Role of the Federal Government in Advancing DM Science and Care – the FDA

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What does FDA do?

- Assures the safety, effectiveness and quality of drugs, medical devices, food, cosmetics and products that emit radiation…

- Mainly by reviewing information collected and submitted by industry, academia, and others

What FDA doesn't do with drugs

- Make or have access to experimental drugs
  - Drugs are made and owned by industry and academia
- Conduct animal or human studies
  - FDA requires information before drugs can be studied or marketed; industry and academia conduct the studies
- Set or limit price
- Regulate "Practice of medicine"
  - e.g. an approved drug *can* be used, but FDA has only indirect role in decisions about *if or when* it is used
- Require new drugs to be better than old drugs

FDA Organization

- Part of Department of Health and Human Services
  - Sister agencies include NIH, CDC, CMS and 8 others

- Centers:
  - Drugs (CDER)
  - Biologics (CBER)
  - Devices and radiology (CDRH)
  - Food (CFSAN)
  - Tobacco (CTR)
  - Veterinary medicine (CVM)
  - Toxicological Research (NCTR)

Key Laws

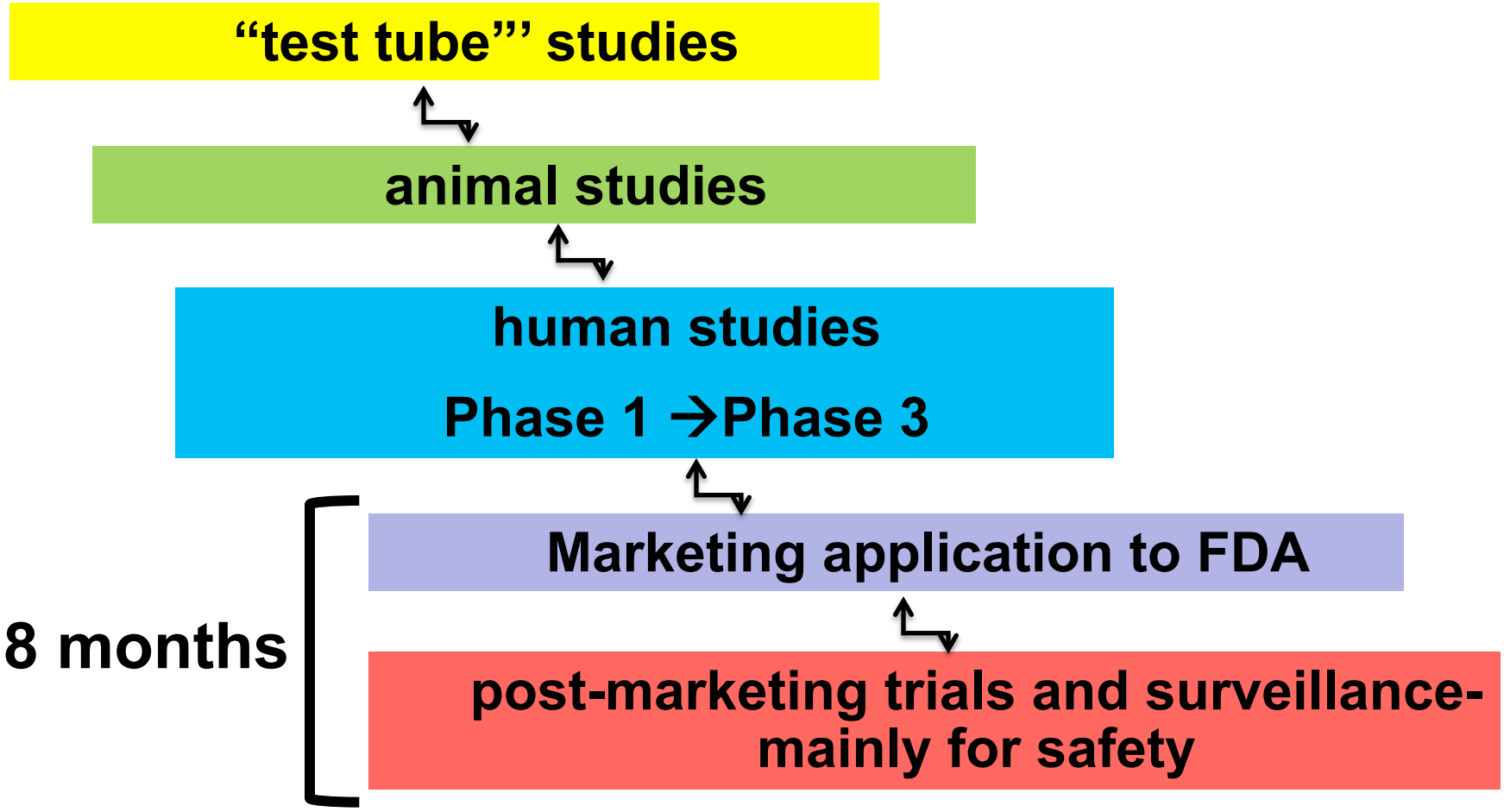
1906 FDA created to prevent adulterated food and drugs

