTH IMPERATIVE

## INTRODUCTION

Hormone therapy is life-saving for many transgender individuals, and the current shortage of injectable estrogen is a public health crisis. Over the past two years, a reliable supply of 40 mg/mL injectable estrogen has not been available. In this brief, we explain why the U.S. Food and Drug Administration (FDA) and pharmaceutical companies' failure to guarantee a supply of injectable estrogen for transgender individuals is a violation of their right to comprehensive medical treatment, free of discrimination. We propose a short-term solution to the shortage—restocking all formulations of injectable estrogen immediately. We also discuss the need for long-term solutions that address the lack of federally-funded research and, consequently, evidence-based practice, on hormone therapy for gender affirmation. Finally, we detail the steps that have already been taken to address this shortage and suggest ways in which individuals and organizations can contribute to this ongoing effort.

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## HORMONE THERAPY AND TRANSGENDER HEALTH

Hormone therapy to affirm gender identity is a medically necessary intervention for many transgender individuals.<sup>1</sup> Studies have shown that gender affirmation through hormone therapy can improve psychological adjustment and quality of life.<sup>2</sup> One study found that social, psychological, and medical gender affirmation were all predictors of lower depression and higher self-esteem in a sample of 573 transgender women.<sup>3</sup> Furthermore, another study found that once estrogen therapy began, transgender women experienced improvement in social functioning and reduced anxiety and depression.<sup>4</sup>

Feminization is achieved primarily through the use of estrogen, typically in combination with androgen blockers.<sup>5</sup> The doses used for gender affirmation are several times higher than those used for contraception or for post-menopausal treatment. The class of estrogen used for feminizing therapy is 17-beta estradiol and is commonly delivered to transgender women through a patch, oral or sublingual tablet, or injection.<sup>6</sup>

There are no studies that compare the benefits or risks of varying injectable, transdermal, and oral formulations.<sup>7</sup> However, intramuscular injection does avoid potential primary effects on the liver.<sup>8</sup> Furthermore, patients report that injectable estradiol may offer faster and earlier breast development.

Patients who do not achieve adequate feminization through oral and transdermal estrogen are often referred to injectable forms. Due to the lack of studies that examine the risks and benefits of various forms of estrogen for gender affirmation, there is a significant lack of empirical data.

In the last 10 years, many professional associations, including the American Medical Association, American Association of Family Physicians, the Endocrine Society, American Psychiatric Association, American Psychological Association, American College of Obstetricians and Gynecologists, and the American Public Health Association, have issued statements or guidelines supporting effective treatment protocols for gender dysphoria.<sup>9</sup> Review articles have been published in major peer-reviewed journals such as *the Journal of the American Medical Association*<sup>10</sup>, *Nature*<sup>11</sup>, the *Journal of Clinical Endocrinology*<sup>12</sup>, and *Archives of Pediatric and Adolescent Medicine*<sup>13</sup>, among others.

## INJECTABLE ESTROGEN SHORTAGE

There is a current shortage of estradiol valerate injection.<sup>14</sup> This shortage is affecting the availability of Delestrogen and its generic counterpart estradiol valerate. The shortage includes Delestrogen injection from Par Sterile Products and estradiol valerate injection from Perrigo, in the 10mg/mL, 20 mg/mL and 40 mg/mL formulations.<sup>15</sup> Injectable estrogen at the 40 mg/mL dosage is the highest dosage and the most frequently prescribed to transgender women.<sup>16</sup> The shortage began over 20 months ago and these formulations of injectable estrogen have not since returned to the market.

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In July 2016, the Callen-Lorde Community Health Center in New York City received none of the 40 mg/mL and 20 mg/mL formulations in its weekly drug shipment and was told that the shortage would last until at least October 2016, which was reflected on the FDA Drug Shortages list, which is accessible to the public.<sup>17</sup> As of late November 2016, the FDA website states that Perrigo's 40 mg/mL estradiol valerate supply is tentatively scheduled for release in December; the release of the 20 mg/mL supply is listed as tentative for November. Frustrating matters is the fact that the tentative release dates for Perrigo's estradiol valerate have changed over the past several months in accordance with continued delays. Hence it is difficult to determine when, in fact, product will be available.

Information pertaining to Par's product has been even more vague. Whereas "shortage of an inactive ingredient component" is listed by the FDA as the reason for the shortage of the Perrigo product, the reason for the Delestrogen formulations—which now includes 5 mL vials containing 10 mg/mL, 20 mg/mL, and 40 mg/mL dosing strengths—is listed as "other." Tentative release dates are not provided. As per the FDA, "All presentations are currently on backorder. Company working to have this available as soon as possible."

