

The contribution of tumoral D3 to sunitinib-associated hypothyroidism probably varies from one tumor type to another. The findings of Foukakis et al. show that D3 induction by sunitinib extends beyond GISTs to breast cancer, and the absence of D3 induction that we observed in isolated breast-cancer cells suggests that sunitinib may indirectly stimulate tumoral D3 *in vivo*. Although we agree that the role of tumoral D3 in the absence of therapy should be further investigated, the ability of tumoral D3 to cause hypothyroidism without treatment with tyrosine kinase inhibitors is well established in hemangiomas and other tumors.⁴ With regard to GISTs, the index patient we described had extremely high D3 expression in tumor tissue obtained from his original surgery (before any medical treatment), and the unusually high prevalence of hypothyroidism among adults with GISTs before sunitinib treatment (22%)⁵ suggests that consumptive hypothyroidism occurs in untreated patients. For this reason, vigilance is justified in this population, and we recommend that thyroid

function be assessed in any patient with a large GIST burden, even if tyrosine kinase inhibitors have never been used.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1405198

New FDA Breakthrough-Drug Category — Implications for Patients

TO THE EDITOR: Darrow et al. (March 27 issue)¹ present an incomplete and misleading review of the Food and Drug Administration (FDA) programs that are available to expedite drug development, review, and approval. As the authors note, drug regulation involves balancing the potential benefits of access to a therapy against the potential risks associated with the drugs and the prognoses of patients with the diseases that the therapies are intended to treat, on the basis of evidence of safety and effectiveness. Any evaluation of drug regulation should present a complete picture of the available evidence regarding the effect of reforms, including their impact on facilitating the generation and effective use of evidence.

The FDA has four distinct mechanisms to speed the development and availability of drugs for treating serious or life-threatening conditions: priority review, accelerated approval, fast-track review, and most recently, breakthrough therapy.² Although these approaches all aim to advance the availability of safe and effective

products, they use different selection criteria and target different parts of the drug-development process.

Darrow et al. claim that the FDA applies expedited-approval programs too liberally, noting that 56% of drugs approved in 2012 used expedited-approval pathways. However, the authors offer no analysis of these drugs and do not acknowledge that almost half the new drugs that were approved in 2012 were for orphan diseases or cancers, many of which had no effective treatment option.

Most drugs that have received accelerated approval have completed rigorous postmarketing studies, been converted to full approval, and often become standard of care. Furthermore, the FDA has taken notable steps, including its Sentinel Initiative, to enhance the availability of postmarketing safety evidence that is very difficult to obtain in the premarket setting.³

Nothing in law or FDA guidance indicates that the breakthrough-therapy designation lowers the standards for approval, nor do the au-

thors provide evidence to support this claim. The breakthrough-therapy designation was created to facilitate a collaborative “all hands on deck” approach between the FDA and the drug sponsor on the basis of preliminary clinical evidence of substantial improvement over existing therapies for a serious or life-threatening disease.⁴ This approach does not confer a less rigorous path to approval. The majority of the drugs receiving the designation are still undergoing clinical trials, and only four have received FDA approval. All four are clear advances in the treatment of life-threatening diseases that previously lacked effective therapies. FDA programs have evolved over recent years to support the development and review of products that have had a lasting effect on disease treatment in the United States, positively affecting thousands of lives.

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DOI: 10.1056/NEJMc1405337

TO THE EDITOR: The Infectious Diseases Society of America (IDSA) is concerned that the article by Darrow et al. misrepresents new legislation that would allow the FDA to approve antibiotic agents on the basis of small clinical trials in limited populations — specifically, in patients with serious or life-threatening infections and no other treatment options. New antibiotics that are ap-

proved through this pathway must be shown to be safe and effective and would carry a special label telling clinicians to use them with extreme care and only for patients with unmet needs. The bill also directs the FDA to review marketing materials in advance and directs the Centers for Disease Control and Prevention to monitor the use of these drugs.

As an infectious diseases physician, I share the authors' concern about approving potentially risky drugs. But that concern must be balanced with the reality that patients are dying because we lack effective antibiotics to treat the infecting organisms. For years, the IDSA has been fearful of a return to a preantibiotic era. Sadly, for more and more patients, that fear is today's reality because the antibiotic pipeline is nearly dry.

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DOI: 10.1056/NEJMc1405337

TO THE EDITOR: Darrow et al. imply that the ability of severely ill patients to make critical decisions about their therapy is impaired by their dire situations. The Leukemia and Lymphoma Society (LLS) believes that patients, in concert with their physicians, are in the best position to determine what is right for them and how much risk they are willing to take. Such treatment decisions are increasingly personalized, thus making it difficult for broad populations to be treated similarly. Therefore, the LLS is fully supportive of early-access programs, including compassionate-use programs, for patients who are out of other options. Moreover, our patients have benefited from expedited-approval pathways at the FDA, because such approaches accelerate access. We applaud the FDA for approving two breakthrough-therapy medications for hematologic cancers (ibrutinib [Imbruvica, Pharmacyclics and Janssen Biotech]

and obinutuzumab [Gazyva, Genentech]) that are offering promise for patients with limited alternatives. We do agree that regulations requiring pharmaceutical and biotechnology companies to follow through on postmarketing studies to confirm data in a timely fashion should be strictly enforced and that the FDA should continue to ensure compliance with these regulations.

