Recent FDA 3Rs Efforts- CDER, CVM, CDRH, CTP, and NCTR

Abby Jacobs, PhD, ATS
on behalf of
USFDA  May 2017
ICH and Human Pharmaceuticals

• Worldwide participation in ICH guidance development:
  • Founding members: US, EU, and Japan; other members-The Health Canada; The Swissmedic; The Agência Nacional de Vigilância Sanitária (ANVISA, Brazil); The Ministry of Food and Drug Safety (MFDS, Republic of Korea)

• International harmonization has already reduced repetition of studies and reduces and refines animal use in overall drug development
• Already receive a myriad of alternative assays from drug developers, used in drug discovery- will give info on more recent developments
CDER Nonanimal Assessment of Skin Sensitization

- Contributed to the development of an assessment framework for integrated non-animal approaches that could serve as replacements for the current animal test, the local lymph node assay (LLNA)
ICH S3 Q and A on PK

Microsampling

• A method to collect a very small amount of blood (typically ≤50 µL) to measure TK parameters of the drug and/or its metabolites
• Matrices: blood and its derived plasma or serum, in liquid or dried form
• Can minimize pain and distress in animals (improvement of the animal welfare: refinement)
• Can reduce or eliminate the number of required animals in a TK satellite group for rodents (reduction), particularly for mice
ICH5R3-Repro-Developmental

- Will describe the circumstances under which the outcome of “preliminary EFD studies” (per ICH M3(R2)) could determine the ultimate risk assessment for EFD

- Will include basic principles that would assist in the development and potential regulatory use of *in vitro*, *ex vivo* and non-mammalian assays
International Cooperation on Alternative Test Methods (ICATM)

• All product sectors: including U.S., Canada, EU, Brazil, Japan, Korea, China

• Participated in Workshop in October 2016 on acceptance of non-animal test methods for assessing skin sensitization potential
ICH57 and CiPA initiative

• The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative nearing completion
VICH

• For CVM/FDA
• For veterinary drugs and drug residue issues
• Japan, EU, and U.S.--Harmonization
Examples of Medical Devices Regulated by CDRH

Biocompatibility assessments are recommended for all medical devices that come into **direct** or **indirect** contact with the human body.

*Biocompatibility is the ability of a device material to perform with an appropriate host response in a specific situation.*
CDRH Risk-based Focus for Biocompatibility Evaluation

To reduce unnecessary animal testing, when conducting risk assessment, CDRH recommends that all available relevant information be considered:

- Literature and other publicly available information
- Clinical experience
- Animal study experience
- Medical device standards
- Devices previously reviewed by CDRH
**In Vitro Alternative Methods Included in Reviews to CDRH**

**In vitro alternative:**
- Chemical characterization & risk assessment
- Battery of *in vitro* thrombogenicity assays (for coagulation & platelets)

Instead on *in vivo* testing for:
- Systemic toxicity (including genotoxicity, carcinogenicity, and reproductive and developmental toxicity)
- Thrombogenicity

ISO validation efforts for Device-Specific Methods

• ISO/TC 194/WG 08 (irritation and sensitization):
  – Round robin testing completed 1/2017*: dermal irritation (*in vitro* method refinement for *in vivo* replacement)
  – Round robin testing planned: dermal sensitization (*in vitro* method refinement for *in vivo* replacement)

• ISO/TC 194/WG 09 (hemocompatibility):
  – Round robin testing completed Fall 2016*: hemolysis (*in vitro* method refinement with confirmation of equivalent results for animal/human blood)
  – Round robin testing ongoing: thrombogenicity (*in vitro* method refinement for *in vivo* replacement)

*not yet published
Communicating with CDRH

Medical Device Development Tools (MDDT) program:
Promotes the development of tools to facilitate more timely device evaluation, including:

• Nonclinical assessment model: test method to simulate device function or *in vivo* performance (e.g., *in vitro* models to replace animal testing)

• Biomarker test: clinical method used to detect or measure an indicator of biologic processes or pharmacologic response (e.g., method for measuring serum proteins)

See CDRH’s MDDT website:
https://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/
Communicating with CDRH (continued)

Pre-submission program:
Mechanism to request agency’s feedback on proposed testing protocols/validation plan (e.g., in vitro alternative methods for biocompatibility testing of medical devices).

See CDRH’s 2014 Pre-Submission Guidance:
Device Master File (MAF): Mechanism to submit validation data for Agency consideration from testing protocols/validation plan agreed to under pre-submission process if outside MDDT program (e.g., *in vitro* alternative methods for biocompatibility testing of medical devices)

See CDRH’s 2014 Device Master File (MAF) webpage:
https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtemarketyourdevice/premarketsubmissions/premarketapprovalma/ucm142714.htm
NCTR

• Research for FDA
• *In vitro* human airway tissue model
  – Tight junction disruption by cadmium
NCTR: Differentiated Air Liquid Interface Human Airway Cultures

Normal human airway bronchial epithelium (tissue biopsy)

Day 1 - confluent monolayer
Day 28 - complex columnar epithelium with basal cells, goblet cells and ciliated cells
Effect of Cadmium on Pulmonary Epithelium

Cadmium is a constituent of air pollutants and cigarette smoke

Alterations in tight junction integrity

Cao et al., Respir Res. 21;16:30, 2015
OECD

• IATAs for dermal sensitization
• Working on IATA for nongenotoxic carcinogenesis
• GUIDANCE DOCUMENT FOR THE USE OF ADVERSE OUTCOME PATHWAYS IN DEVELOPING INTEGRATED APPROACHES TO TESTING AND ASSESSMENT (IATA) Series on Testing & Assessment No. 260
3-D Human Micro Organs

• The FDA gives feedback on NIH/NCATS projects and DOD projects on human tissues from human cells

• We are closely following progress

• In the near term hope that cells/tissues from patients could be used instead of some animal disease models to study human disease and effects of pharmaceuticals

• Of great interest for medical counter-measures
Acceptance of Alt Assays

- Already major use in several product sectors for screening
- *In vitro*/alternative assays will be accepted/used if they can answer the regulatory questions; formal validation/qualification is not always needed
- Assessment of systemic tox is a very big challenge and international harmonization of acceptance is needed
Acknowledgements

Abby Jacobs, CDER
Paul Brown, CDER
Cecilia Aguila, CVM
Simone Bancos, CDRH
Jennifer Goode, CDRH
Donna Mendrick, NCTR
Manjanatha Mugimane, NCTR