

# Pharmacy Compounding Quality Control and Pharmaceutical Development Strategies for Seventeen alpha Hydroxyprogesterone Caproate in Prevention of Preterm Delivery

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## Abstract

Seventeen alpha hydroxyprogesterone caproate (17-OHPC) is the only FDA-approved drug labeled for prevention of preterm delivery. This drug is also available as a compounded product from licensed compounding pharmacies. This article reviews the FDA approval history and pharmacy compounding quality control data of 17-OHPC, as well as briefly discusses possible future pharmaceutical development strategies for 17-OHPC.

**Keywords:** Seventeen alpha hydroxyprogesterone caproate; Quality; Pharmaceutical development

## Introduction

According to the March of Dimes, one in eight births in the United States is a preterm birth. Preterm birth, defined as childbirth occurring at < 37 weeks of gestational age, is the leading cause of neonatal morbidity and mortality. Based on the promising effects seen in clinical trials [1,2] in reducing the risk of preterm birth, intramuscular injection of 17 alpha hydroxyprogesterone caproate (17-OHPC) has recently become the only Food and Drug Administration (FDA)-approved therapy labeled for reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. In addition to the FDA-approved product (Makena<sup>®</sup>), compounded 17-OHPC prepared by licensed compounding pharmacies is also available for women with risk of preterm delivery.

Over 80% of clinical obstetricians have reported prescribing 17-OHPC for the prevention of preterm birth [3]. Disappointingly, the surveyed physicians reported that there was about half of eligible patients seen in their practice but not prescribed 17-OHPC [3], and the financial and logistical barriers carried the most weight (approximately 75%) in the decision not to prescribe FDA-approved 17-OHPC to an eligible patient [4]. Additionally, thirty-nine percent of respondents had professional liability concerns regarding prescribing compounded 17-OHPC.

Furthermore, the current use of 17-OHPC oil formulation is largely empirical. From the perspective of pharmaceutical development, more therapeutically advantageous 17-OHPC formulations need to be explored.

Hence, the purpose of the present document is to summarize the quality control of compounded 17-OHPC and to this end discuss certain strategies for pharmaceutical development of 17-OHPC.

## Prevention of preterm birth by 17 alpha hydroxyprogesterone caproate

The causes and mechanisms of preterm birth are not completely understood. Some of the known causes of preterm birth include short cervix, multiple pregnancies, infections and chronic conditions, such as diabetes and high blood pressure; however, often no cause can be specifically identified [5]. Most preterm births happen spontaneously. Consequently, several pharmacologic strategies, including tocolytics (e.g., oxytocin antagonists, betamimetics, calcium channel blockers, magnesium sulphate) [6], or progestational agents (e.g., vaginal progesterone [7], intramuscular 17-OHPC) have been employed to prolong pregnancy.

The initial evidence that weekly injections of 17-OHPC improved the outcomes of selected high-risk pregnancies was shown in a small trial by Johnson in 1975 [8]. The 2003 landmark randomized placebo-controlled trial sponsored by the National Institute of Child Health and Human Development (NICHD) demonstrated a 34% reduction in recurrent preterm birth before 37 weeks for singleton pregnant women who received compounded 17-OHPC versus a control group receiving placebo [1]. Based on the results of the 2003 trial [1,9], intramuscular 17-OHPC became the only FDA approved drug, for the prevention of preterm birth in singleton pregnant women with a history of a prior spontaneous preterm birth. The exact mode of action of 17-OHPC therapy in preventing preterm labor and delivery is not known [10]. Inhibition of tumor necrosis factor (TNF)-alpha-induced apoptosis in term fetal membranes by 17-OHPC may explain in part the mechanism by which 17-OHPC prevents preterm birth in some high-risk women [11]. The benefit of 17-OHPC to prolong pregnancy was neither demonstrated in women with short cervix [12-15], nor in women with multiple pregnancies [16-18]. 17-OHPC had no effect on the pathways known to be involved in uterine contractility or quiescence. 17-OHPC had no effect on the cervical remodeling. Key mechanism by which 17-OHPC prevents preterm birth requires further study [19].

