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

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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)**

ICHS3 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**

ICHS5R3-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**

ICHS7 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:**	**Instead on *in vivo* testing for:**
• Chemical characterization & risk assessment	• Systemic toxicity (including genotoxicity, carcinogenicity, and reproductive and developmental toxicity)
• Battery of *in vitro* thrombogenicity assays (for coagulation & platelets)	• Thrombogenicity

See CDRH's 2016 Biocompatibility Guidance:
https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf

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:
https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

Communicating with CDRH (continued)

Device Master File (MAF):

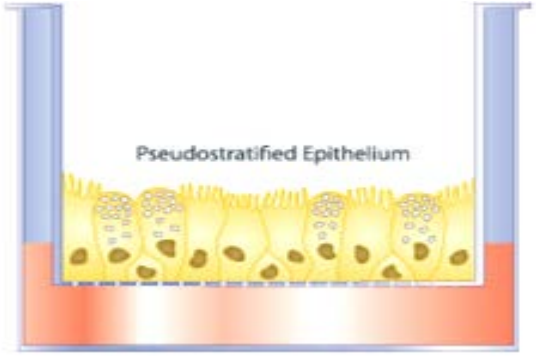
Mechanism to submit validation data for Agency consideration from testing protocols/validation plan agreed to under pre-submission process if outside MDDT program (e.g., *in vitro* alternative methods for biocompatibility testing of medical devices)

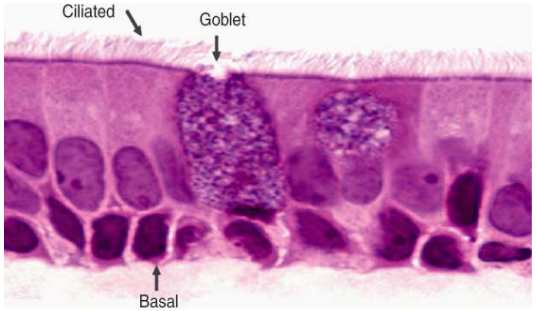
See CDRH's 2014 Device Master File (MAF) webpage:
https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketapprovalpma/ucm142714.htm

NCTR

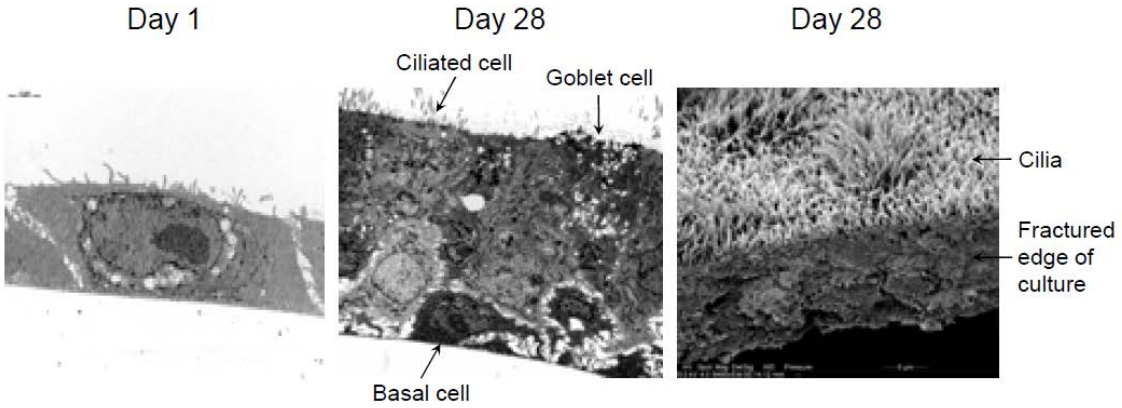
- **Research for FDA**
- *In vitro* human airway tissue model
  - Tight junction disruption by cadmium

NCTR: Differentiated Air Liquid Interface Human Airway Cultures





Normal human airway bronchial epithelium (tissue biopsy)