1938 Drugs required to be safe

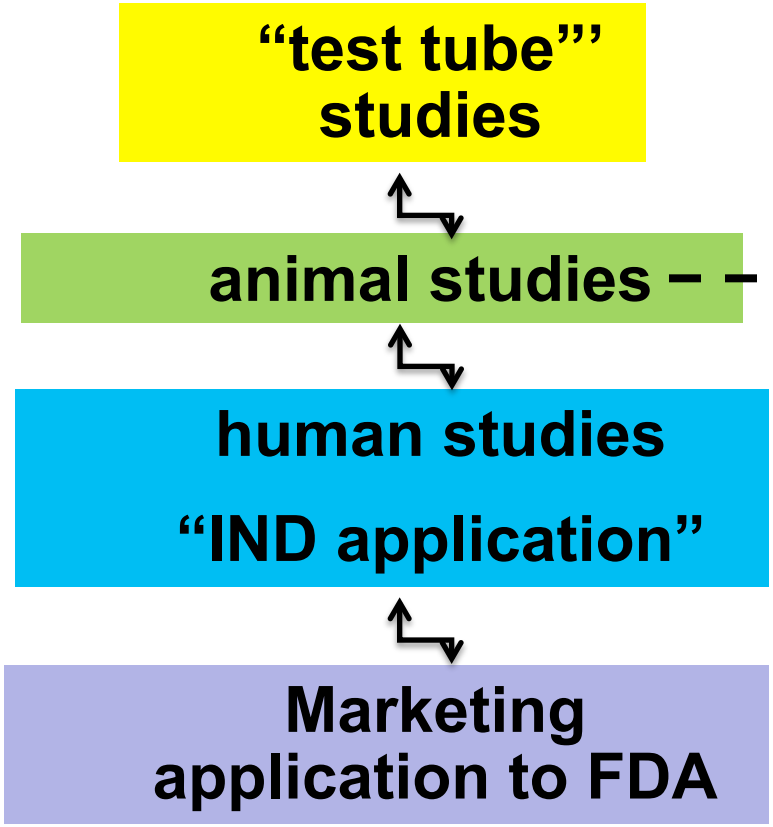
1962 Drugs required to be effective

Need to show benefit before FDA can consider "risks vs. benefits"