## Chemistry of 17 alpha hydroxyprogesterone caproate

The long lasting and potent progestational activity of 17-OHPC on endometrium is attributed to its chemistry [20]. 17-OHPC is a synthetic progestin, an ester derivative of 17 alpha hydroxyprogesterone formed with caproic acid (hexanoic acid) [21]. It is not identified from natural body fluids or tissues in any living organism [21].

17-OHPC in solid state is a white to practically white crystalline powder with a molecular weight of 428.6, logarithm of partition coefficient (logP) of 5.88, logarithm of distribution coefficient (logD) of 5.91, hydrogen bond donors of 0, hydrogen bond acceptors of 4, and water-insolubility [obtained from Pubmed ([http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=12419&loc=ec\\_rcs](http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=12419&loc=ec_rcs)) and Chemicalize (<http://www.chemicalize.org/structure/#!mol=hydroxyprogesterone+caproate&source=fp>)]. Due to the logP value > 5 being highly lipophilic, 17-OHPC does not fully follow drug-likeness defined in the Lipinski's rule of five [22]. 17-OHPC is classified as class II drug according to the Biopharmaceutics Classification System (BCS) [23-26]. High lipophilicity of 17-OHPC leads to poor aqueous solubility [27]. Given the poor aqueous solubility, dissolution becomes the rate limiting step for the absorption of 17-OHPC from solid state to enter into systemic circulation.

## FDA approval history of 17 alpha hydroxyprogesterone caproate

The FDA originally approved 17-OHPC with new drug application (NDA) 010347 in 1956 and NDA 016911 in 1972, under the trade name Delalutin<sup>®</sup> (17 alpha hydroxyprogesterone caproate) injection, held by Bristol Myers Squibb Company (BMS) [28]. Both NDA 010347 and NDA 016911 referenced the same drug product and utilized the same labeling. Delalutin<sup>®</sup> contained 250 mg/mL of 17-OHPC in castor oil, with 46% benzyl benzoate as a solvent and 2% benzyl alcohol as a preservative. The approved indications for Delalutin<sup>®</sup> injection, other than the indication for treatment of female hormone disturbances and advanced adenocarcinoma of the uterine corpus in non-pregnant women, also included threatened miscarriage. In the past, several generic forms (NDA 017439 by Watson Labs, NDA 018004 by Akorn, NDA 089330 and NDA 089331 by Quad Pharms) of Delalutin<sup>®</sup> injection were approved by FDA (Table 1). In 2000, FDA announced the withdrawal of approval of NDA 010347 and NDA 016911 for Delalutin<sup>®</sup> at the request of the patent holder, BMS, due to the availability of superior treatments for uterine cancer, and not due to safety or efficacy reasons.

Shortly after the publication of the NICHD-sponsored study [1] in 2003, the American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice issued a Committee Opinion recommending that progesterone supplementation to prevent preterm birth be considered for a select group of women (i.e., those with a prior spontaneous birth at < 37 weeks of gestation) [29]. On February 3, 2011, based on the result of this NICHD-sponsored study, the FDA conditionally approved Makena<sup>®</sup>, 17 alpha hydroxyprogesterone caproate injection by KV Pharmaceutical, under the Orphan Drug Act to reduce the risk of preterm delivery before 37 weeks of pregnancy, in pregnant women with a history of at least one spontaneous preterm birth.

## FDA-approved product and compounded version

The FDA-approved product, Makena<sup>®</sup> is a clear, yellow, sterile, non-pyrogenic solution for intramuscular injection in 5 mL multi-dose vial containing 250 mg/mL of 17 alpha hydroxyprogesterone caproate (25% w/v), in castor oil (28.6% v/v) and benzyl benzoate (46% v/v) with the preservative benzyl alcohol (2% v/v) (shown in Makena<sup>®</sup> label). Makena<sup>®</sup> is identical to Delalutin<sup>®</sup>, the formulation that was previously approved. The approved dosage of 17-OHPC in pregnant women is weekly 250 mg intramuscular injection, initiated from 16 weeks of gestation and continued until week 36 or delivery. The initial price of Makena<sup>®</sup> was set at \$1,500 per injection, compared with \$10 to \$20 for identical compounded version that has been used for decades before Makena<sup>®</sup> was approved. The total list price for a 20-weeks supply of Makena<sup>®</sup> was approximately \$30,000 per pregnancy. The ACOG stated, "This price remains prohibitively high for a safe and effective treatment that is currently available at a much lower price in the form of compounded 17-OHPC" [9].

