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Information to Contributors appears on pages 36–38 of the 3 January 1992 issue. Editorial correspondence, including requests for permission to reprint and reprint orders, should be sent to 1333 H Street, NW, Washington, DC 20005. **Science Telephone:** 202-326-6500. London office: 071-435-4291. **Subscription/Member Benefits Questions:** 202-326-6417. **Other AAAS Programs:** 202-326-6400.

LETTERS

Chirality and Drug Development

In his article "Looking glass chemistry" (Research News, 15 May, p. 964), Ivan Amato predicts, on the basis of statements by some industry researchers, the demise of racemates as viable new drug candidates. While few would argue that a single purified enantiomer is the better drug substance candidate in many cases, attaining this goal is not always technologically or economically practical.

Amato states that "regulatory incentives . . . are . . . pushing drug companies toward single-enantiomer chemistry." However, the Food and Drug Administration (FDA) policy statement he cites (*1*), which was issued after the article appeared, actually says, "Although it is now technologically feasible to prepare purified enantiomers, development of racemates may continue to be appropriate." A 1990 paper (*2*) by a Pharmaceutical Manufacturers Association committee agreed with this view, concluding, "The sponsor should decide whether to market one enantiomer or the racemate on a case-by-case basis, considering all available data, and provide regulatory bodies with information that delineates the safety and efficacy of the proposed drug substance."

There are several situations in which development of a racemate may be preferred. For example, each enantiomer may exhibit pharmacological and toxicological profiles similar to those of the racemate or be rapidly interconverted in vivo. Ibuprofen, pictured in the article, is a case in point. The less active R enantiomer of ibuprofen is metabolically converted to the active S enantiomer in the body; therefore, administering the racemate to a patient offers no disadvantage relative to the active enantiomer alone (*3*). With other compounds, one enantiomer may be found to be pharmacologically inactive, while the racemate is demonstrated to be safe and effective. Also, a separation of enantiomers that can be performed on drug quantities sufficient for laboratory testing cannot always survive the scale-up process to production volumes. In some cases, the enantiomers may even produce different therapeutic effects. As noted in the FDA policy statement, this situation occurs with sotalol (*1*).

It now takes 12 years and an investment of $231 million before the average new molecular entity reaches the pharmacy shelf (*4*). A pharmaceutical company will carefully consider the expected benefit before embarking on a course that may substantially increase the cost of a new medicine or delay its availability to patients who need it.

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1. "FDA's policy statement for the development of new stereoisomeric drugs" (Food and Drug Administration, Rockville, MD, May 1992).
2. PMA Committee on Racemic Mixtures, *Pharm. Technol.* 14, 46 (1990).
3. A. J. Hutt and J. Caldwell, *J. Pharm.* 35, 693 (1983).
4. J. A. Di Masi *et al.*, *J. Health Econ.* 10, 107 (1991).

In the boxed piece "Government smiles on one-handed drugs" (Research News, 15 May, p. 965), it is mentioned that I expected that a forthcoming policy statement would officially make single enantiomer the standard in drug development. The policy statement to which I referred does not mandate development of single isomers and is flexible enough to allow for the development of racemates when adequate data are available to ensure the safety and effectiveness of resulting drug products.

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Thrombin and Its Inhibitors

With respect to Jean Marx's interesting article "A new link in the brain's defense" (Research News, 29 May, p. 1278), I would like to say that the work performed in my laboratory during the past 20 years would not have been possible without the dedication of a number of students and postdocs who made contributions that were decisive in the characterization of glia-derived nexin or protease nexin–1 (PN-1) and in suggesting the importance of the regulation of thrombin-like activity in the nervous system. These include the first authors of the publications referred to in Marx's article: