

Bioequivalence Between Brand-name and Generic Oral Contraceptives

a report by

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Introduction

Since their introduction in the early 1960s, oral contraceptive (OC) formulations have changed considerably. Low-dose pills available at the time of press contain substantially less oestrogen and progestin than their early predecessors. OCs containing 100µg ethinyl estradiol (EE) or more were commonly prescribed in the 1960s, whereas nearly all (99%) birth control pills dispensed at the time of press contain 35µg EE or less.¹ Moreover, the proportion of women using 20µg EE pills – the lowest dose available in the US – is rising steadily.

High intra- and inter-individual variability causes plasma EE levels to differ substantially from woman to woman following OC ingestion.² Moreover, the same woman may metabolise EE and progestin differently from day to day. These variations make it nearly impossible to predict how a given woman will respond to any particular OC.

“With OCs, every woman makes her own individual cocktail on a day-by-day basis,” says Dr Joseph Goldzieher, Distinguished Professor in the Department of Obstetrics and Gynecology at Texas Tech University and former Associate Editor of *The Contraception Report*. “Studies have shown that on two successive Mondays or two successive Tuesdays, you cannot predict the second pattern from the first pattern. The body does different things on different days. A woman on OCs creates her own mixture of oestrogen and progestin on a daily basis. Despite this, we still see contraceptive efficacy, which has never failed to amaze me.” For this reason, large studies with many women are typically performed to demonstrate efficacy in a wide range of users.

US Food and Drug Administration (FDA) Requirements for Generics

Following the patent expiration of a branded product, generic manufacturers may submit an abbreviated new drug application (ANDA) to the FDA. The requirements for approval of an ANDA are less stringent than those mandated for an innovator drug. The generic manufacturer need only

demonstrate that the product is therapeutically equivalent to the brand-name drug, which requires evidence that the two drugs are pharmaceutically equivalent and bioequivalent (BE). Two products are considered pharmaceutically equivalent if they contain the same active ingredient(s) and are identical in strength, dosage form and route of administration. BE is achieved if the generic product demonstrates no substantial difference in rate or extent of absorption compared with the reference drug.³

The FDA does not specify a minimum number of participants for studies demonstrating bioequivalence. According to the agency, “The total number of subjects in the study should provide adequate power for BE demonstration, but it is not expected that there will be sufficient power to draw conclusions for each sub-group.”⁴ Consequently, BE testing for generic drugs typically involves a small cross-over study of 20 – 30 individuals.³

BE studies compare the rate and extent of absorption of the active ingredient(s) following administration of the generic and brand-name product in the same individuals under similar conditions. Outcome measures evaluated include the area under the drug concentration time curve (AUC), which indicates the extent of absorption, and the maximum concentration (C_{max}) and the time of maximum concentration (T_{max}), which indicate the absorption rate.⁴

The FDA definition of therapeutic equivalence allows differences in BE parameters between products. The AUC values for the generic and reference drug may differ by as much as 20% to 25% and still fall within the acceptable range for BE. Typically, the FDA considers two drugs to be BE if the 90% confidence interval limits for the mean AUC of the generic drug, fall within the range of 80% to 125% of the value for the reference product.⁵ In general, these results must be demonstrated for at least 75% of the individuals studied.⁶ A less-stringent standard is applied to differences in C_{max} and T_{max} values, which are considered less crucial for demonstrating therapeutic equivalence than AUC. The minimum circulating levels at the end of the dosing period are not specified.

Specific Concerns with OCs

Some have questioned whether the FDA standards for BE are stringent enough for certain classes of drugs, including OCs.^{3,6-9} If the FDA guidelines are applied to an OC formulation containing 20µg EE, the hormone dose in a therapeutically equivalent generic product could be as low as 16µg EE (80% of 20µg). According to some analyses, the difference may even be greater – given the acceptable potency variation of $\pm 10\%$ between lots of a reference product, the difference in AUC between a generic and a brand-name product could theoretically be as much as 28% (80% of 90%), potentially resulting in a dose of 14.4µg EE.³ Progestin doses could be similarly affected.

“Today’s OCs have extremely small amounts of active ingredients,” says Dr Rudi Ansbacher, Professor in the Division of Reproductive Endocrinology at the University of Michigan. “The potential problem is that when you use these small microgram doses and you’re allowed to have just 72% of what’s in the brand-name pill, you actually may be giving only about 14.4µg of ethinyl estradiol.”

