Organs on a chip: regulatory perspective

AIMBE/NIBIB Workshop

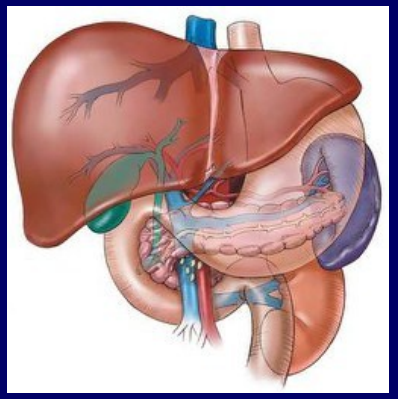
March 6-7 2014

David Jacobson-Kram, Ph.D., DABT

Office of New Drugs

Center for Drug Evaluation and Research

US FDA



Food and Drug Administration

Human on a chip: the next wave in toxicology or snacks for cannibals?

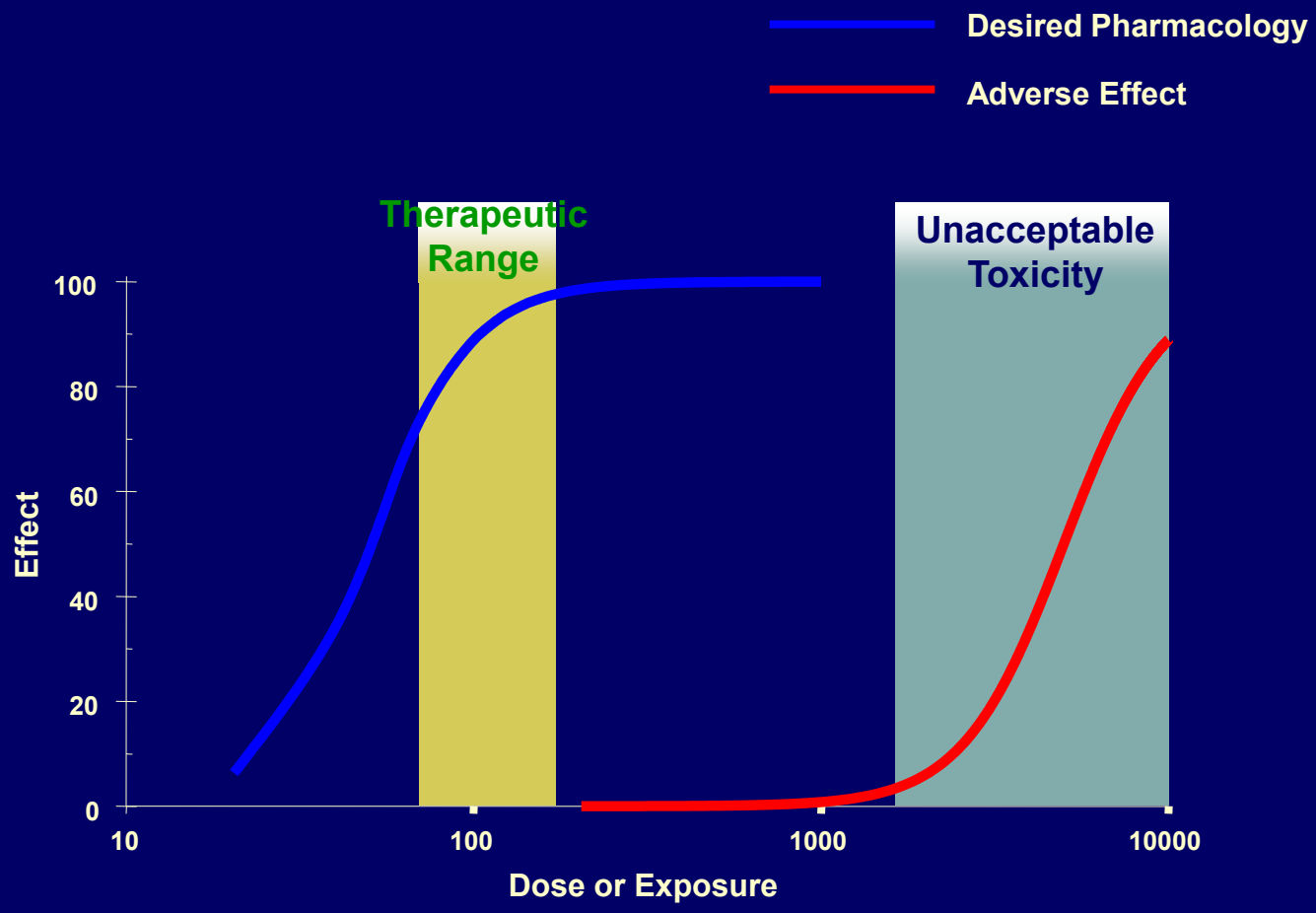
What information is currently derived from animal studies?

