effective as Indocin; the third indicates the drug to be no more effective than a placebo, a pill containing an inert substance.

The reports raise questions not only about the agency's handling of Indocin, which was approved in June, 1965, but also about the law's strict requirement that "substantial evidence" of efficacy be demonstrated.

Merck & Co., the manufacturer, said Thursday that Indocin's safety and efficacy were established "by more than 300 clinical investigators" and by "a wealth" of experience.

The three journal reports were prepared by experts who performed well-controlled clinical investigations. And only selected patient groups got Indocin; other groups got aspirin, Indocin and aspirin, or aspirin and/or a placebo. These were highly sophisticated double-blind studies.

Neither patients nor physicians knew what was being administered until a code was broken at the end of the trials. Some patients were crossed over, that is, switched without disclosure from one group to another.

But Merck said some of the studies in behalf of Indocin it had submitted to the FDA also were double-blind. It also protested that Indocin worked with some rheumatoid arthritis victims with whom aspirin failed; and that in the other diseases for which Indocin is approved it allows successful control while aspirin does not.

VALUES IRREGULAR

In addition, the relative value of drugs in rheumatoid arthritis is hard to measure objectively, Merck said. Many patients are relieved of pain by aspirin; investigators are unwilling to substitute a placebo for test purposes, the company said.

Last October, Merck revised its prescribing brochure and mailed a copy accompanied by a letter to the Nation's practicing physicians. The letter cited "new cautionary information" but made no mention of fatalities.

By December, FDA knew of 329 adverse reactions, including seven deaths in children and nine in elderly persons. It termed the relation to Indocin clearcut in one fatality, "possibly clearcut" in three others and highly questionable in the rest.

The October Merck letter said that "144,000,000 patient days of therapy" had been accumulated with indomethacin, and that it "has become, next to aspirin, the most frequently prescribed antirheumatic drug." The characterization of Indocin as "antirheumatic" was later disallowed by the FDA.

DEATHS CITED

In November, a jolting warning letter was sent Canadian physicians by the Food and Drug Directorate, the FDA's north-of-the-border counterpart. The letters told of several indomethacin deaths in children and of a number of unexpected adverse reactions.

These included "not uncommon" and sometimes severe effects on the central nervous system, and blood diseases and blurred vision.

In upper case, The Canadian government letter said in capitals "That Indomethacin Should Not Be Used in Children . . ." In addition, doctors were warned that the drug "can mask the signs and symptoms of an infectious process or activate a latent bacterial infection."

In Washington, the FDA called in Merck. In December the company sent out a 2-paragraph letter which warned against Indocin use in children and called attention to the enclosed prescribing brochure which had again been revised to emphasize that warning.

Several months before the FDA approved Indocin in 1965, warnings against its use were published in the Medical Journal of Australia by physicians who "detailed an imposing list of side effects."

SUGGESTION'S ROLE

The double-blind study, reported in the British Medical Journal last Jan. 14 involved 28 persons for 10 weeks.

Although side effects "occurred more often with indomethacin" than with a placebo, the report inferred that "suggestion played a large part in determining both the incidence and variety . . ." The authors were three Welsh physicians, Phelim Donnelly, Kenneth Lloyd and Hubert Campbell.

The New England Journal of Medicine study, published March 2 by Drs. Robert S. Pinals and Sumner Frank of Boston, was done on 24 patients for a month. Two