

# **Alternative Methods in CDER/FDA**

**A. Jacobs**

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**(not an official opinion)**

# Overall

- **Organizational activities**
- **Combining of endpoints**
- **Elimination of assays**
- **In vitro assays**
- **QSAR**
- **'Omics/biomarkers**
- **Flexibility**
- **Implementation**

## **Organizational Activities**

- **Active participants in ICCVAM**
  - **Overall committee and most working groups**
- **Contribute to OECD expert pharm/tox working groups and guidelines**
- **Contribute to interagency efforts in area of ‘omics**
- **Have an active CDER QSAR research group**
- **Minimal funding for research**

## **Drug Discovery/Lead Selection vs Drug Evaluation**

- **Many alternative assays may be used by drug companies for screening, to help in compound discovery and selection**

## **Eliminate Assays (a)**

- **LD50 not required for safety evaluation; more interested in sub lethal effects**
- **Photoallergy not required; test in humans**
- **Draize skin irritation/corrosion assay not required;**
- **2-yr mouse carc study can generally be replaced by a 6-mo transgenic mouse assay**

## **Eliminate Assays (b)**

- **Draize eye test not required; could use an in vitro alternative**
  - **No separate assessment needed if formulation has a high or low pH or if irritating to skin**
- **1 yr photocarc study very rarely needed**
  - **Human skin biopsies**
  - **2-yr mouse study rarely needed-replaced by a 6-mo transgenic mouse assay**

## **Combining of Endpoints**

- **No separate skin irritation test needed**
- **Multiple endpoints measured within a single study**

## **In vitro Assays (a)**

- **May be used for the API but may have limitations for entire formulations**
- **At some “high” concentrations, the incidence of false positives increase**
- **Genetox assays**

## **In vitro Assays (b)**

- **LAL Limulus bacterial endotoxin test for pyrogenicity generally used in place of rabbits**
  - **Can't detect non-endotoxin pyrogens and susceptible to interference high protein levels of test substances or by glucans**
  - **Can't detect pyrogenicity associated with implanted devices**
- **Currently evaluating assays in human whole blood, PBMC and monocytoid cells**

## **In vitro Assays (c)**

- **3T3 assay for photoirritation accepted, but a large percentage of false positives**
  - **Some formulations are incompatible with 3T3 cell**
  - **Primarily for UVA absorbing since cells can't tolerate very much UVB**
- **Some endpoints involve systemic interactions**
- **Need to relate effects to exposure**

# QSAR

- **A very active group**
- **Often used for evaluation of new impurities**
- **To supplement genetox**
- **To supplement carc predictions**
- **To supplement reprotox**
- **Evaluation of impurities for structural alerts**

# **‘Omics/Biomarkers**

- **Used by drug sponsors in drug discovery and lead compound selection**
- **To look at biomarkers for liver, renal , and cardiac toxicity-much fewer animals**

## **Flexibility in What Specifically is Needed (a)**

- **Follow ICH agreements on what is needed when in development**
- **Rather than a list of tests, consider what concerns need to be addressed during development**

## **Flexibility in What Specifically is Needed (b)**

- **Have potential human adverse effects at particular exposures been identified?**
- **What is a safe first dose in humans?**
- **How much toxicity is reasonable for humans at the particular stage of drug development?**
- **Is an identified adverse effect reversible?**

## **Flexibility in What Specifically is Needed (c)**

- **How high is it reasonable to dose humans?**
- **What should be monitored in humans and how frequently?**
- **Is the drug reasonably safe for person who wants to get pregnant or is pregnant**
- **What are the long-term effects of taking the drug?**

## **Implementation (a)**

- **Alternatives mentioned in guidances**
  - **Phototoxicity**
  - **Exploratory Guidance**
- **PreIND meeting with companies/sponsors**

## **Implementation (b)**

- **Don't ask for unnecessary studies**
- **Monthly supervisor meetings**
- **E-mail**
- **Presentations at reviewer retreats**

## **Near-Term Goal**

- **Reduce animal use whenever possible without jeopardizing human health**

## **Long-Term Goal**

- **Replace All Animal Testing**
- **Need alternatives that can address the questions that need to be answered in order to make regulatory decisions**