Even if contraceptive efficacy is maintained, says Dr Ansbacher, the increase in breakthrough bleeding could lead to OC discontinuation – and eventual unintended pregnancy. “Breakthrough bleeding itself may contribute to increased pregnancy because many women who experience bleeding discontinue the pill without using an effective subsequent contraceptive, placing them at risk from pregnancy,” he explains. “In the other direction, where allowable hormone levels in generic OCs are considerably higher than in the brand-name product, you could see an increase in nuisance side effects such as nausea and breast tenderness.”

No data is available to determine whether the occurrence of side effects, breakthrough bleeding or unintended pregnancy differs between generic versus brand-name OCs. The FDA does not require such studies for approval of generic products.

However, even if this research were required for OCs, the number of participants necessary to detect a difference would be likely to be prohibitive. According to Dr Goldzieher, “Studies are simply not sensitive enough to be able to detect these small differences. Even under the best circumstances, the human failure component overwhelms the pharmacology that we would like to study.”=

Narrow Therapeutic Index Drugs

In 1995, the FDA created a list of drugs considered to

have a narrow therapeutic range, including low-dose OCs.^{10,11} The FDA does not require more stringent BE standards for generic versions of narrow therapeutic index drugs, nor does it provide guidance regarding therapeutic substitution. Rather, the agency “recommends that sponsors consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs. The approach is designed to provide increased assurance of interchangeability for drug products containing specified narrow therapeutic range drugs. This guidance recommends that the traditional BE limit of 80% to 125% for non-narrow therapeutic range drugs remain unchanged for the bioavailability measures (AUC and C_{max}) of narrow therapeutic range drugs.”¹⁴

Mixed Data

No data exist comparing the clinical performance of generic versus brand-name OCs. However, clinical BE between generic and branded products has been studied in other therapeutic areas. Results of these trials are mixed.

Some randomised controlled trials have demonstrated similar clinical effects between generic products and their brand-name counterparts.¹²⁻¹⁶ In a 90-day trial involving 40 patients with epilepsy, generic carbamazepine performed as well as the branded version, resulting in statistically identical blood levels and seizure frequencies.¹² Similarly, an eight-week study involving 64 patients with mental retardation and seizure disorders reported no statistical differences in seizures or blood levels between generic and brand-name valproic acid.¹³ In an eight-week trial of generic versus brand-name inhaled beclomethasone dipropionate, no statistically significant differences in clinical variables were reported among 36 adults with asthma.¹⁴

On the other hand, some randomised controlled trials have found significant clinical and pharmacokinetic differences between generic and branded drugs.¹⁷⁻²¹ A 16-week trial studied generic versus brand-name clozapine in 45 patients with schizophrenia, schizoaffective disorder, bipolar disorder with psychosis or atypical psychosis with mood disorder.¹⁷ Two groups of patients each received one product for eight weeks, then were switched to the other drug for the following eight weeks. Efficacy measures significantly favoured the branded product and five patients relapsed when switched from brand-name to generic clozapine. Other trials have reported significant differences in composition and bioavailability between generic and brand-name versions of theophylline,¹⁹ mefloquine,²⁰ and conjugated oestrogens.²¹

Editorial Comment

The author is concerned that potential differences between generic and brand-name low-dose OCs may increase rates of breakthrough bleeding (and other side effects) and may interfere with contraceptive efficacy. As described previously, therapeutic equivalence of a generic product requires testing only for BE – not efficacy or safety. For OCs, these studies usually involve small numbers of women and are not representative of the population as a whole. Importantly, the contraceptive efficacy and side effect profiles of generic OCs have not been investigated in large clinical trials.

Two questions must be asked when evaluating the concerns regarding generic substitution for OCs:

- do generic products prevent pregnancy? and
- do these products cause a different level of side effects that could result in contraceptive discontinuation, thereby resulting in an increased number of unplanned pregnancies?

Without appropriate testing, it cannot be known if the generic 'equivalent' is sufficient to provide adequate contraception. The question of whether the potential variation in hormone levels could lead to different rates of side effects and higher discontinuation also arises. Without comparative studies of acceptability, side effect profile and continuation rates with the generic products, however, there is no way of knowing if these are clinically BE.

Unless the FDA changes its requirements for approval of generic OCs, patients are at least owed the explanation that these products have not been proven to be effective (or ineffective) in clinical trials. For some women, the reduced cost of a generic product is needed to allow them to afford contraception. Others may consider the potential consequences of using an unproven product to be excessive. Either way, discussing these issues with patients allows them to make an informed decision.

Are generic OCs clinically equivalent to brand-name OCs? The answer is unknown and is likely to remain so. ■

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