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

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on behalf of
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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)
ICH53 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
ICH S5 R3 - 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

See CDRH’s 2016 Biocompatibility Guidance:
ISO validation efforts for Device-Specific Methods

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

• ISO/TC 194/WG 09 (hemocompatibility):
  – Round robin testing completed Fall 2016*: hemolysis (\textit{in vitro} method refinement with confirmation of equivalent results for animal/human blood)
  – Round robin testing ongoing: thrombogenicity (\textit{in vitro} method refinement for \textit{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/howtomarketyourdevice/premarketsubmissions/premarketapprovalma/ucm142714.htm](https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/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

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
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