product, which on being administered to a patient gives rise to appropriate and desired therapeutic response significantly.

In short, it may be added that both the **Pharmacist** and the **Pharmaceutical Scientist** may have to play a big, pivotal and responsible job with utmost concerned efforts to understand thoroughly these intricate, transcrucial and complex relationships so as to apprehend the appropriate ***usage*** **and** ***meaningful*** **development of Pharmaceuticals of the Future.**

1.5. VARIANTS IN BIOPHARMACEUTICS

Biopharmaceutics refers to the science that:

"**Examines critically the inherent relationship of the so-called *Physicochemical characteristic features* of the Drug substance, the *Dosage Form* in which the drug is being administered, and finally the route of administration upon the rate and the *degree of systemic absorption of the Drug*".**

The enormous scientific revelations and literature survey that the discipline **Biopharmaceutics** essentially involves are the following ***four*** **cardial aspects** perceptively, such as:

(a) **Stability of the *Drug* within the *Drug Product* (or Dosage Form);**
(b) **Release pattern of the *Drug* from the *Drug Product*;**
(c) **Rate of Dissolution/Release profile of the *Drug* at the *absorption site;*** and
(d) **Critical *Systemic Absorption* of the *Drug*.**

Fig:1.2 depicts a *general scheme* between the **Drug Substances** and the **Drug Product** *vis-a-vis* the resulting **Pharmacologic Effect.**

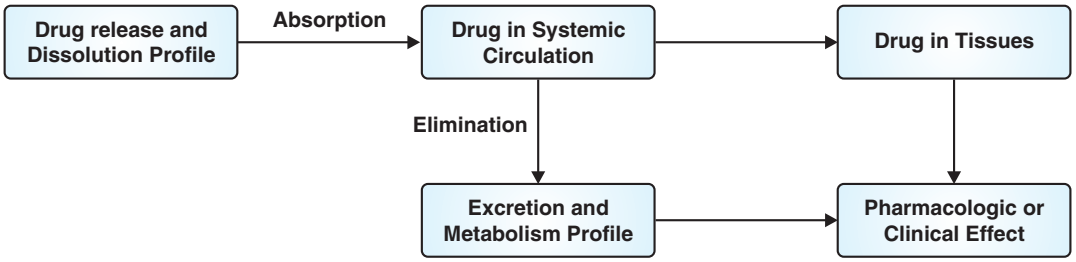

Fig. 1.2: Representation of the Scheme Depicting Dynamic Relationship between the Drug and the Drug Product *vis-a-vis* the Pharmacologic Effect.

Having mustered a fairly sufficient understanding of the **Basics of Biopharmaceutics**, it is indeed a prime requirement to have a closer look at the various **Variants in Biopharmaceutics**, such as:

- **Pharmacokinetics**,
- **Clinical Pharmacokinetics,**
- **Pharmacodynamics**,
- **Toxicokinetics and Clinical Toxicology,** and
- **Bioavailability**.

which shall now be discussed briefly in this introductory chapter so as to familiarize the readers with these above-mentioned terminologies. The objective is to recognize the inherent importance

The survey of literature reveals that there are several excellent examples of drug substance that obviously illustrates and expatiate the fundamental clinical usage of the **Principles of Pharmacokinetics** in accomplishing a positive improvement in the prospects related to the **magnificent success in drug therapy.**

Thus, one may come across *individualized* **'Pharmacokinetics Variations'**, which may categorically come into play in such ***in vitro*** processes, namely **ADME**. Consequently, the aforesaid biological phenomena are duly influenced, affected and guided by disease conditions, age, drugs and the like.

Clinical Pharmacokinetics in true sense makes use of the **well-defined, recognized and accepted methodologies so as to counteract or negate these influences by intelligently and skillfully affording individualization of drug therapy.** It has been duly observed and established that two major situations invariably come into being on account of either **intra-individual variation or inter-individual variation, for instance:**

- **Subtherapeutic response of a drug product, wherein the concentration of the drug stands below the minimum effective concentration (MEC), or**
- **Toxic response of drug product, wherein the concentration of the drug remains above the minimum toxic concentration (MTC),**

which would perhaps predominantly need an immediate adjustment to the prevailing dosing regimen. Thus, **Clinical Pharmacokinetics** predominantly involves the broad application of various **Pharmacokinetic Methodologies** in the domain of **drug therapy**. It will be worthwhile to impress at this point in time that '**Clinical Pharmacokinetics**' critically embraces a purely multidisciplinary approach with respect to the individually optimized dosing strategies that are exclusively based upon the patient's actual disease condition *vis-a-vis* patient-specific related careful thoughts.

In the light of the aforesaid statement of facts and observations, one may safely come to a meaningful conclusion. That the valuable and informative inputs derived from the extensive and intensive studies pertaining to the **Clinical Pharmacokinetics of drug products in various disease conditions do require input from medical research as well as pharmaceutical research.**

Based on the **National Vital Statistics Report (2003)*** of the **rate of death**** from 10 most glaring causes of death in the United States, which has been duly provided in Table 1.1.

1.7.1. *Therapeutic Drug Monitoring (TDM) and Pharmacokinetics*

Quite recently, the tentacles of **Pharmacokinetics** have been duly explored, evaluated and utilized effectively in most versatile and urgently needed **Therapeutic Drug Monitoring (TDM)**. Importantly, TDM is generally applicable to extremely **potent drug substances,** *viz*. **Aminoglycosides: Streptidine, Spectinamine** and **Anticonvulsants: Sulthiame, Valproic Acid**, usually having a narrow therapeutic range in order to accomplish the following **two main objectives:**

- **To optimize efficacy of drug product,** and
- **To check and prevent any possible adverse toxicity.**

Therefore, in order to carry out **TDM** in a methodical manner, it is absolutely necessary to place the patient under constant vigil for monitoring in ***two*** **accepted means**, namely:

* National Vital Statistics Report (USA): **52** (3), 2003.

