FDA Protocol for Drug Development

1. Preclinical Testing

starts with the discovery of a new molecule

FDA issues a **17 year exclusive "patent"** to produce/market that molecule

More recently, companies patent a protein (made by gene X), and then look for uses for that protein, "knowing" that the protein must have some action in the body…

mean average length = 1 ½ to 3 years (can be longer)

non-human subjects

rats, mice, rabbits, etc.

average cost = 10 million dollars +

3 major considerations of this testing:

medical uses/needs for substance

commercial potential

feasibility for mass production (manufacturing costs)

"Orphan Drug" Act of 1983

special privileges & market incentives to companies willing to produce less profitable drugs (smaller markets, N<200K affected Ss, reduced profit potentials)

"Me Too" molecules (official & sanctioned version of street/unsanctioned "designer drugs")

a limitation of the patent which is for a specified molecule

preclinical data can begin to provide data on **safety**

some 175K substances evaluated annually, about 200 (about l/1000) actually become new drugs eventually

1. Preclinical Testing (cont.)

in order for testing of drugs for later clinical use in psychiatry, must first attempt to develop **animal models** for psychiatric symptoms/disorders – such as anxiety, depression, ob-comp, schizophrenia….difficult but not impossible

much of initial work is on **assessing toxicity** of substance

single doses of increasing strength

small groups of Ss, 2+ species
both sexes, young and older Ss
observed 1-7 days
different routes of administration
determine ED50, LD50, duration of effects
Ss are autopsied for cause of death

Once the toxic and lethal doses are determined in a species, subacute toxicity is explored

at least 3 or more routes of administration
at least 3 different dose levels, 2+ species, small groups of Ss
observed 2 to 12 weeks
estimate what the human dosages will be
esp. note effects on liver, kidneys and NS

Chronic toxicity is studied, following the Ss for 3 to 24 months

Must wait at least until **6 months** of animal testing has been completed before any testing of humans is allowed
also check for **carcinogenic effects** (6 months, 2+ species, same route of administration to be used in humans)
also check for **teratogenic effects** (substance given to pregnant females and during lactation (usually rats & rabbits)

1. Preclinical Trials (cont.)

At end of 2 or so years enough data has been obtained usually from animal data that drug company now can submit a report to the Secy of Health, Education, & Welfare to let HEW know that drug is/is not advancing to the stage of **Investigational NewDrug Application**
the IND application is reviewed by FDA (takes 1+ months)
If approved, drug company can now move on to clinical testing in humans

Chronic animal studies still continue as human testing begins

2. Clinical Testing

range is 2 to 10 years duration (average is 5 to 7 years)

Phase I:

1+ years duration
healthy, normal adult volunteers (N = 20 – 100)
usually done in a hospital (using medical interns, residents, nurses, etc.)
under close medical supervision
purpose: determine safety & dosage
biological effects, pharmacokinetics (how body affects drug)
tolerability of side effects

Phase II:

2+ years duration
patient volunteers (N = 100 – 400)
purpose: determine efficacy
continued evaluation of safety, side effects

Phase III:

3+ years duration
patient volunteers (N = 1000 – 3000)
purpose: continue to verify effectiveness
monitor adverse side effects from longer-term use

Now drug company files **New Drug Application** (NDA) with FDA

p.4 (Drug Development)

NDA is usually 100,000+ pages in length, takes at least 6 months to review
Range is 2 months to 7 years (average is 2 years)
Reviewed by a group of physicians/scientists, chaired by a physician (the Medical Officer)
If approved, can now go to Phase IV (drug released to general marketplace)

Phase IV:
Often takes a total of 12 years from original patent to reach Phase IV…
Is **post-marketing "testing"**
Drug is being prescribed by physicians, dentists, podiatrists, nurse practictioners, psychologists (in New Mexico & Guan, at least)
Much wider, varied pool of subjects (patients), different ages, races, etc.
Prescribing healthcare providers continue to report in on efficacy & safety Issues
Different formulations of drugs, dosages, durations of treatments are used
Drug interactions begin to surface more

NDA can be rejected outright or can be sent back for more study (in Phase III)

Even after given NDA status, FDA closely monitors results:
1st year – quarterly reports; 2nd year – biannual reports; 3rd year & thereafter – annual reports

Note: Of some 5000 compounds in preclinical testing, only 5 will enter clinical trials and only 1 of the 5000 will be given FDA approval for NDA status

Note: **Controls**: Placebo, current drug of choice (active standard)
Some studies are not blind or are single blind in Phases I & II
Most studies are double blind in Phase III