Chapter 7.
Investigator’s brochures

Linda Fossati Wood

MedWrite, Inc., Westford, Massachusetts, USA

Introduction

All marketed drugs and biologics are sold accompanied by the package leaflet (European Union [EU]) [1] or a package insert (Japan and the United States) [2–5], documents that describe product characteristics (active and inactive ingredients, chemical structure, formula, and pharmaceutical properties), summarize all known nonclinical and clinical information, and provide guidance for dosing and administration. The contents of these ‘labels’ represent the culmination of all research and development testing and of negotiations with the health authority from whom marketing approval is requested. For a marketed product, labeling documents constitute the primary method of communication with the physician prescribing the product.

Package leaflets and package inserts do not exist in the pre-approval stage of drug and biologics development because the research necessary to write an insert is in progress. Therefore, the function of communicating all known product information is under the purview of a document called an investigator’s brochure, which contains a compilation of all known nonclinical and clinical information essential to use of the product in humans. During the course of product development, as additional studies are performed and the product’s safety and efficacy profile are better characterized, the investigator’s brochure goes through substantial changes and eventually provides the basis for labeling.

As with all written communication, an understanding of the audience is essential. The audience for an investigator’s brochure is clinical investigational site personnel, people actively involved in clinical medicine, who are generally found in hospitals or clinics. They are seldom in a position to sit and read, but they are directly in contact with study subjects so they must be thoroughly familiar with a product’s characteristics to ensure safe use. Therefore, a good investigator’s brochure is brief (approximately 50 pages for the United States; see side bar for more information concerning investigator’s brochures in Japan), focuses clearly on details most critical to subject
safety and potential benefits, and refers the reader to additional materials available from the sponsor if expanded information is desired. Use of bulleted lists, tabular displays, and figures is particularly helpful.

Investigator’s brochures are written using the ICH E6 Guidance [6] and in close collaboration with a multidisciplinary team that usually includes medical, nonclinical, manufacturing, and regulatory expertise and possibly other groups at a company. The guidance contains an outline of suggested contents in three fundamental areas:

- Nonclinical: testing in animals
- Clinical: testing in humans
- Drug description and chemical or biologic characteristics: formulation, dosing, administration, and storage information

It is not necessary to follow this outline exactly. Instead, the organization should always be dictated primarily by logic and good communication principles, but careful consideration should be given to including all content if possible. This chapter describes writing an investigator’s brochure in terms of these areas of content and describes changes in the balance of nonclinical and clinical information during the life cycle of the brochure.

Side bar: Lessons learned

When preparing investigator’s brochures for use in Japan, it is important to know that this document is used somewhat differently in Japan compared with Europe and the United States. In Europe and the United States, the investigator’s brochure is considered to be the beginning of the package insert for a marketed product. The investigator’s brochure is quite an extensive package insert. It includes a large amount of nonclinical data because clinical data on the product or the indication are limited in the early stages of development. As more human data are collected, the usual procedure is to reduce the volume of nonclinical data, either by additionally summarizing or completely eliminating some of the nonclinical studies. This procedure is modified in Japan, where the regulatory agency uses the investigator’s brochure almost like an IND. Nonclinical data are not removed, and as new studies are added, the brochure can become larger. Many companies that develop drugs globally place the nonclinical data in appendices to the brochure. In this way, the main body of the brochure is the same globally – important because it is labeling and a product must be labeled consistently – but the need for all nonclinical data, particularly animal toxicology studies, is met for the Japanese authorities.