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DOI: 10.1056/NEJMc1405337

TO THE EDITOR: The article by Darrow et al. summarizes prior government efforts to expedite the availability of new therapeutics and discusses the implications of the breakthrough-therapy designation. It is worth clarifying that gemtuzumab ozogamicin was not approved for the treatment of pediatric leukemia.

Three trials evaluated the efficacy and safety of the single agent gemtuzumab ozogamicin. The population for the initial report included 142 patients with a median age of 61 years who had a first relapse of acute myeloid leukemia (AML).¹ A total of 30% of the patients had remission. The FDA granted approval for gemtuzumab ozogamicin in the treatment of patients with a first relapse of CD33-positive AML who were 60 years of age or older and who were not considered candidates for cytotoxic chemotherapy.^{2,3}

However, the required postapproval study, combining gemtuzumab ozogamicin with daunorubicin and cytarabine in adults under the age of 61 years with new-onset AML, did not confirm clinical benefit.⁴ This confirmatory study was performed in a clinical setting that differed from the setting of the original studies.² The sponsor voluntarily withdrew the new drug application in 2010.

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DOI: 10.1056/NEJMc1405337

THE AUTHORS REPLY: McClellan and Sigal overlook the fact that the FDA itself acknowledges that its innovations expediting drug approval lower the required evidentiary threshold. The agency describes the fast-track designation as a result of patients' willingness to accept "greater risks" from products treating life-threatening illnesses¹ and has noted that accelerated approval may expose patients to "drug[s] that will ultimately not be shown to provide an actual clinical benefit."²

The new breakthrough-therapy designation may not lower evidentiary standards in the same manner as other expedited-approval programs, but it can do so indirectly by generating premature enthusiasm that increases pressure to approve and prescribe a drug. This approach can lead to uncontrolled or truncated trial designs that are less robust than standard trials, and it can normalize the regulatory use of biomarkers that are less likely to predict clinical outcome.² These expedited-approval programs have indeed altered approval standards: although the legal standards of "safe" and "effective" remain, the evidentiary standards for meeting those criteria have been loosened. Although the FDA Sentinel Initiative can provide some postmarketing information, the agency is still learning how to use this tool,³ and postmarketing surveillance should not replace adequate premarket assessment.

Although Murray's warning of a return to a preantibiotic era is a call to action, so too is the possibility of regressing to the pre-1962 era during which ineffective drugs often received FDA approval. This concern is particularly salient for

new antibiotics, which are usually approved on the basis of trials showing noninferiority (rather than superiority) to comparator agents. These agents are also withdrawn from the market more commonly than all other drug categories.⁴ Early access can benefit patients, as Velleca asserts, but only if the drug is in fact effective — the very question that only rigorous evidence development can answer. His contention that patients and physicians “are in the best position to determine . . . how much risk they are willing to take” may be true but minimizes the crucial role of governmental benefit–risk assessment of medications. Pressing treatment needs should be met with intensified development efforts, not new designations.

Ricart clarifies the original indication of gemtuzumab ozogamicin, which is now reflected in the online version of our article.

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DOI: 10.1056/NEJMc1405337

Procedural Sedation and Analgesia in Children

TO THE EDITOR: The video by Krauss et al. on procedural sedation and analgesia in children (April 10 issue)¹ was thorough and detailed. However, I am very concerned that 45 seconds into the video an injection into intravenous tubing pushes air bubbles toward the patient. The potentially disastrous consequences of air in intravenous lines are well known, particularly in children with intracardiac shunts.

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DOI: 10.1056/NEJMc1405676

TO THE EDITOR: Pediatric patients have limited respiratory reserve and are susceptible to the rapid development of hypoxemia. The emergency equipment mentioned by Krauss et al. does not address the management of an unanticipated difficult or impossible bag-mask–ventilation scenario or the use of emergency airway devices,

including a laryngeal mask airway of the appropriate size,¹ an endotracheal tube, and a laryngoscope, which should also be available. Furthermore, the authors state that the administration of supplemental oxygen before and during sedation renders pulse oximetry ineffective with regard to early warnings of respiratory depression and recommend the use of capnography when supplemental oxygen is used. These aspects of the video could lead to the misconception that the observation of ineffective pulse oximetry in the early detection of hypoventilation is related to the administration of supplemental oxygen or that capnography cannot be used if supplemental oxygen is not used simultaneously. Nevertheless, supplemental oxygen is recommended before and during sedation, especially in pediatric patients, owing to their greater susceptibility to hypoxemia.

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