5.2: Clinical Investigations and Other Types of Human Data

For Drugs

The focus of this section is on the U.S. Food and Drug Administration (FDA), but regulatory agencies worldwide have very similar approaches. The main methods of determining the toxicity of drugs to humans are:

- **Clinical investigations** — administration of chemicals to human subjects with careful clinical observations and laboratory measurements.
- **Epidemiological studies** — observation of humans who have been exposed to xenobiotics in the normal course of their life or occupation.
- **Adverse reactions to drug reports** — reports voluntarily submitted by physicians to the FDA after a drug has been approved and is in widespread use.

Figure 5.2.1. Drugs can be toxic to humans
(Image Source: iStock Photos, ©)

Clinical Investigations

Clinical investigations are a component of **Investigational New Drug Applications (INDs)** submitted to the FDA. Clinical investigations are conducted only after a minimal battery of nonclinical laboratory studies has been completed.

Toxicity studies using human subjects require strict ethical considerations. They are primarily conducted for new pharmaceutical applications submitted to the FDA for approval.

Generally, toxicity found in animal studies occurs with similar incidence and severity in humans. Differences sometimes occur, thus clinical tests with humans are needed to confirm the results of nonclinical laboratory studies.

FDA clinical investigations are conducted in three phases, as outlined below.

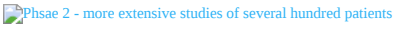
Figure 5.2.2. *Portion of the Investigational New Drug Application (IND)*
(Image Source: FDA)

Phase 1 consists of testing the drug in a small group of 20 to 80 healthy volunteers. Information obtained in Phase 1 studies is used to design Phase 2 studies, in particular, to determine the drug's:

- Initial tolerability in human subjects.
- Pharmacokinetics and pharmacological effects.

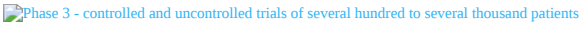
Phase 2 studies are more extensive, involving several hundred patients and are used to:

- Determine the short-term side effects of the drug.
- Determine the risks associated with the drug.
- Evaluate the effectiveness of the drug for treatment of a particular disease or condition.
- Elucidate the drug's metabolism.



Phase 3 studies are **controlled** and uncontrolled trials conducted with several hundred to several thousand patients. They are designed to:

- Gather additional information about effectiveness and safety.
- Evaluate overall risk:benefit profile of the drug.
- Provide the basis for the precautionary information that accompanies the drug.



For Consumer Products

Health-related data for a chemical in a consumer product (and for the consumer product itself for the human studies) can come from the following types of studies:

- *In silico* data — from computer programs that estimate toxic properties based on data for similar chemicals, and/or from the physical chemical properties.
- *In vitro* data — from the results of alternatives to animal tests, such as from cell cultures used to assess the potential for eye or skin irritation.
- Animal (toxicological) study data — for example, from studies that assessed eye or skin irritation potential.
- Human data – from studies conducted before (**premarketing**) and after (**postmarketing**) a product had been sold to consumers. More specifically, from:
  - Premarketing **clinical studies**, such as from patch tests to assess skin irritation potential.
  - Premarketing **"controlled use" studies** that are designed to assess the skin effects from using a new type of personal care product.
  - Postmarketing **studies conducted by physicians or dermatologists**, such as testing a diagnostic patch with their patients.
  - Postmarketing **epidemiological studies**, including studies developed by Poison Control Centers, companies, and academia that look at the "real world" health reports of effects associated with consumer use of a product.

Figure 5.2.3. *Toxicologists in a lab, using a computer for research*
(Image Source: iStock Photos, ©)

Did you know?

Bisphenol A (BPA) and **phthalates** are chemicals that have been widely found in consumer products. BPA has been used in some food can linings, polycarbonate food and beverage containers, tooth sealants applied to dentists, and even in cash register receipts! Examples of potential exposures to BPA include eating or drinking foods or liquids from those containers, and skin exposures from handing the cash register receipts. Workers involved in making products with BPA can be exposed during production.

Often called plasticizers, phthalates are used to make plastics more flexible. Some phthalates are used as solvents. They can be found in vinyl flooring and shower curtains, children's toys, personal care products, and as contaminants in the food supply. As with BPA, exposures can come from many sources.

Toxicologists and others are still assessing the full extent of the potential impacts on health. Studies suggest that BPA and phthalates affect the reproductive system, impacting how hormones such as estrogen and testosterone work in the body. The impact of fetal or early childhood exposures is still being assessed. Because of the ubiquity of the possible products containing these chemicals, thorough assessments of potential exposures, toxicities, and potential substitutes are essential.

Figure 5.2.4. *Plastic food and beverage containers are common sources of BPA and phthalates in consumer products*
(Image Source: iStock Photos, ©)
