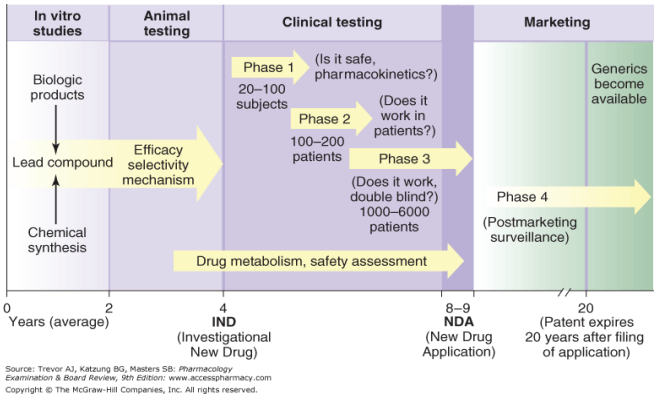
PHARMACEUTICAL ASPECTS AND DRUG DEVELOPMENT

The four main phases of drug development

Trials of drugs in human beings in the U.S. generally are conducted in three phases, which must be completed before an NDA can be submitted to the FDA for review. Although assessment of risk is a major objective of such testing, this is far more difficult than is the determination of whether a drug is efficacious for a selected clinical condition. Usually about 2000–3000 carefully selected patients receive a new drug during phase 3 clinical trials. At most, only a few hundred are treated for more than 3–6 months regardless of the likely duration of therapy that will be required in practice. Thus, the most profound and overt risks thatoccur almost immediately after the drug is given can be detected in a phase 3 study if they occur more often than once per 100 administrations. Risks that are medically important but delayed or less frequent than 1 in 1000 administrations may not be revealed prior to marketing (e.g., COX-2 inhibitors). Consequently, a number of unanticipated adverse and beneficial effects of drugs are detectable only after the drug is used broadly. Many countries, including the U.S., have established systematic methods for the surveillance of the effects of drugs after they have been approved for distribution.



STEREOCHEMISTRY (Chirality)

Enantiomer of Carvedilol	Kd for alpha receptors	Kd for beta receptors
(+)R	14	45
(-) L	16	0.4
Racemic	11	0.9

The R-enantiomer of carvedilol is a potent beta blocker but the enantiomers are roughly the same for alpha blockade.

Stereochemistry is the study of how molecules are structured in three dimensions. Enantiomers (substances of opposite shape) are pairs of molecules existing in two forms that are mirror images of one another (right- and lefthand) but that cannot be superimposed. A pair of enantiomers is distinguished by the direction in which, when dissolved in solution, they rotate in polarized light, either clockwise (dextrorotatory, d [+]) or counter-clockwise (levorotatory, l [-]). When the two enantiomers are present in equal proportions (50:50), they are referred to as a racemic mixture. The most rapidly applicable and unambiguous convention for designating isomers is the sinister (S) and rectus (R) classification that specifies the absolute configuration in the name of the compound. Pharmacologically, not all enantiomers are created equal. Enantiomers can exhibit differences in absorption,distribution, clearance, potency, and toxicity (drug interactions). The administration of a racemic drug mixture may in fact pharmacologically represent two different drugs with distinct pharmacokinetic and pharmacodynamic properties. More than one third of all synthetic drugs are chiral (thiopental, ketamine, inhaled anesthetics except sevoflurane, local anesthetics, neuromuscular-blocking drugs, opioids), although most of them are utilized clinically as racemic mixtures.