| Drug Name | NDA    | Dosage Form/Route          | Strength, mg/mL | Company              | Approval timeline | Marketing Status |
|-----------|--------|----------------------------|-----------------|----------------------|-------------------|------------------|
| DELALUTIN | 010347 | Injectable;<br>Injection   | 125, 250        | Bristol Myers Squibb | 1956              | Discontinued     |
| DELALUTIN | 016911 | Injectable;<br>Injection   | 125, 250        | Bristol Myers Squibb | 1972              | Discontinued     |
| 17-OHPC   | 017439 | Injectable;<br>Injection   | 125, 250        | Watson Labs          | 1974              | Discontinued     |
| 17-OHPC   | 018004 | Injectable;<br>Injection   | 125             | Akorn                | 1979              | Discontinued     |
| 17-OHPC   | 089330 | Injectable;<br>Injection   | 125             | Quad Pharms          | 1987              | Discontinued     |
| 17-OHPC   | 089331 | Injectable;<br>Injection   | 250             | Quad Pharms          | 1987              | Discontinued     |
| MAKENA    | 021945 | Solution;<br>Intramuscular | 250             | KV Pharm             | Feb, 2011         | Prescription     |

NDA: new drug application; 17-OHPC: 17 alpha hydroxyprogesterone caproate

**Table 1:** FDA approval history of 17 alpha hydroxyprogesterone caproate.

Shortly after the approval of Makena®, in response to the harsh criticism from Congress and professional groups on Makena® pricing [4], in order to support access to this important drug, FDA did not intend to take enforcement action against pharmacies that compound hydroxyprogesterone caproate based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products [30], and maintained that compounded versions would not violate the availability of FDA-approved drug Makena®. This solution avoids excessive drug-related acquisition costs and provides patients with easy access to this important drug. The difference between Makena® and the compounded version of 17-OHPC, is the quality assurance provided by an FDA-approved product compared with the potential variability in quality associated with compounding practices of pharmacists who are trained to “compound and dispense” medications [4]. The composition of the compounded 17-OHPC consists of 250 mg/mL 17-OHPC in oily carriers, such as castor oil, sesame oil, olive oil or similar carriers, to which yet other excipients may, if desired, be added, such as benzyl alcohol and benzyl benzoate. Such addition is desirable in the preparation of 17-OHPC injection in order to, one hand enhance dissolution, the other hand lower the viscosity to make the preparation easier to be injected through a needle of the desired bore.

## Quality control of the active pharmaceutical ingredients and compounded products of 17 alpha hydroxyprogesterone caproate

Recently, concern about the quality of the active pharmaceutical ingredient (API) used for compounding purpose as well as the quality of compounded 17-OHPC products have been expressed [31,32]. Inconsistent results (Tables 2 and 3) among different laboratories [31,33] based on the identical specification methods have been generated on the quality testing of API and compounded products of 17-OHPC. On June 15, 2012, FDA has stated that “although the analysis of this limited sample of compounded hydroxyprogesterone caproate products and APIs did not identify any major safety problems, approved drug products, such as Makena, provide a greater assurance of safety and effectiveness than do compounded products. One factor that the agency considers in determining whether a drug may be compounded is whether the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available drug product” [33]. In addition, the safety and effectiveness of compounded 17-OHPC was confirmed in the pregnancy outcomes study of women receiving for prophylactic prevention of preterm birth [34].

Further, our stability-indicating study [35] (Table 4) also demonstrated that 17-OHPC appeared to be fairly stable when exposed for a short term to high temperature, light, strong acid, different preservatives, and different dispensing containers under respective experimental conditions. In addition, our recent studies [36,37] (Table 3) have shown acceptable content, sterility and pyrogenicity of 17-OHPC compounded by pharmacies in the USA. Soon after the publication of our research on testing the quality of compounded 17-OHPC, the American Journal of Obstetricians and Gynecologists editors commented that “... the Obstetrical-Fetal Pharmacology Research Units (OPRU)-funded investigators were able to perform the most extensive study to date of compounded 17-OHPC products ... The study ... demonstrates that compounded 17-OHPC should provide an effective, safe, and inexpensive alternative for patients who require treatment with 17-OHPC” [38].

Very recently, the FDA published a draft guidance on Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [39,40]. Compounding conditions of section 503A include: (1) drug product is compounded for an identified individual patient based on a valid prescription order approved by a prescribing practitioner; (2) compounding is performed by a licensed practitioner in limited quantities; (3) drug product is compounded in compliance with the United States Pharmacopoeia (USP) chapters; (4) drug product is compounded using bulk drug substances that are manufactured by an FDA-registered establishment; (5) drug product is compounded using bulk drug substances with valid certificates of analysis; (6) drug product is compounded using ingredients (other than bulk drug substances) that comply with the standards of an applicable USP or NF monograph, if one exists, and the USP chapters on pharmacy compounding; (7) compounded drug product does not include products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective; (8) the licensed practitioner does not compound any drug products that are essentially copies of commercially available drug products regularly or in inordinate amounts; (9) compounded drug product is not a drug product identified by FDA as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product; (10) drug product is compounded in a state that has entered into a memorandum of understanding (MOU) with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a state agency of complaints relating to compounded drug products distributed outside such state; or in states that have not entered into such an MOU with FDA, the licensed practitioner does not distribute more than 5% compounded drug products of the total prescription orders out of the state in which they are compounded. Following appropriate compounding conditions regarding a compounded product by compounding pharmacies may prevent or alleviate the reoccurrence of quality problems experienced with the use of compounded products by the New England Compounding Center (NECC, Framingham, MA). Since the NECC disaster in 2012 [41], the importance of correct procedures during every phase of customized pharmacy has been a focus of governmental interest and action as well as public scrutiny [42].

| Testing site | Sample size | Sample source   | Assay | Total impurity | Unidentified impurity | Safety concerns |
|--------------|-------------|---|-------|----------------|-----------------------|-----------------|
| FDA          | 16          | pharmacies, physicians, API distributors, imported APIs in US | Pass  | Pass           | Fail                  | No              |
| KV           | 10          | manufacturers not registered with FDA and 3 repackagers in US | Fail  | Pass           | Fail                  | Yes             |

NDA: nAPI: active pharmaceutical ingredient

Note: standard for assay: 97 – 103%; standard for total impurity: ≤ 2 %; standard for unidentified impurity: ≤ 0.1%

**Table 2:** Quality testing of the active pharmaceutical ingredient of 17 alpha hydroxyprogesterone caproate.

| Testing site   | Sample size | Sample source            | Potency    | Impurity   | BB   | BA   | Sterility | Endotoxin |
|----------------|-------------|--------------------------|------------|------------|------|------|-----------|-----------|
| FDA            | 13          | 8 pharmacies             | 12/13 pass | 11/13 pass | NA   | NA   | NA        | NA        |
| FDA            | 26          | Samples retained from KV | 23/26 pass | 19/26 pass | NA   | NA   | NA        | NA        |
| KV             | 30          | 30 pharmacies            | 25/30 pass | 13/30 pass | NA   | NA   | NA        | NA        |
| Our laboratory | 3           | 1 pharmacy in Pittsburgh | 3/3 pass   | NA         | NA   | NA   | pass      | pass      |
| Our laboratory | 18          | 15 pharmacies over US    | 18/18 pass | Pass       | Pass | Pass | pass      | pass      |

PD: post-compounding duration; BB: Benzyl benzoate; BA: Benzyl alcohol; USP: the United States Pharmacopoeia;

NA: not available

Note: standard for potency: 90-110%; standard for impurity: <0.2%; standard for BB: 46%; standard for BA: 2%; standard for sterility by USP71: 90-110%; standard for endotoxin by USP85: <0.5EU/mg

