every report of an adverse reaction if, in our best judgment, there does not appear to be a reasonable relationship to the drug. An attempt has been made to provide the physician with some guidance as to the relative frequency with which the listed adverse reactions may occur. We are following the clinical experience with this drug closely and will make further labeling revision if and when indicated."

12. *September 30–October 6, 1966.* No reply to our September 2 letter had been received from the Food and Drug Administration. On September 30, we started our mailing to doctors, and on October 6 notified the FDA that the revised circular had "just been mailed." Enclosed in the letter was the circular, the transmittal letter and the envelope which contained in large red letters, "Do Not Discard Before Reading—Drug Safety Information." The revisions were noted in boldface type so that they would not be missed by the readers.

Although the letter sent out to doctors was clearly marked as noted above, and the enclosed revised insert was made easy for the physician to read, and the body of the letter conveyed what it was intended to convey, it did contain first and last sentences that tended to give it a promotional overtone. In retrospect, we think it should not have had those sentences in it. We do not do everything perfectly, and did not do so here. Nevertheless, we think that the essential intent and message of the letter was clear, and that Dr. Jennings' categorical opinion that original intent was "completely lost" (page 4695) is overstated.

During the course of these discussions with the FDA, we found ourselves involved in differences of medical opinion about the implications of the reports of adverse reactions and side effects of the drug. In terms of telling physicians about them, we were of the opinion that placing before them a mass of detail, much of it repetitious, would tend to obscure the really important warnings. As to the reports themselves and their significance, there were not unnatural differences of opinion. Our medical staff felt, and still does, that nothing essentially new was emerging from these reports, that the increasing number of reported reactions reflected the increasing use of the drug rather than an increasing incidence of reactions, and that as more experience was gained what was emerging was an expected refinement of the original essential pharmacologic profile. The Food and Drug Administration people appeared to think differently. It did not—and does not now—follow that they were right in this opinion.

A good example of this difference of opinion is our view of the value and proper use of the drug in cases of juvenile rheumatoid arthritis. Dr. Jennings, during his testimony, refers to reports of deaths in children associated with the use of indomethacin. He disposes of a number of these cases as probably not due to the drug, but reserves opinion as to several. There is a considerable difference between a drug's being possibly linked to a death, and definitely related to it. The FDA is understandably cautious and has consistently singled out pediatric age groups as a patient population bearing risks beyond the adult group.

From the beginning, because the FDA did not accept our pediatric data, our domestic package circular included a specific contraindication against the use of 'Indocin' in children of pediatric ages.

During our discussions with the FDA in the spring and summer of 1966 about the revision of our labeling, the FDA itself *did not request us* to include any statement in the circular referring to fatalities in children. The only difference between us at that time was whether the existing contraindication of 'Indocin' for children was sufficient, or whether it should be strengthened by the addition of a phrase at the beginning of the circular stating "Not for Use in Children."

We did not believe then and we do not believe now that this addition was necessary or desirable. In the light of the FDA's desire for more emphasis, we did italicize the portion of the circular containing the specific contraindication for use in children, so that it would come even more prominently to the attention of doctors. Moreover, we added an additional paragraph, printed in boldface type in the revised circular, calling attention to the fact that 'Indocin' could mask the existence of infection and reminding physicians that it should be used with caution in patients with existing infections. In our scientific opinion, the reported deaths in children were related more to the existing complications of a serious infection in these patients than to the fact that they were children.

FDA insisted in meetings that followed the events summarized above that we make a further amendment adding a specific statement at the beginning of the circular that the drug should not be prescribed for children, and it requested for the first time that we refer in the contraindications to reports of severe reactions, including fatalities, in a few cases of severe juvenile rheumatoid arthritis.