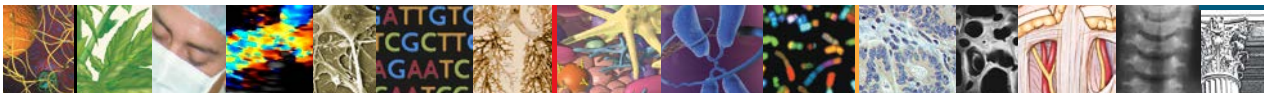

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Perspective

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FDA Approval of Doxylamine–Pyridoxine Therapy for Use in Pregnancy

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In 1983, the combination-drug product Bendectin (Merrell Dow), consisting of 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride per tablet, was voluntarily withdrawn from the U.S. market by the manufacturer. For the next 30 years, there were no medications that had been approved by the Food and Drug Administration (FDA) for the treatment of nausea and vomiting of pregnancy. Recently, the FDA approved Diclegis (Duchesnay), a product with the same combination of doxylamine and pyridoxine that had been marketed as Bendectin. The Bendectin experience serves as an informative case study of how decisions that are not science-based may affect the marketing and availability of a drug product and lead to adverse public health consequences.

Nausea and vomiting occur in as many as 80% of all pregnant women between 6 and 12 weeks of gestation. Symptoms are usually self-limiting and resolve with nonpharmacologic conservative measures. Roughly one third of women with nausea and vomiting of pregnancy have symptoms that are clinically significant, resulting in diminished quality of life. About 1% of pregnant women may have progression to hyperemesis gravidarum, a condition characterized by persistent vomiting, loss of more than 5% of body weight, ketonuria, electrolyte imbalance, acidosis, nutritional deficiencies, and dehydration, all of which pose further health risks to both mother and fetus.

Bendectin had originally been approved in 1956 as a three-agent formulation, consisting of 10 mg of dicyclomine hydrochloride (an antispasmodic agent), 10 mg of doxylamine succinate (an antihistamine), and 10 mg of pyridoxine hydrochloride (vitamin B_6). In the 1970s, dicyclomine hydrochloride was determined to be ineffective for treating nausea and vomiting of pregnancy, and Bendectin was consequently reformulated as a two-drug combination that the FDA approved in

1976. From 1956 to 1983, Bendectin was widely prescribed; at the peak of its use, as many as 25% of pregnant women in the United States took the product.[1]

In the historical context of two notorious teratogens, thalidomide and diethylstilbestrol, initial reports questioning the safety of Bendectin ignited public fears. In the late 1960s and through the 1970s, letters to the editors of medical journals began to report an association between Bendectin use and birth defects. The mainstream media reported stories as well, and law firms launched publicity campaigns claiming that Bendectin was a teratogen. In January 1980, the first major lawsuit (*Mekdeci v. Merrell National Laboratories, a Division of Richardson-Merrell, Inc.*) was heard in Florida, and by the time the product was withdrawn in 1983, there were more than 300 pending lawsuits attributing various birth defects to the use of Bendectin. Limb-reduction deformities, cardiac defects, oral clefts, and genital tract malformations were among the conditions alleged to be associated with Bendectin use. However, courtroom testimony claiming that Bendectin was a human teratogen was markedly devoid of evidence-based corroboration.[2] Merrell Dow indicated that its decision to withdraw Bendectin was based not on safety issues but on financial concerns. In the wake of the Bendectin allegations, the company's insurance premiums had risen to $10 million per year, only $3 million less than the total income from Bendectin sales.

In 1979, the FDA issued a "Talk Paper" stating that studies in animals and several large epidemiologic studies had provided "no adequate evidence linking Bendectin with an increased risk of birth defects." In September 1980, the FDA Fertility and Maternal Health Drugs Advisory Committee reviewed 13 epidemiologic studies, 11 of which had found no association of Bendectin with an increased risk of birth defects and 2 of which suggested a weak association with heart defects and cleft palate. The committee took into account the strengths and limitations of these epidemiologic studies and unanimously concluded that, overall, the data did not show an association between Bendectin and birth defects. Nevertheless, the committee recommended that product labeling be revised to include a patient package insert and to narrow the indication to nausea and vomiting of pregnancy that had not been alleviated with conservative measures. In addition, the continuation of epidemiologic studies was encouraged.

The decades-long history of doxylamine–pyridoxine emphasizes the importance of making clinical decisions on the basis of scientific evidence. The FDA's approval of Diclegis was based on data showing that the combined treatment is not teratogenic.

