transplantation — therapy that is associated with infertility and a greater risk of long-term toxic effects. These complications might have been avoided if such patients had been treated with mechlorethamine. Moreover, it is unknown as yet whether salvage therapy has been successful in all patients who have had a relapse.

Almost 80% of children and adolescents with cancer can be cured with current therapy. Most of the curative treatment regimens are based on chemotherapeutic agents that have been available for decades, but some of these have recently been in short supply. These shortages are likely to have devastating effects on patients with cancer and must be prevented. For many of these agents, no adequate substitute drugs are available. Our results suggest that even promising substitute regimens should be examined carefully before adoption; what might appear to be a suitable alternative regimen may result in an inferior outcome — an intolerable situation for young people with curable diseases.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Withdrawal of Generic Budeprion for Nonbioequivalence

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The Food and Drug Administration (FDA) has completed a head-to-head bioequivalence study of single doses of the generic drug Budeprion XL 300 mg (extended-release bupropion hydrochloride, manufactured by Impax Laboratories and distributed by Teva Pharmaceuticals) and the brand-name drug Wellbutrin XL 300 mg (Biovail). The agency has concluded that Budeprion XL 300 mg cannot be considered therapeutically equivalent to the brand-name product. We at the FDA are therefore changing our bioequivalence recommendations for extended-release bupropion products and have asked other manufacturers of 300-mg extended-release bupropion products to conduct additional bioequivalence studies.

Within a year after gaining approval at the end of 2006, Budeprion XL 300 mg became the subject of intense media coverage describing adverse events in patients being treated for major depressive disorder who had switched to the generic drug from Wellbutrin XL. Approval of Budeprion XL 300 mg was based on the results of a bioequivalence study of Budeprion XL 150 mg and Wellbutrin XL 150 mg, which were extrapolated to the 300-mg product. Our new data provide direct comparative pharmacokinetic analyses of the 300-mg products.

According to current guidance from the FDA Center for Drug Evaluation and Research, conclusions that two drug products are bioequivalent should reflect significant agreement in pharmacokinetic parameters such that the entire 90% confidence interval associated with the generic-to-reference ratio of geometric means should fall within the bioequivalence limits of 80 to 125%.[1] Budeprion XL 300 mg did not meet these criteria in our bioequivalence study, which involved 24 healthy fasting volunteers and used a single-dose crossover design (see graph). The extent of bupropion absorption after the administration of the generic product, as reflected in the area under the curve of the plasma concentrations plotted over time, was 86% of the absorption with the brand-name product (see graph), but the corresponding 90% confidence interval was 77 to 96%. In addition, the mean peak plasma concentration (C_{max}) observed after the administration of Budeprion XL 300 mg was only 75% of that observed after the administration of Wellbutrin XL 300 mg (90% confidence interval, 65 to 87). In certain study participants, the C_{max} and the area under the plasma-concentration curve for Budeprion XL were less than 40% of the values with Wellbutrin XL. The C_{max} values for hydroxybupropion, the major active metabolite of bupropion hydrochloride, also failed to meet the FDA bioequivalence criteria.

The other major difference observed between Budeprion XL

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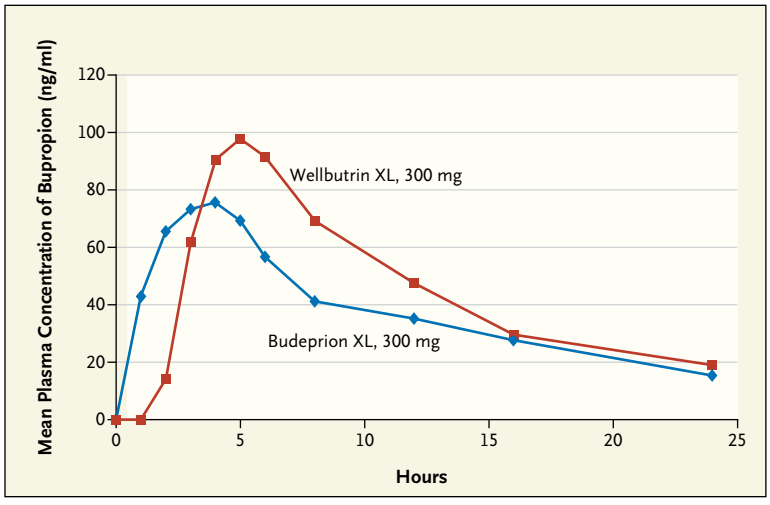

Mean Plasma Concentration of Bupropion (Budeprion XL and Wellbutrin XL) as a Function of Time in 24 Fasting Healthy Volunteers.

300 mg and Wellbutrin XL 300 mg was in the time to peak drug concentration in the blood (T_{max}) (see graph). Although FDA guidance does not include T_{max} as a criterion for bioequivalence of bupropion hydrochloride products, the T_{max} for Budeprion XL (4 hours) is shorter than that for Wellbutrin XL (5 hours). A similar difference in T_{max} values was also observed in the bioequivalence study of the 150-mg products that was originally used for extrapolation of data for Budeprion XL 300 mg. But because the comparative area-under-the-curve and C_{max} values for the 150-mg products fell within FDA parameters and were supported by data on the performance of the product in vitro, Budeprion XL 300 mg was approved.

The use of data extrapolation for the approval of Budeprion XL 300 mg should be considered in historical context. When applications for generic versions of Wellbutrin XL 300 mg began to come under FDA review in 2005, more than 11 million prescriptions for the brand-name product were being written each year. Programs to develop generic bupropion products, and the requisite bioequivalence studies, were important for addressing the widespread need for the treatment of major depressive disorder. At the same time, the FDA and sponsors recognized that bupropion conferred a dose-related risk of seizures, which the agency believed warranted a conservative approach to bioequivalence testing of bupropion in healthy volunteers. Bioequivalence studies that used only the lower strength (150 mg) reflected this conservative approach.

After the approval of Budeprion XL, the T_{max} disparity between Budeprion XL 150 mg and Wellbutrin XL 150 mg remained a source of concern. This concern, along with the reports that began surfacing after initial marketing of Budeprion XL 300 mg, prompted the FDA to recommend, in November 2007, that the sponsor conduct a clinical comparison with the 300-mg product. The FDA believed that the most appropriate population for this study would be patients who had reported a lack of efficacy or unwanted side effects after switching from Wellbutrin XL 300 mg to Budeprion XL 300 mg; the protocol therefore stipulated the enrollment of such patients. By early 2008, the sponsor had begun preparing to conduct the recommended study. Unfortunately, the study was terminated because of an inability to enroll a sufficient number of patients who met the entry criteria.

Given continuing questions about the efficacy of the 300-mg product, the FDA decided to conduct, under its own auspices, the bioequivalence study described here. Because the results indicated that Budeprion XL 300 mg cannot be considered therapeutically equivalent to Wellbutrin XL 300 mg, the FDA requested that the sponsors of Budeprion XL (Impax Laboratories and Teva Pharmaceuticals) voluntarily withdraw the 300-mg version from the market, which they agreed to do.

The results of the FDA-sponsored study have led the agency to review its approach to other 300-mg extended-release generic bupropion products. The agency has determined that direct bioequivalence studies using the 300-mg strength of the brand-name and generic products are appropriate and feasible. Accordingly, the FDA has requested that other makers of generic extended-release bupropion hydrochloride (Anchen, Actavis, Watson, and Mylan) perform bioequivalence studies of their 300-mg products. The agency is also updating its bioequivalence guidance for these products. As new information regarding these products becomes available, the agency will take any appropriate regulatory actions and will inform the public. Patients who are taking the 300-mg strength of generic extended-release bupropion products and have questions about their medication should be encouraged to

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speak with their health care provider.

The long delay between the approval of Budeprion XL 300 mg in late 2006 and the appearance of the bioequivalence results reported here, during which the product remained listed by the FDA as a generic substitute for Wellbutrin XL 300 mg, is problematic. Because of the risk of seizure associated with high doses of bupropion, the agency initially took a conservative approach to trial design. Today, the FDA has greater understanding of the risk of seizure with bupropion. At the time of the sponsor's 2007 study, some critics considered its design to be flawed. The results of the recent study by the FDA show that a design entailing the enrollment of a more accessible trial population might well have brought the bioequivalence data to light sooner. In retrospect, the conservative approach did not provide the right conclusions regarding therapeutic equivalence in a timely manner.

We do not believe that the results of the FDA study should cause concern regarding the overall reliability of the agency's approval process for generic drugs, including the use of extrapolation, when scientifically appropriate. Technical aspects of the Budeprion formulation may have led to the failure of extrapolation in this case. More information on this issue will be generated by the other sponsors' bioequivalence studies. The other 300-mg generic bupropion products do not use the same technology as Budeprion. The use of extrapolation for the approval of multiple strengths of generic drugs, which incorporates science-based reasoning, has been generally successful, and the FDA will continue to refine its approach to this method. The agency will also move more aggressively to perform its own studies when data are urgently needed. We wish to assure the public that drug products that are approved for generic use will continue to be held to high standards of quality, safety, and efficacy.

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Higher-Complexity ED Billing Codes — Sicker Patients, More Intensive Practice, or Improper Payments?

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A recent analysis of Medicare billing data for evaluation-and-management services, conducted by the Office of Inspector General (OIG) of the Department of Health and Human Services, showed that between 2001 and 2010, the proportion of claims for lower reimbursement categories decreased while the use of higher-paid categories increased across all visit types.[1] The largest increase reported was in level 5 emergency department (ED) visits (Current Procedural Terminology [CPT] code 99285; average reimbursement, $173) — from 27% to 48% of Medicare discharges (see graph).

Although the report didn't assess the reasons for higher billing levels, its findings have been amplified by investigative reports in the media suggesting that fraud is the cause. On September 24, 2012, a formal letter from the U.S. Departments of Justice and Health and Human Services to hospital leaders warned of an escalated effort to prevent fraud and abuse and explicitly linked higher bills to "gaming" made possible by new electronic health record (EHR) technology. The OIG report addressed only physician billing, not hospital billing, and the office has initiated further study into usage of all CPT codes. Although it's possible that "up-coding" facilitated by increasing use of EHRs has contributed to the trend, other causes such as changing demographics, shifting practice patterns, and the ED's evolving role in the health care system must also be considered.

To explore these potential contributors, I analyzed a nationally representative sample of Medicare ED discharges in the National Hospital Ambulatory Medical Care Surveys, using methods described previously and detailed in the Supplementary Appendix (available with the full text of this article at NEJM.org).[2] Like the OIG report, my analysis excludes the 35% of

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