In an interview with *Out* magazine, Par Pharmaceutical's spokesperson, Heather Zoumas Lubeski, claimed that the company decided to switch the supplier of Delestrogen, but that it cannot begin distribution until it has received FDA approval.<sup>18</sup> The company has not provided additional details since.

FDA staff, in recent communications with the authors of this briefing document, have been unable to provide any clarity regarding the status of any approval applications submitted to address these shortages.

The opaque drug shortage reporting practices by the FDA and by the manufacturers highlight the need for a more transparent and accountable process to ensure that these medications are returned to market. The FDA and the pharmaceutical companies both have an obligation to restore the supply of injectable estrogen because it is the preferred regimen for many transgender women and, when drug shortages occur, resolution must be prioritized. Many patients started their transition with injectable estrogen decades ago. One Callen-Lorde patient stated, “I’ve been on injectables for 16 years. I started my transition on injectables. This is not good.”<sup>19</sup>

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When the 40 mg/mL dosage first became unavailable, health care providers were able to make due by doubling up on the 20 mg dosage. However, most providers would not prescribe the 10 mg dosage. In order to maintain the estrogen levels that patients were able to achieve with the 40 mg dosage, patients would need to inject four times as much liquid into their muscles every one to two weeks, which can be very painful. Now that all formulations are no longer available, providers are being forced to dramatically change the regimens of their patients.

Compounding is another option to address the shortage; however, this is not a long-term solution. Compounding is the reformulation of medications in order to provide a specific strength, concentration or dosage that is needed for a specific patient if it is not commercially available.<sup>20</sup> While manufacturing commercial products is approved and regulated by the FDA in compliance with stringent federal quality and safety standards, compounding is overseen by state pharmacy boards. This oversight and enforcement can vary state to state, despite universal quality standards. With compounded drug products, there is a risk of adulteration—including contamination and sub- or super-potent doses.<sup>21</sup> There are also liability concerns among prescribers, along with challenges securing coverage for compounded drug products from both public and private payers.

Unfortunately, there is a lack of research on the relative benefits of various estrogen modalities in transgender women. Though not enough research has been done to prove the effectiveness of injectables over patches or pills, many patients note more benefits and a smoother transition when using injectable estrogen. Patients who go from patches to injectables notice more significant changes. Patients have mostly positive experiences with injectable estrogen, which causes them to view pills and patches as second-tier options. Therefore, injectable estrogen is a necessary product for the health and wellbeing of transgender women.

## SHORT AND LONG-TERM SOLUTIONS

This shortage is a public health crisis. Patients could likely turn to street injections to replace what they were receiving in clinics, which could put themselves at risk. Black market injectable estrogen is often diluted or laced with other potentially harmful ingredients. This shortage could contribute to further marginalization of the transgender community, putting women at risk of injecting adulterated estrogen.

The U.S. Department of Health and Human Services (HHS) affirms that the sex-based discrimination provision of Section 1557 of the Affordable Care Act includes discrimination on the basis of gender identity. With transgender people reporting the highest rates of discrimination and barriers to care among LGBT people<sup>22</sup>, securing much needed services can pose a significant barrier to care. In effect, Section 1557 has become a catalyst for health care providers and both public and private payers to move toward more competent and affirming care for transgender patients.

The FDA drug shortages list merely provides a broad explanation of the reason for the shortage and an estimated release date. Consumers are not provided any information regarding what is required in order for the shortage to be resolved, and reported release dates are posted and then repeatedly not met. In the case of the injectable estrogen shortage, it is unclear if the release is being delayed by the pharmaceutical company or by the FDA, and the release date has been pushed back nearly every month for the past several months. The FDA should not merely reiterate vague, manufacturer-provided information regarding drug shortages and delays.

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This lack of proactive leadership regarding stock-outs of essential drugs only makes it more difficult for transgender people to access comprehensive health care and clinicians to provide high quality services to their patients.

We encourage the FDA, as well as Par and Perrigo, to prioritize and expedite the various regulatory and manufacturing requirements to promptly end the 40 mg/mL injectable estrogen shortage. We realize that this is only a stopgap measure. Gender affirmation therapy has certainly advanced since early treatment protocols were shown to be associated with high rates of thromboembolic disease. Over time, we have developed safer treatments and a wider range of options, including transdermal patches, oral/sublingual tablets, and injectable medications. Despite this, there are no studies comparing the risks and benefits of these formulations. Consequently, there are currently no medications or other treatments that are FDA-approved for the purpose of gender affirmation.<sup>23</sup> In contrast, there are over 17 estrogen medications with approved FDA labels for menopausal women.<sup>24</sup>