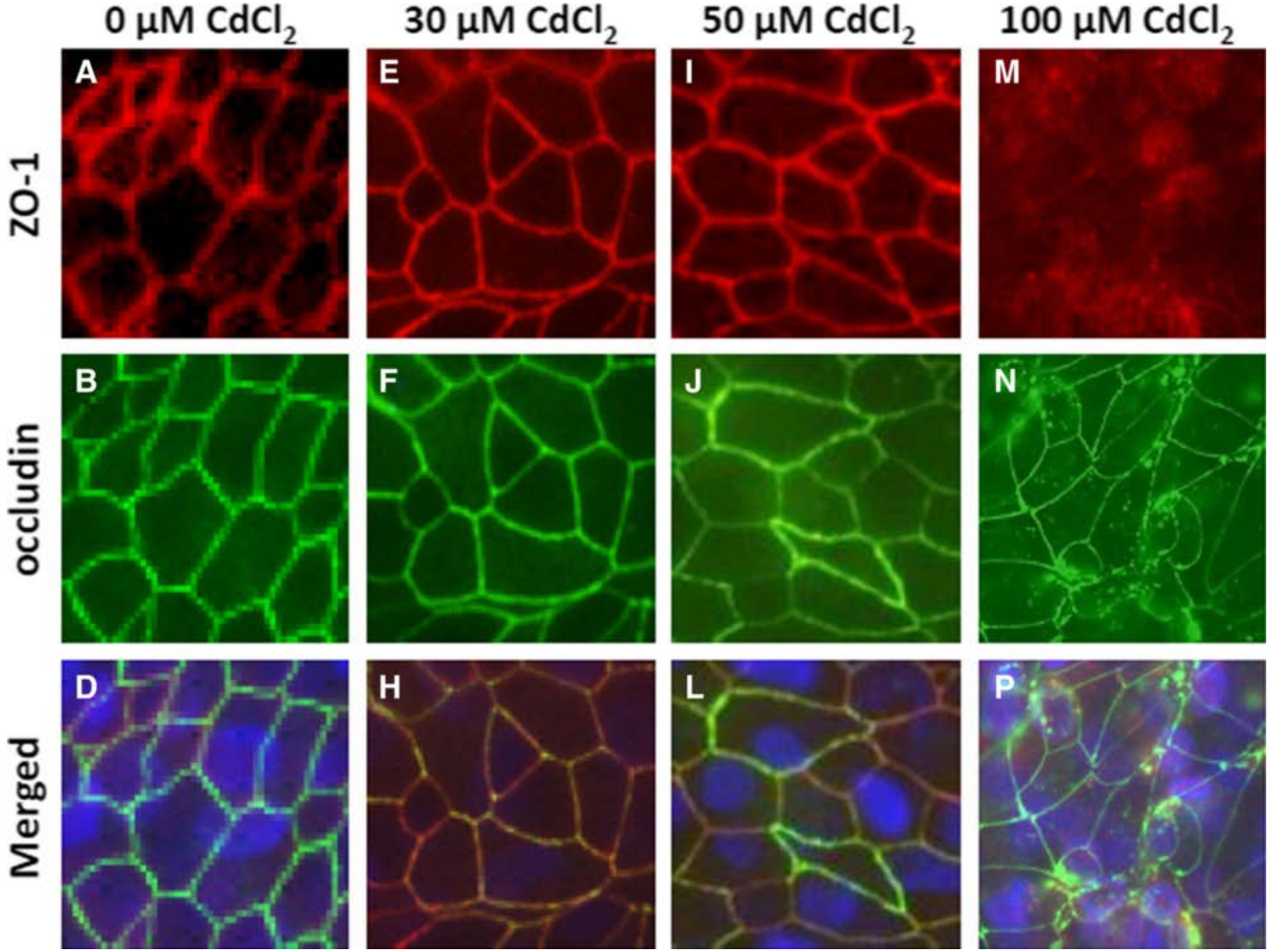


Day 1- confluent monolayer

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