Two independent meta-analyses (pooled observational studies) of Bendectin and congenital birth defects, published after the product was withdrawn from the market, similarly concluded that Bendectin is not a human teratogen.[3,4] The first of these analyzed 17 cohort and case–control studies conducted between 1963 and 1985, and the second involved 27 cohort and case–control studies conducted between 1963 and 1991. In addition, data maintained by the Birth Defect Monitoring Program of the Centers for Disease Control and Prevention (CDC) did not show an association between birth defects and Bendectin use. These data show that during the period from 1985 through 1987, which was after the product was withdrawn, the incidence of birth defects was the same as that seen during the peak period (1978 through 1980) of Bendectin use. Given that as many as one quarter of U.S. pregnant women were using Bendectin by 1980, the fact that birth-defect incidence did not fall after product withdrawal is inconsistent with drug teratogenicity.[5]

Aside from the fact that a considerable quantity of data, both direct and indirect, has failed to produce evidence of Bendectin-associated teratogenicity, the withdrawal of Bendectin may actually have had adverse effects on pregnant women. According to data from the National Center for Health Statistics, the number of hospitalizations in the United States for nausea and vomiting of pregnancy increased from 7 per 1000 live births (baseline data from 1974 to 1980) to 15 to 16 per 1000 live births during the period from 1981 through 1987.[5] Furthermore, it is not possible to

know how many women, fearing that they had caused harm to their fetus, underwent elective abortions; anecdotal reports suggest that some did.

The decades-long history of doxylamine–pyridoxine emphasizes the importance of making clinical decisions on the basis of scientific evidence. The FDA's approval of Diclegis was based on efficacy and safety data from a randomized, placebo-controlled clinical trial and also took into account the extensive data described above showing that combined treatment with doxylamine succinate and pyridoxine hydrochloride is not teratogenic. These data reveal a favorable risk–benefit profile for Diclegis in the treatment of nausea and vomiting of pregnancy that has been refractory to nonpharmacologic treatment. Although combined doxylamine–pyridoxine treatment is already the single most studied pharmacologic therapy for use in pregnancy, the FDA will continue to carefully monitor postmarketing data related to Diclegis use. The Diclegis story reminds us that reliance on evidence-based practices, with the use of multiple streams of data, is the most appropriate way to evaluate drug safety.

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

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1. Holmes LB. Teratogen update: bendectin. Teratology 1983;27:277-81.
2. Brent RL. Bendectin: review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent tortogen-litigen. Reprod Toxicol 1995;9:337-49.
3. Einarson TR, Leeder JS, Koren G. A method for meta-analysis of epidemiological studies. Drug Intell Clin Pharm 1988;22:813-24.
4. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. Teratology 1994;50:27-37.
5. Kutcher JS, Engle A, Firth J, Lamm SH. Bendectin and birth defects. II: Ecological analyses. Birth Defects Res A Clin Mol Teratol 2003;67:88-97.

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Point-of-Care Ultrasound in Medical Education — Stop Listening and Look

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In 1816, the French physician René-Théophile-Hyacinthe Laennec, inspired by children communicating by tapping a pin on one end of a long piece of wood and listening at the other end, rolled a "quire" of paper into a cylinder to listen to the heart of a sick young woman, instead of placing his ear directly on her bare chest. This improvised tool designed to protect a patient's modesty evolved into the wooden instrument that eventually became the modern stethoscope. Nearly 200 years later, the stethoscope is unique among medical devices in that it is used by virtually every type of physician and, with the exception of electronic versions offering amplification and filtering, has changed minimally in style and technology. A fixture around the necks of physicians and medical students, it endures as an icon of our profession.

Yet during the past 50 years, diagnostic ultrasonography has replaced auscultation as the primary method of evaluating the mechanics of the heart and peering into the abdomen, vasculature, and uterus without exposing patients or fetuses to ionizing radiation. In cardiovascular medicine, echocardiography is the most used and cost-effective imaging method, despite the development of many other powerful new technologies. Ultrasound machines were once uniformly bulky, cartlike devices that were rolled awkwardly around hospital wards and into cramped patient rooms, but they have shrunk drastically with the advent of faster microprocessors and improvements in miniaturization. Now, fully functional ultrasound machines are available in the form of laptop computers, and devices with slightly reduced functionality that are not much bigger than a smartphone fit in clinicians' pockets or palms (see photo).[1] Moreover, as these devices become less expensive — they're currently priced under $10,000 — they're becoming more accessible to physicians and specialists beyond radiologists and cardiologists.

Despite some protectionist attempts to restrict the use of new imaging technologies to professionals with comprehensive training, the broadening use of these devices has served to demystify and universalize ultrasonography.