The FDA ensures the safety and efficacy of estrogen for menopausal, cisgender women through on-label use informed by clinical trials, but allows off-label use of estrogen for transgender women to remain the standard of care. Such disparate treatment is not acceptable. The FDA should acknowledge that off-label use of injectable estrogen is common among transgender women, often at higher doses than those used by menopausal women, and that the agency is therefore responsible for ensuring correct prescribing and usage information as a public health priority. This will require agency engagement with manufacturers to conduct the necessary studies in support of expanded indications for transgender women. The FDA should also work with manufacturers of products used for masculinizing therapy among transgender men, notably testosterone. All existing regulatory frameworks to incentivize this research and supplemental approval filings, including orphan drug designations<sup>1</sup> and expedited review pathways<sup>2</sup>, should be considered.<sup>3</sup>

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The pressing need for clinical research in support of supplemental FDA approvals of injectable estrogen for transgender women; safety, tolerability, efficacy, and acceptability comparisons with other estrogen-based formulations; and emerging hormonal products with potential for transgender women requires HHS-wide attention. For example, intramural and extramural research programs funded by the National Institutes of Health (NIH), under the direction and leadership of the National Institute of Minority Health and Health Disparities (NIMHD), should be engaged to help fill critical gaps in the clinical science required to strengthen standard-of-care guidance for transgender women; support evidence-based policies; and safeguard against deprioritized and protracted disruptions in access, such as those associated with drug shortages.

## ADVOCACY

Due to the severity of the effects of this shortage on the wellbeing of transgender women, we urge the manufacturers to take immediate action by restocking the 40 mg/mL dosage of injectable estrogen. The FDA should also formally indicate estrogen for gender affirmation purposes. This shortage necessitates a community response that acknowledges the urgency and importance of this issue.

<sup>1</sup> Orphan drug designations provide orphan status for drugs and biologics for rare diseases and conditions that affect fewer than 200,000 people in the U.S. or that affect more than 200,000 people but are not expected to recover the costs of developing and marketing a treatment drug. The designation defines them as intended for the safe and effective treatment of the rare disease or condition, incentivizing production and further scientific development. (<http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm>)

<sup>2</sup> Expedited review pathways allow for a faster approval process for drugs that treat serious conditions and fill unmet medical needs. (<http://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm>)

*What has been done already?*

- ✓ Sign-on letter
  - A sign on-letter co-authored by Fenway Health, Callen-Lorde, and Treatment Action Group received 570 signatures, including physicians, public health professionals and institutions, advocates, and members of the LGBT community.
  - After the letter was delivered in September, Callen-Lorde heard from Par Pharmaceutical President Paul Campanelli, who said that a new raw material in the Delestrogen requires FDA approval. He stated that the product was manufactured, and they estimated FDA approval would be received by early 2017. He also expressed that the company understood the importance of the product to the American consumer.
- ✓ Meetings with FDA representatives
  - FDA representatives expressed that they are prioritizing the shortage and that the 40 mg/ml drug from Perrigo would be released in November 2016. However, to our knowledge, this gap in supply had not been fully addressed when we went to press on December 5<sup>th</sup>, 2016.

*What can you do?*

- **Submit public comment to the FDA**
  - The FDA is now requesting input for all stakeholders – including consumers and activists – to better understand the pros and cons of these limitations on what a manufacturer can and cannot tell healthcare providers about the off-label uses of its drugs. You may also include any additional comments you would like the FDA to consider (i.e. demanding the FDA take a more proactive role in gaining agency-regulated approval for hormones used for gender affirmation).
  - The agency is asking stakeholders to consider a number of questions, which are adapted and reviewed here:
    - How might off-label promotion impact care and treatment for transgender women and men?
    - Should manufacturers of the drugs used off-label for feminizing or masculinizing purposes prioritize conducting the safety and effectiveness research necessary to support FDA approvals for transgender men and women? Will off-label promotion impact incentives for manufacturers to do this research and seek approval?
    - How should the FDA go about considering whether or not off-label use information being communicated by manufacturers is truthful and non-misleading?
    - Should manufacturers be required to provide the FDA with data from clinical trials that support their off-label communications? Should manufacturers be required to publicly disclose the data from clinical trials they are using to support off-label communications?
    - How should the FDA regulate off-label communications to ensure they are not misleading or harmful?
  - You can submit electronic or written comments to the public docket by January 9, 2017.

- Submit electronic comments to <https://www.regulations.gov/document?D=FDA-2016-N-1149-0001>.
  - Submit written comments to the Division of Docket's Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
    - All comments must be identified with the docket number FDA-2016-N-1149.
- **Mobilize and engage with the National Institute of Minority Health and Health Disparities (NIMHD) to develop clinical research priorities to strengthen the evidence base required for clear regulatory guidance and transgender health best practices.**

## ACKNOWLEDGEMENTS

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