

Table of Contents, Investigator's Brochure, Clinical Study Protocol, and a document called Chemistry, Manufacturing, and Controls (CMC) (97,98).

The Investigator's Brochure must include sections with the information indicated by the following bullet points (21 CFR §312.23 (a)(5)):

- A description of the drug substance and the formulation, including the structural formula.
- A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
- A summary of the pharmacokinetics and disposition of the drug in animals and, if known, in humans. This author points out that "disposition" can refer to Absorption, Distribution, Metabolism, and Excretion (ADME).
- A summary of information relating to safety and efficacy in humans obtained from prior clinical studies.
- A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

The Investigator's Brochure is like a typical review article, as might be published in an academic journal, in that it provides information that provides summaries on various topics. A goal of these summaries is to establish a

context for understanding other documents in the FDA-submission, such as the Clinical Study Protocol.

XIII. SPECIAL PROTOCOL ASSESSMENT

The Special Protocol Assessment (SPA) is a procedure involving meetings with FDA and a binding agreement from the FDA. The SPA takes the form of a submission from the Sponsor, where this submission addresses specific questions about, for example, study design, endpoints, data analysis, and package labeling. According to FDA's Guidance for Industry, the request for an SPA must include "specific questions about the protocol design and scientific or regulatory requirements to which the Agency can respond" (99).

The SPA includes a cover letter that reads, "REQUEST FOR SPECIAL PROTOCOL ASSESSMENT," a protocol, and a document containing questions from the Sponsor. Form FDA 1571 is used to transmit the SPA to the FDA. Usually, the SPA is used to submit questions about a protocol that is the Clinical Study Protocol. However, the SPA can also be used to submit questions about two other types of protocols, namely, Carcinogenicity Protocol and Stability Protocol. Since the SPA is submitted only after an IND is already in place, it should be noted that the SPA must be submitted in the form of an amendment to the

⁹⁷U.S. Department of Health and Human Services. Food and Drug Administration Guidance for Industry. INDs for Phase 2 and Phase 3 Studies. Chemistry, Manufacturing, and Controls Information; May 2003 (22 pp.).

⁹⁸Sheinin E, Williams R. Chemistry, manufacturing, and controls information in NDAs and ANDAs, supplements, annual reports, and other regulatory filings. *Pharm. Res.* 2002;19:217–26.

⁹⁹U.S. Department of Health and Human Services. Food and Drug Administration Guidance for Industry. Special Protocol Assessment; May 2002 (11 pp.).