and hence they have the potential to reflect species-level extinctions more closely than do family-level data. Generic-level data, on the other hand, suffer larger problems in determination, both taxonomically and stratigraphically. The available generic-level data set (*4*), not yet published, is a developing assemblage of information from many sources, and it makes no claim to be complete, unlike the available family-level data sets (*2*, *5*), which are both best efforts at a complete coverage of all available paleontological data.

Culling of raw data on fossil distributions can be justified in various ways for different purposes (*4*). However, I decided to present the data in a raw form, corresponding precisely to the available published data base (*2*). The information is now widely available in printed and electronic form (*6*), and further studies, using different styles of cull, may be carried out.

Rampino and Haggerty find that the seven extinction events identified in my article give a periodic signal of about 27 million years on the basis of Fourier analysis, although the result is not statistically significant. They note also that my identification of additional events that do not fit the periodic signal in no way denies the possibility of a mix of periodic and nonperiodic extinction events. This is obviously the case (*4*), but I found seven possibly periodic, and seven nonperiodic peaks. These two classes of extinction peaks do not fall into two distinctive classes.

The proposal of periodicity in mass extinctions was based on analyses by Raup and Sepkoski in 1984 (*1*), and their subsequent work (*4*, *6*) apparently strengthened the quality of the periodic signal they found. I have no strong view either way about the existence, or not, of a periodic cause of mass extinctions, but I had expected a stronger match of timings than I found in my article. The data are improving all the time (*7*), and it is the responsibility of the proponents of periodic extinction to show that paleontological data support their view. Ten years of data analysis and of search for astronomical drivers have not produced dramatic confirmation of periodicity.

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FDA Antibody Rules

Richard Stone's article "Companies fear FDA rule on antibodies" (News & Comment, 28 Apr., p. 494) raises legitimate issues of concern in the regulation of antibodies. It does not, however, describe the complexity of the current Food and Drug Administration (FDA) review system, which allows FDA considerable latitude in performing a risk-to-benefit analysis of new products and requesting an appropriate data set based on this analysis.

Whether FDA classifies a product as Class-I, -II, or -III, it has three very different administrative review options predicated on the risk, technical features, and intended use of the product. For low-risk products, FDA can use a focused labeling review aimed at ensuring proper information is present, but without requiring a detailed

analysis of a submission; for intermediate risk products, FDA can require submissions to undergo more extensive review of performance and labeling based largely on analytical data; for high-risk products, in-depth and intensive FDA review, including analysis of clinical data, can be required. Although the petition submitted by the College of American Pathologists and supported by the October advisory panel meeting did call for classification of immunohistochemical stains as Class-II devices, this panel decision was made with the understanding that a large number of well-characterized stains would be reviewed as Tier-I products and handled in an expeditious and streamlined manner. Appropriate labeling and data requirements for these submissions are outlined in several guidance documents developed with extensive input from both the user and manufacturing communities.

It is also important to note that antibodies may be marketed in the United States with three different labels: "for research use only," "for investigational use only," or "for in vitro diagnostic use." The FDA believes that products labeled "for research use" should be appropriately labeled and used for basic research, that products labeled "for investigational use" should be appropriately labeled and used for applied clinical research, and that products labeled "for in vitro diagnostic use" should be reviewed by FDA so that performance characteristics, labeling, and compliance with good manufacturing practices are ensured. FDA efforts dating back to 1991 have been solely directed at providing compliance with these rules of product transmission from research to clinical use. As FDA continues to develop guidance in this matter, the agency has been keenly aware of and sensitive to the need to accommodate existing clinical practice.

A final decision about how to handle immunohistochemical stains has not been made by the agency. On the basis of input derived during and after the October panel meeting, FDA is assessing options. We plan to publish a notice in the *Federal Register* in the near future that will outline a program but allow for continued public input.

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Pending FDA regulation of antibodies can potentially have a significant negative impact on both research and clinical diagnostic laboratories. The stated goal of the FDA is to match the level of regulation with the level of risk associated with the product. In this light, there are clear scientific and statutory facts that support the regulation of antibodies as Class-I devices. Many of these were noted in a September 1994 position paper presented to the FDA by the Joint Council of Immunohistochemical Manufacturers (JCIM) in conjunction with the Health Industry Manufacturers' Association (HIMA).

Immunohistochemistry (IHC) stains are, in practice, safety, and effectiveness, close to the biological stains, which are Class-I devices. Indeed, the level of risk associated with IHCs may be lower than that with the biological stains (*1–3*). Leading pathologists speaking at the June 1994 FDA workshop on IHCs emphasized the low level of risk associated with these products (*1*).

The College of American Pathologists (CAP), in reiterating their support for Class-II, have referenced the "potentially greater degree of interlaboratory variability" associated with IHC (*4*). That variability is related more to the tissue fixation process and the interpretation, not the quality of the antibody, as attested by the CAP's own proficiency testing results. Therefore, no degree of FDA regulation of the antibody alone will have an impact on interlaboratory variability.

Although, as Stone's article emphasizes, there will be substantial financial impact of a Class-II regulation on both end users and manufacturers, the manufacturers' position in support of Class-I regulation is soundly based in statutory and scientific-clinical fact. These products have achieved the level of standard of care without FDA review. Increased regulation, while limiting access and raising costs, offers no "value added," that is, it contributes nothing to the safety and effectiveness of the pathologist's interpretation—the ultimate outcome affecting the patient.

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