**Table 3:** Quality testing of compounded 17 alpha hydroxyprogesterone caproate products.

## Pharmaceutical development strategies of 17-OHPC

### Dispensing 17-OHPC in single-dose container

Delivery of 17-OHPC in single-dose container may be justified, in order to minimize patient dosing errors and reduce the risk of contamination that is associated with repeated use of multidose vials. Our studies indicated that both stability and sterility of 17-OHPC over 19 weeks post-preparation were observed independent of the container size or material in which it was stored [36]. The FDA-approved product is dispensed in 5-mL multidose vials with weekly injections; the contents in a vial normally are consumed successively for 5 weeks. Likewise, if 1-mL single-dose container is used, the patient can receive 20 injections for gestation of 16 till to 36 weeks and be more confident that the drug will not deteriorate or precipitate in that time frame.

| Experimental conditions            | Testing conditions  | Change in Strength | Change in Impurity | Sterile/Pyrogen-free |
|------------------------------------|---|--------------------|--------------------|----------------------|
| <b>17-OHPC powder</b>              |   |                    |                    |                      |
| Heat                               | 150 °C, 1 hour  | ↔                  | NA                 | NA                   |
| Light                              | overall illumination ≥ 200 Wh/m <sup>2</sup> , 3 days                           | ↔                  | NA                 | NA                   |
| In presence of acid                | 5 M hydrochloric acid, 72 hours   | ↔                  | D                  | NA                   |
| In presence of base                | 5 M sodium hydroxide, 5 hours   | ↓                  | ↑                  | NA                   |
| <b>Compounded 17-OHPC products</b> |   |                    |                    |                      |
| Light                              | overall illumination ≥ 100 Wh/m <sup>2</sup> , 10 weeks                         | ↔                  | NA                 | NA                   |
| Preservative                       | benzyl alcohol vs none, 10 weeks  | ↔                  | NA                 | ↔                    |
| Container                          | 10-mL multidose glass vial vs 1-mL glass vial vs 1-mL plastic syringe, 10 weeks | ↔                  | NA                 | ↔                    |
| Sterilization                      | Dry-heat, 2.5 hours vs filtration sterilization                                 | ↔                  | ↔                  | NA                   |
| Storage duration post-compounding  | Up to 56 weeks  | ↔                  | NA                 | ↔                    |

NA: not available; ↑: increase; ↓: decrease; ↔: no change

**Table 4:** Impact of various experimental conditions on the quality of compounded 17 alpha hydroxyprogesterone caproate based on the data from our laboratory.

Furthermore, either a plastic syringe or a glass vial can be used to dispense 17-OHPC [36]. In principle, the high lipophilicity of 17-OHPC could lead to the binding of certain percentage of the drug onto the surface of a plastic container. Our findings do not support this concern [36]. The use of single-dose plastic syringe will enhance patients' and healthcare providers' convenience due to operational simplicity.

### Sterilization of 17-OHPC

Dry-heat sterilization during compounding of 17-OHPC may be utilized to obtain more confidence in the safety of compounded products. Our study showed that the content of 17-OHPC in compounded products was not affected either by dry-heat sterilization or by filtration sterilization [35]. A critical step for safe 17-OHPC products involves assurance of sterility. FDA-approved product, Makena® is manufactured using filtration sterilization process. Sterilization by filtration is considered to have a sterility assurance level (SAL) of 10<sup>-3</sup>; that is, if one million units are sterilized, there will be one thousand sterilization failures. In contrast, dry-heat sterilization relative to filtration is considered to be more effective allowing for terminally sterilization, with a SAL of 10<sup>-6</sup>: one sterilization failure per million units sterilized.

### Preservative-free in 17-OHPC products

Omitting the preservative in 17-OHPC products for an identified individual patient may be performed by compounding pharmacies. One ingredient added to current 17-OHPC products in order to avoid the alteration and degradation by microorganisms and to prolong the shelf life during storage is the preservative of benzyl alcohol. Our study demonstrated that 17-OHPC was stable and retained sterility over 10 weeks post-preparation without any pyrogen independent of preservative use [36]. This modification may have many potential benefits. Recently, the FDA cautioned about serious adverse events and death from the administration of benzyl alcohol to pregnant women and infants [43]. Our results suggest that omission of benzyl alcohol in compounded 17-OHPC in single dose vials does not pose substantial additional risk of infection to the mother and the fetus. Another potential benefit of modification in preservatives may be the avoidance of local skin reactions from current 17-OHPC formulation.

