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## Brand Versus Generic Oral Contraceptives

### Committee on Gynecologic Practice

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**ABSTRACT:** The U.S. Food and Drug Administration considers generic and brand name oral contraceptive (OC) products clinically equivalent and interchangeable. The American College of Obstetricians and Gynecologists supports patient or clinician requests for branded OCs or continuation of the same generic or branded OCs if the request is based on clinical experience or concerns regarding packaging or compliance, or if the branded product is considered a better choice for that individual patient.

To control pharmaceutical costs and standardize national practice, the U.S. Food and Drug Administration (FDA) was given the authority to approve generic versions of branded pharmaceutical products by the Drug Price Competition and Patent Term Restoration Act. Before 1984, manufacturers of generic products had to submit clinical safety and efficacy data for their products just as the innovator drug manufacturer had to do for initial approval. Since 1984, generic products, including generic oral contraceptive (OC) products, must demonstrate pharmaceutical equivalence, meaning that this new generic product contains the same active ingredients, identical in strength and dosage, as the branded product. This generic product also must be bioequivalent, meaning that blood levels obtained in clinical trials demonstrate a rate and extent of absorption not substantially different from the branded product (1).

Studies demonstrating bioequivalence of generic OC products are submitted by the generic pharmaceutical company after a crossover study of adequate power (usually of 20–24 women) with pharmacokinetic calculations of serial blood levels of the progestin or its active metabolite and ethinyl estradiol, plasma concentration time curves (AUC), peak concentration, and the time to peak concentration. The average blood level deviation from the brand must be in the range of 80–125%. If these criteria are met, the FDA Office of Generic Drugs does not request or recommend clinical efficacy or safety studies for the generic product before granting marketing approval, and it considers the generic product to be interchangeable

with the branded product. No clinical trial is needed given that the safety and efficacy of the generic product is expected to be that of the clinically tested and FDA-approved branded product. Brand name and generic drug facilities are required to meet the same standards of good manufacturing practices.

Patients and clinicians have questioned whether generic and brand name OC products are clinically equivalent and interchangeable, as effective in preventing pregnancy, and have similar occurrences of side effects, such as breakthrough bleeding. The FDA considers generic and brand name OC products clinically equivalent and interchangeable; however, others imply that this may not be true (2). The statistical methods used by the FDA to determine bioequivalence have been challenged. The FDA Center for Drug Evaluation and Research has taken a firm stand upholding the therapeutic equivalence and interchangeability of generic and branded products (3).

Oral contraceptive pills are the most commonly used form of reversible contraception in the United States. Overall, the FDA lists more than 90 combination hormonal contraceptives containing ethinyl estradiol. Most OCs are no longer patent protected and are available for the development of generic pharmaceutical copies. The 2007 27th edition of *Approved Drug Products With Therapeutic Equivalence Evaluations*, the so-called “Orange Book,” lists only seven combination OCs that do not have a generic alternative (4). Although new OC formulations are protected by patent for 20 years from initial patent filing, in practice there is a much shorter inter-



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val from final approval and marketing to loss of patent protection.

Although considered clinically equivalent by the FDA, branded and generic OCs may differ in shape, packaging, color, flavor, and shelf life. In addition, nonactive ingredients such as preservatives and labeling and storage requirements also may differ. Products are considered bioequivalent if they fall within the required parameters; the mean bioequivalence cannot be more than 20% lower or 25% higher, with 95% certainty. In practice, the reported ranges of generics are much narrower. Given the range of acceptable generic bioequivalence, switching between generic OCs or from branded to generic OCs might be associated with increased side effects or other problems, but similar problems theoretically might occur when switching between two batches made by the same manufacturer. Additionally, some firms package their own branded drugs and sell them under a generic or other brand label.

When taken correctly and consistently, combination OCs and other hormonal contraceptives have failure rates of less than one pregnancy per 100 couples over 1 year. Published studies report different failure rates for various brands, but few head-to-head studies have been performed, and there is no evidence that with perfect use different combination products have different failure rates (5).

Although there are no clinical data on any difference in compliance between different branded OCs or between generic and branded OCs, patients and clinicians anecdotally report problems when switching occurs. It is possible that side effects or pregnancy occur as a result of poor compliance because patients are confused by new packaging, they fear that they received the wrong pill, or they lack confidence in generics. Although this likely affects compliance and effectiveness, there are no evidence-based data addressing these issues. Even though some patients may perceive generic products to be less effective, there are no clinical data on how this perception affects continuation rates.

Given an individual's variations in metabolism, it is probably impossible to improve our knowledge of OCs by completing larger studies; effectiveness and side effects will tend to be overwhelmed by other nonpharmaceutical effects. Breakthrough bleeding, which is a common cause of OC discontinuation, is related to missed pills, smoking, infection, and possibly drug interactions, which will tend to overwhelm subtle variations between already confirmed bioequivalent and pharmaceutically equivalent products. As the FDA has pointed out, patients may be more likely to be aware of symptoms when substitutions occur or if they have been told they are taking a generic brand.

Oral contraceptive pills are obtained by patients in a variety of settings and with different reimbursement plans, and cost clearly influences access and use. For a patient whose insurance will pay only for a generic product on formulary or in cases where a patient is paying

out of pocket, the difference in price can be as much as 70% less for a generic, especially when multiple generic choices for a specific branded product are available. Often, the difference is much less. Cost has been shown to be among the most important factors in OC continuation, and less expensive generic OCs may have better continuation rates than more expensive alternatives (6).

Generic OCs approved by the FDA have been shown to be bioequivalent and pharmaceutically equivalent to the branded product and are interchangeable. There are no evidence-based data to challenge this conclusion. However, because of possible effects on patient compliance, the American College of Obstetricians and Gynecologists supports patient or clinician requests for branded OCs or continuation of the same generic or branded OC if the request is based on clinical experience or concerns regarding packaging or compliance, or if the branded product is considered a better choice for that individual patient. Women should be informed when a different OC is substituted for a previously prescribed OC.

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