Drug Development Steps and FDA



Drug Development Steps and FDA



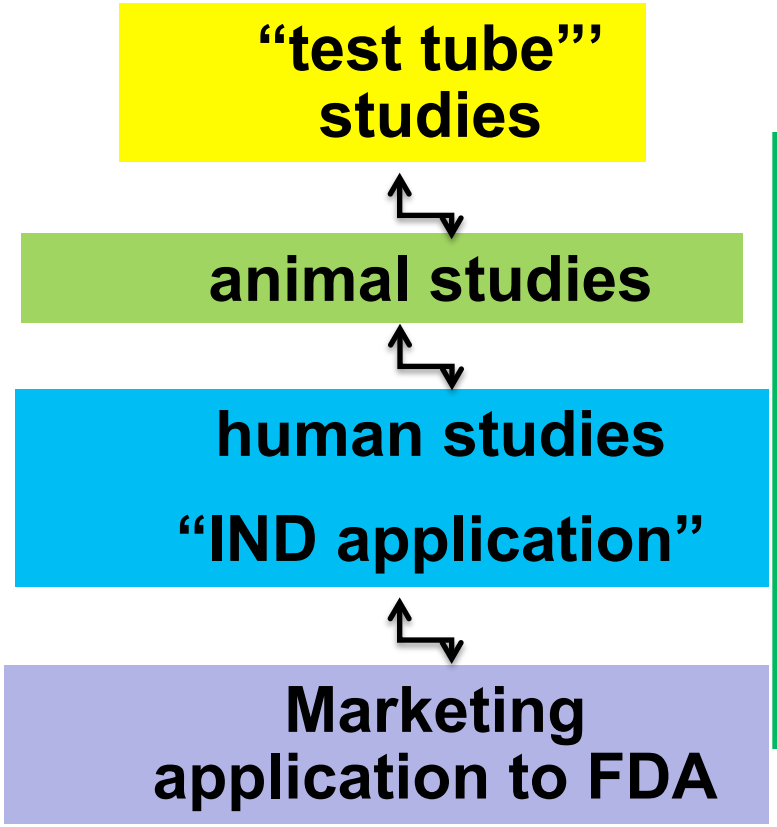
Before an experimental drug is given to people, FDA has to review the plan and conclude it doesn't present "unreasonable risk"

IND = investigational new drug

Unreasonable Risk

- Depends on the disease; if life-threatening *or* debilitating, some amount of life-threatening risk may be reasonable
- Importantly, to support human studies developers *required* to study amount of risk, and reduce to degree that's *reasonable*
  - e.g. if a drug injures kidneys in animals, choose dose based on that for humans, and use specialized tests to detect kidney injury early

What Kind of Study or Use?



FDA can't allow use in patients or uncontrolled studies if will impede trials capable of showing if the drug works

…studies are rarely stopped by FDA for a number of other reasons, like faulty design that won't lead to useful information

Expanded Access

- Drug used to treat patients
- The law allows, and FDA encourages, when won't impede studies needed to show if a drug works or not, and the disease, risks, and possible benefits fit
- Evidence that a drug works almost never provided by use in treatment setting

How do you know if a drug works?

- If the drug effect is large, immediate and clearly different from what could happen to untreated patients, efficacy can be shown fairly easily – like for drugs that produce surgical anesthesia

- But drugs for most diseases aren't likely to have such clear efficacy

- FDA is eager to approve drugs with small benefits – but that benefit needs to be reliably shown

Historical Controls in Efficacy Studies

- Treat all patients with the experimental drug and compare to how they did in the past, or to other patients in the past

- The major problem with this approach is called “bias” – as used in science, it includes not only believing a drug works only because you want it to work (although *is* a major concern), but also accidental and invisible differences between present and past that mislead

Historical Controls

- Many sources of accidental bias
  - Supportive care for patients in a study more intensive than supportive care outside, so patients often do better in study
  - Supportive care *today* often better than *yesterday,* sometimes much better
  - Patients doing worse than average more likely to *leave* the study – the remaining patients are "better than average" even if the drug didn't work
  - and many more…

"Drug vs. Drug" Trials

- *Can* sometimes use to support FDA approval, but often not possible or practical
- Best when a new drug might be more effective than a drug that is already approved
  - but still risky for drug developers if new drug might not be better than approved drug
  - And bigger study needed to show new drug beats old drug compared to showing new drug beats placebo
- And doesn't actually get rid of concern to some that patients don't get immediate access to new drug

Placebo-Controlled Trials

- Not without cost or risk, but usually the best bet in a world made of costs and risks
- Use when drug *not* obviously effective
  - Even if drug works, the difference between drug- and placebo patients will be so small when detected that patients still can't tell who got drug and who got placebo
- Much of the objection to placebo based on belief new drug likely is effective; hard experience tells us most are not

Rare Diseases/Orphan Drugs

- Diseases that affect <200,000 persons in the US
- Orphan Drug Act passed in 1983
  - does not lower requirement for showing drug works
- FDA is required [and very willing] to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards

Thank you

Questions?