of informing the FDA of their work. However, where the safety may be an issue, the U.S. law prohibits testing of drugs outside of the United States, to overcome the barrage of testing done by the big pharma on new molecules in non-U.S. subjects, some with disastrous results. Incidentally, this restriction applies only to the U.S. companies; other companies can still do such studies without penalty.

1.3.6 Stage 6: Phase II and Phase III Studies and Launch (4–6 Years)

The longer-term safety and clinical studies come under phases II and III, wherein patients suffering from the disease are studied. In phase II studies, the goal is to perform studies on different dose ranges in perhaps a few hundred patients to evaluate the effectiveness of the drug and its common side effects. It is at this stage that commercial formulation is developed and its scale-up is optimized. This is necessary because whatever formulation goes into phase III trials becomes the final formulation. In phase III studies, several thousand patients may be involved. Most regulatory authorities require sufficient data to demonstrate the safety and efficacy, and almost always, it is a mutually agreed-upon limit to which the drug companies are required to conduct the studies. The EMA has started a program of technical consultation, wherein for a sizeable fee of around $150,000, companies can sit down with the review staff and fine-tune their protocols; the investment is worth the effort. Once the regulatory authorities declare an application to be approvable, a marketing authorization request is made, and trucks are loaded pending issuance of the letter of approval that may have cost companies hundreds of million dollars.

- Sequence of clinical trials (4–6 years):
  - *Phase I*: Tolerance in healthy volunteers, pharmacokinetics in man, and supplementary animal pharmacology
  - *Phase II*: First controlled trials on efficacy in patients, dose range studies, chronic toxicity, and carcinogenicity studies in animals
  - *Phase III*: Large-scale trial at several centers for the final establishment of therapeutic profile (indications, dosages and types of administration, contraindications, and side effects), proof of efficacy and safety in the long-term administration, the demonstration of therapeutic advantages in comparison with known drugs, and the clarification of interactions with other medication
- Registration, launch, and sales (2–3 years):
  - *Registration with health authorities*: Documentation of all relevant data; expert opinions on clinical trials and toxicology; preparation for launch; information for doctors, wholesalers, and pharmacists; training of sales staff; preparation of packaging and package inserts; and dispatch of samples
  - *Launch and sales*: Production and packaging of the final form and quality control

1.3.7 Stage 7: Postmarket Surveillance (3–5 Years)

Although the intent of larger phase III trials is to bring out any statistically driven side effects, it is impossible to predict them even with several thousand patients. Phase IV studies continue to collect clinical efficacy and toxicity data; the pharmacovigilance