see whether the data available to us suggested the need for package circular revisions.

4. *May 2, 1966.* As a follow-up to the April 19 conference our Dr. Shaffer telephoned Dr. Seife and asked if he would provide us with the type and number of adverse information reports they had received through the FDA Adverse Reaction Reporting Program. Dr. Seife called back the same day and gave us this information, characterizing the reports with regard to the role "Indocin" may have played. He promised to keep us informed as additional reports came in to FDA.

5. *May 5, 1966.* Letter from Dr. Ruskin of the FDA Division of New Drugs, primarily relating to the pending NDA on an "Indocin" formulation. It "recommended that revised labeling be submitted supplemental to your approved application for the capsule form to contain the most recent reports of adverse reactions which are not in the current labeling. . . ." In this letter Dr. Ruskin requested that a statement be added in boldface type to the warning section of the labeling that this was "not an innocuous drug," and should not be used for other than recommended indications, and not be used in women of childbearing age. *"We recommend that these labeling revisions be discussed with the New Drug Surveillance Branch. . . ."* (Italic added.)

6. *May 27, 1966.* Our Dr. Shaffer telephoned Dr. Seife of the New Drug Surveillance Branch to arrange for the requested discussion. We suggested a meeting on June 6, but Dr. Seife was "occupied with another problem" and said he "would like to arrange for such a conference before the end of June." It was left that Dr. Seife would let us know when he was available. Additional adverse information FDA had received from March 24 through May 5 was communicated in this conversation.

7. *July 1, 1966.* Our Dr. Shaffer telephoned Dr. Seife of FDA to ask about the proposed meeting. Dr. Shaffer learned that Dr. Seife was "out of town" and that Dr. Jennings, Acting Director of the Drug Surveillance Branch, should be called.

Dr. Shaffer called Dr. Jennings and learned that the matter had been reassigned to him. He said he would discuss with Dr. Ruskin the May 5 letter we had from Dr. Ruskin, but that if any *urgent changes in labeling were necessary,* these could be made without submitting a new drug application supplement for FDA approval. Dr. Shaffer told Dr. Jennings that *"in order to avoid subsequent changes requiring reprinting etc., we requested an opportunity to discuss labeling revisions with them as requested by the Ruskin letter of May 5, 1966."*

Dr. Jennings asked that we "check back with him in about one week."

8. *July 15, 1966.* Conference in Washington between FDA and Company medical representatives. Dr. Seife was to enter the hospital for surgery and our labeling matter had been assigned to Dr. Standard.

A summary of major labeling changes prepared by Dr. Seife was reviewed in detail. Dr. Seife told us *the recommendations outlined during this discussion would be sent to us in the form of a letter.*

9. *August 4, 1966.* Dr. Shaffer wrote to Dr. Jennings as follows:

"As you know, we met with Dr. Seife, Dr. Bryan, and Dr. Standard July 15 to discuss proposed revisions of the 'Indocin' Package and Direction Circulars. It was our understanding that Dr. Seife's proposed revisions would be submitted to us by letter. *We would appreciate receiving this communication so we may prepare an appropriate revision based both upon your proposals and our evaluation of the available data."* (Italic added)

10. *August 22, 1966.* No further communication from FDA had been received. On this date, the Merck Sharp & Dohme Division Counsel advised that, since we were willing to accept a number of the FDA recommended changes, we should make the changes voluntarily, notify the FDA, and mail the revised circular to physicians.

11. *September 2, 1966.* We submitted a supplemental NDA containing the added contraindications, precautions, and adverse reaction information, stating in the transmittal letter to the FDA: "We feel it important that these changes be placed into effect at the earliest possible time." The majority of the FDA's suggestions were adopted. We gave our reasons in that letter for not adopting all of them.

Our letter ended with the following paragraph:

"We appreciated the opportunity to discuss suggested changes in the Indocin labeling with your staff. We believe that the revised labeling submitted with this supplemental application accomplishes the mutual goal of providing the physician with the most useful information about this drug. To accomplish this goal, we have taken the position that the labeling should be unencumbered by a listing of