FDA-ICCVAM 3Rs

A. Jacobs

May 25, 2016

FDA-DARPA-NIH Microphysiological Systems Program

Started in 2011 to support the development of human microsystems, or organ “chips,” to screen for drugs swiftly and efficiently (before human testing)

Collaboration through coordination of independent programs

Engineering platforms and biological proof-of-concept (DARPA-BAA-11-73: Microphysiological Systems)

Underlying biology/pathology and mechanistic understanding

(RFA-RM-12-001 and RFA RM-11-022)

Advise on regulatory requirements, validation and qualification

CDRH-skin irritation/corrosion

- CDRH will be participating in an EpiDerm model round robin evaluation, followed by evaluation of the SkinEthic model--- for revision of the current ISO standard for medical devices
- These in vitro assays could then replace the current in vivo assays for assessment of skin irritation/ corrosion

CBERs 3Rs Activities: Alternatives to the Histamine Sensitization Test (HIST)

- Member of the *International Working Group for Alternatives to HIST*, a multi-national consortium of interested stakeholders representing government, industry, animal welfare organizations, research and regulatory institutions
- After completing its mission of: *reviewing and discussing the implementation of in vitro assays as alternatives to the HIST (an animal-based method) for the testing of residual pertussis toxin(PTx) activity in acellular pertussis vaccines*, the Working Group was dissolved
- Preparation of reports of the meeting: "Alternatives to HIST Workshop (London): *What is Possible and Practical?"* (March 4-5, 2015), including the review of the results of a collaborative study of the CHO cell assay (an *in vitro*, cell-based alternative to HIST) sponsored by EDQM

Recommendations from March 2015 Alternatives to HIST Workshop (a)

- CHO cell assay suitable alternative to HIST – Measures PTx whole function
- CHO cell assay reasonably well developed to be considered suitable for regulatory purposes (protocol transferability demonstrated)
  - Each manufacturer will have to optimize the method for their specific product & regulatory requirements
  - Implementation - Stepwise approach, initially used for release, then extend to stability testing after a period of demonstrated performance

Recommendations from March 2015 Alternatives to HIST Workshop (b)

- In certain cases, waiving of the HIST altogether is an option (based on science & manufacturing history)
- Other *in vitro* assays (i.e. measuring PTx binding & enzymatic activity) have utility as supplemental manufacturing control information, but not for final lot release on their own
- Publication of meeting report and collaborative study results should facilitate international regulatory acceptance (PharmaEuropa Bio & Scientific Notes)

CDER

- **Participant in ICH guidance development:**
  - **International harmonization reduces repetition of studies and reduces animal use in overall drug development**
  - **No acute lethal tox**
  - **Combine endpoints-no stand-alone assays for local tox**
  - **Exposure and dose limits for tox studies**
  - **Exploratory clinical studies section reduces use of animals needed to support clinical studies**
  - **Defer reprotox studies until later in development for biologics**
  - **Microsampling: reduces number of mice: no need for a satellite TK group**

CDER-Carcinogenicity

- Waive carc studies for most biologics
- Working on criteria for waiving carc for small molecules
- For Impurities: use SAR

CDER-Reprotox

- Considering an alternative (in vitro) battery to sometimes replace one species for regulatory use (already used as screens in drug discovery)
- Discussing how to get harmonization of regulatory acceptance of various batteries and contexts of use
- Considering use of GLP dose-ranging studies as pivotal studies in some contexts
- Considering reuse of animals normally discarded before pre-postnatal studies

CDER-ICH Assays for Proarrythmic Potential

- **Being evaluated:**
- **Use of hESC/iPSC although not fully differentiated, may still possess properties sufficient for drug screening and safety testing**
- **To replace the in vitro hERG assay and animal/clinical TQT (thorough QT prolongation testing)**
- **To test for cardiotoxic potential for first in humans, among other potential uses**

CDER: Assays for Skin Sensitization (human)

- Several proposed batteries have excellent predictivity for humans
- Awaiting some to be available commercially (e.g., at a contract testing lab)
- If commercially available, could be used now as a screen for human studies
- Could also be used for some CBER products (e.g., cosmetics)