### Development of alternative dosage forms

Our pharmacokinetic studies have shown low plasma concentrations (0.02 - 0.16 µM) [44-46], large apparent volume of distribution (9124 - 69600 L) [44,46], apparent overall clearance (0.84 L/min) [46], and long half-life (16 days) [44] of 17-OHPC in pregnant women. Body mass index (BMI) has been found to be a covariate contributing to the interindividual differences in trough plasma concentrations and area under the curve (AUC) of 17-OHPC, with women of higher BMI having lower trough concentrations and lower AUC values [46]. The low plasma concentration of 17-OHPC may be due to extensive distribution of highly lipophilic 17-OHPC in lipid or adipose (fat) tissues. In addition, rapid CYP3A-mediated metabolism to hydroxylated metabolites has been observed upon incubation of 17-OHPC in human hepatic [47-49] and placental microsomes [49,50]. Our study based on *in vitro* interaction data in human liver microsomes also suggested that increased progesterone levels [51] or co-administered medications during pregnancy may also account for some of the large variation in plasma 17-OHPC concentrations that is seen in

pregnant patients who receive a fixed dose of medication. There is also a void in the complete understanding of the pharmacodynamics of 17-OHPC. Very limited evidence has indicated that the effectiveness of 17-OHPC in reducing preterm birth rates was influenced by the achieved plasma concentration [52]. A strong negative association ( $P < 0.05$ ) between plasma 17-OHPC concentration and the risk of spontaneous preterm birth was observed in that study. Women with plasma 17-OHPC concentrations in the lowest quartile had a significantly higher risk of spontaneous preterm birth ( $P = 0.03$ ) and delivered at significantly earlier gestational ages ( $P = 0.002$ ) than did women in the 2<sup>nd</sup> to 4<sup>th</sup> quartiles [52].

So far, intramuscular injectable is only available 17-OHPC treatment. Other formulations or administration of 17-OHPC by routes other than intramuscular may be considered. Firstly, oral dosage forms increase patients' compliance. 17-OHPC appears to be highly permeable based on its physico-chemical characteristics ( $\text{LogP} = 5.88$ ). In light of its stability under gastric pH environment [35], an oral product is probable if a formulation can be prepared to improve its solubility. However, the extensive metabolism by intestinal CYP3A on 17-OHPC would suggest a low oral bioavailability. Secondly, transdermal delivery system without the first-pass effect in the gut and liver, may be promising to achieve higher plasma concentrations for 17-OHPC. In addition, transdermal delivery contains additional reservoir that can effectively retard the release rate of the drug and decrease the dose frequency. However, drug load capacity through transdermal delivery may be relatively limited ( $< 250$  mg). Vaginal administration route of 17-OHPC may provide women with a more user-friendly drug treatment than other methods and results in better patient compliance. Simultaneously, efficacy may be achieved via locally without compromise, while limiting the adverse effects from systemic exposure to 17-OHPC and simultaneously reducing potential induction of 17-OHPC on the metabolism of CYP2C19 substrates [53]. Drugs absorbed in the upper part of the vagina can bypass the liver and, if metabolized, are subject to a reduced hepatic first-pass effect. However, the assessment of the safety and efficacy of potential alternative formulations of 17-OHPC needs to be performed. Therefore, pharmaceutical development for 17-OHPC may be achievable. More thorough studies on its pharmacokinetics and pharmacodynamics should be given due attention.

## Conclusions

The review specifically addresses the quality control of compounded version of 17-OHPC. The 2013 FDA draft guidance on Pharmacy Compounding of Human Drug Products emphasizes compounding human drug products under section 503A of the Federal Food, Drug, and Cosmetic Act. Some strategies of pharmaceutical development for 17-OHPC are also addressed.

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