- Currently CDER requires data from animal studies to ensure that clinical trials can be performed safely.
- Data from animal studies are also collected for endpoints that cannot be studied in clinical trials.

What types of data ensure safe conduct clinical trials?

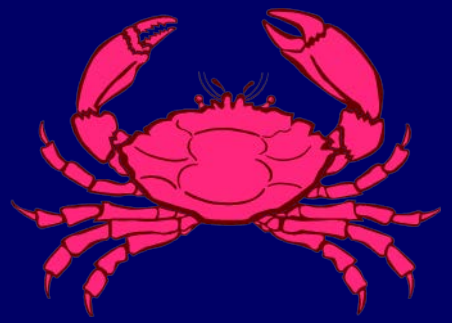
- Safe starting dose for first in human administration; generally based on NOAEL in animal study.
- Safe stopping dose; generally based on unacceptable toxicity.
- Safety monitoring plan; what organ systems at risk?
- Preclinical information discussed in Investigator's Brochure and in Patient's Informed Consent.
- First in man studies generally performed in health volunteer subjects. No risk/benefit balance, only risk. In general, clinical trials have a history of safety.

First-In Human Dose Selection



What toxicities cannot be identified in clinical trials?

- Teratogenicity: don't want to deliberately expose pregnant women.
- Carcinogenicity: long latency period and insensitivity of epidemiological studies preclude identification of this adverse effect.
- Long term toxicities



Nonmonitorable toxicities: teratogenicity, eg thalidomide

- Prescribed to pregnant women for nausea and insomnia.
- Resulted in over 10,000 births with severe limb malformations.
- Link between exposure and adverse effects was possible because of the potency of the drug and relatively short time period between exposure and manifestation of effects.

Nonmonitorable effects: carcinogenesis, diethylstilbestrol (DES)

- Prescribed to pregnant women to maintain pregnancies.
- Increased risk (1 in 1000) for clear cell adenomas of the vagina and cervix in female offspring.
- Link between exposure and risk could be made because of the rarity of tumor type. If exposure increased risk for a common cancer, might not have been detected.

What other nonclinical information do we need in the course of drug development?

- Safety pharmacology (CV, pulmonary, CNS)
- General toxicology
- Genetic toxicology
- Pharmacokinetics
- ADME (absorption, distribution, metabolism and excretion)
- Reproductive toxicology (fertility, teratogenesis, postnatal development)
- Carcinogenicity
- Special studies (e.g. juvenile)
- An alternative in vitro system would have to provide information on all these potential toxicities.

Challenges

- We currently examine approximately 50 tissues per animal in a standard toxicology study.
- Animal studies, depending on the endpoint and species, utilize multiple individuals per dose. How many chips would be needed to supply data for drug development?
- Would they be chips with cells derived from the same source of would chips have tissues from multiple individuals?

Challenges

- What are the sources of human tissues: iPS cells versus primary cultures from biopsies/autopsies?
- Differentiated cell types need specialized cell culture medium. Cells on a chip need to be bathed in a common medium.
- Will the immune cells in a chip recognize the other cell types as foreign and destroy them?

Validation: the Holy Grail

- New candidate replacement assays will need to be run in parallel with traditional assays.
- New assays must have equal or improved predictability over traditional assays.
- We are confident we can get there, the only question is how long will it take?