the prior filing of a New Drug Application (NDA) and approval of the FDA. It became the responsibility of the FDA to either grant or deny permission to manufacture and distribute a new product after reviewing the applicant's filed data on the product's ingredients, methods of assay and quality standards, formulation and manufacturing processes, preclinical (animal, tissue, or cell culture) studies including pharmacology and toxicology, and clinical trials on human subjects.

Although the Act of 1938 required manufactured pharmaceutical products to be safe for human use, it did not require them to be efficacious. Subsequent legislation, as described later in this chapter, requires that a drug approved for marketing in the United States be both safe and effective for the condition for which it is intended. Many drugs that had been on the market prior to this Act were allowed to remain on the market if their formula was unchanged and they were "grandfathered" in by the Act: examples include selected dosage forms of acetaminophen, codeine phosphate, codeine sulfate, hydrocodone, levothyroxine, morphine, nitroglycerin, oxycodone, pilocarpine hydrochloride, potassium chloride, potassium iodide, sodium fluoride, and others.

Durham-Humphrey Amendment of 1951

The Durham-Humphrey Amendment of the Federal Food Drug and Cosmetic Act established a legal distinction between prescription and over-the-counter (OTC) or nonprescription drugs. Until that time, all drugs could be purchased over the counter by consumers.

Medications deemed safe enough by the FDA for self-treatment are made available to consumers for direct purchase whereas medications requiring professional diagnosis for their safe and effective use must be dispensed only upon a valid prescription or institutional medication order. Prescription drugs must bear the symbol "R_x Only" or the legend "Caution: Federal Law Prohibits Dispensing Without Prescription." New drug substances are limited to prescription-only dispensing. However, their legal status may be changed to OTC, albeit usually at lower recommended dosage, should they later be considered useful and safe enough for the lay person's discretionary use. Examples of such drugs include ibuprofen, ketoprofen, cimetidine, loratadine, and ranitidine.

According to the Durham-Humphrey Amendment, prescriptions for legend drugs may not be refilled (dispensed again after the initial filling of the prescription) without the express consent of the prescriber. The refill status of prescriptions for certain legend drugs known to be subject to public abuse was further regulated with the passage of the Drug Abuse Control Amendments of 1965 and then by the Comprehensive Drug Abuse Prevention and Control Act of 1970.

Kefauver-Harris Amendments of 1962

A tragedy in 1960 led to the passage of the Kefauver-Harris Amendments to the Federal Food Drug and Cosmetic Act of 1938. A new synthetic drug, thalidomide, recommended as a sedative and tranquilizer, was being sold OTC in Europe. It was a drug of special interest because of its apparent lack of toxicity even at extreme dosage levels. It was hoped that it would replace the barbiturates as a sedative and therefore prevent the frequent deaths caused from accidental and intentional barbiturate overdosage. A pharmaceutical company was awaiting FDA approval for marketing in the United States when reports of a toxic effect of the drug's use in Europe began to appear. Thalidomide given to women during pregnancy produced birth defects, most notably phocomelia, an arrested development of the limbs of the affected newborn. Thousands of children were affected to various extents (9). Some were born without arms or legs and others, with partially formed limbs. The more fortunate were born with only disfigurations of the nose, eyes, and ears. The most severely afflicted died of malformation of the heart or gastrointestinal tract. This drug catastrophe spurred the Congress to strengthen the existing laws regarding new drugs. Without