** Age-adjusted death rates by male-female ratio.

Bioequivalent (**Biological Equivalent**) relates to '**those equivalents that when administered in the same quantum do provide the same biological or physiological availability profile –as measured precisely by blood-levels and urine-levels**'.

Bioequivalence designates a relative term that essentially denotes that the drug present in two or more *identical dosage forms* (or **drug product**), critically reaches the ensuing systemic circulation usually:

- **At the same relative rate,** and
- **At the same relative degree.***

Obviously, the critical appearance and observations of the statistically significant differences in the *two* or *three* or even more dosage form do indicate the **Bioequivalence.**

1.11.1. *Bioequivalence: The Canadian Regularly Perspective*

Canada enjoys the reputation of being one of the pioneers in the critical application of the '**Concept of Bioequivalence'**, by virtue of the imposition of **compulsory and mandatory 'Licensing Legislation',** which with effect from **1969 to 1988** (almost a span of two decades) not only promulgated but also facilitated the gainful entry of the '**Generic Drug Product****'.

- **Westlake (1973)*** ** postulated an artitrary standard of almost 80% extant of bioavailability with respect to a reference product, The **Exprt Advisory Committee on Bioavailability** was duly established in 1974, which eventually carried out and examined several approaches for the in-house stydies due to the urgent and crucial lack of the much-needed statistical procedures for both **Bioavailability** and **Bioequivalence.**

Examples

Phenylbutazone Equivalence Study: **McGilveray *et al.* (1978)** specifically studied the **Plasma Concentration Derived Data**, for instance:

- **Area under the concentration-time curve (AUC),** and
- **Maximum observed concentration (C_{max}).**

which were adequately examined after

(a) **Transformation to corresponding log value, and**

(b) **Confidence intervals (CI) up to 95%.**

Table: 1.2 records the different categories of complicated drug substances in the critical and precise assessment of the **Bioequivalence Values** perceptively.

The **Canadian Approach** and **Suggestion to Bioequivalence** predominantly helps in the judicious and logical classification of **Orally Administered Drugs** into ***two* main categories**, namely:

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* That is, their ensuing plasma concentration-time profiles shall be more or less quite identical without any appreciable observed '**statistical differences**'.

** **Generic Drug Product**s: It essentially refers to a chemically equivalent copy of a brand-name drug whose patent has expired legally.

*** Westlake (1973): Use of Statistical Methods in Evaluation of *in vivo* Performance of Dosage Forms, *J Pharm Sci.*, **62**: 1579-1589, 1973.

Points to Ponder: These essentially comprise:

1. The *actual site of administration* and the *characteristics* of the **dosage from** (or *drug product*) may critically and effectively influence the so-called **Bioavailability of the Administered Drug**. Hence, once absorbed the respective '***Drug***' is being subjected only to the **DE-Kinetics** perceptively.
2. Besides, either any or all of the ensuing **ADE rate phenomena** could be largely influenced by the following ***two*** **cardinal aspects**, namely:
   - **Physiochemical characteristics of the Drug**; and
   - **Age, health and sex of the patient.**

Another school of thought refers **Biopharmaceutics** to the study of **the relationship between physical, chemical and biological properties of matter specifically in relation to drug substances, dosage forms (or drug products), drug availability *in vivo* (or Bioavailability) and the overall therapeutic actions'.**

It has been experimentally proven that the occurring '**therapeutic response of a drug**' is dependent on the following ***two*** **important aspects**, namely:

- **sufficient concentration of the acting drug,** and
- **sustained presence of the drug either at a particular site or at several sites of action simultaneously**.

In a border perspective, the '**Drug Substances'** which exert their action systematically are considered to be **most preferred for clinical purposes exclusively** because there exists a **'Dynamic Equilibrium'** between the ***two*** **under-mentioned entities**, such as:

- **critical concentration of drug in circulating blood,** and
- **specific concentration of drug at its site(s) of action.**

In other words, there exists a so-called **'Linear Relationship**' between the ***drug-concentration in blood*** **and** ***drug-concentration at the site of action*****.** Obviously, one may easily predict**-'the exact and precise drug-concentration at the site of action based upon the presented concentration of drug in the blood'.**

However, it is pertinent to state here that the actual concentration of drug in **plasma water***: dose serve as a more reliable index of drug concentration prevailing at the site(s) of action compared to the actual concentration of drug occurring in whole plasma. Hence, it may be concluded that only such drug, which is unbound, *i.e.*, practically dissolved in plasma-water, may exhibit a tendency to release from plasma *via*

- **capillary endothelium** and
- **various adjoining tissues**,

and virtually approach other body fluids; and, therefore, gain a viable entry to the site(s) of action appropriately.

To carry out the precise measurements (*i.e.*, determination) of a specific 'unbound drug substance' in protein-free plasma (or plasma water) definitely requires a more sensitive and complex assay techniques rather than estimating the total concentration of both ***bound*** and ***unbound drug*** substance in the '**whole plasma**'**.

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* **Plasma Water**: It refers to the protein-free plasma

** **Whole Plasma**: It contains plasma protein which has a tendency to bind the drug in a reversible manner.