

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)**

ICH S3 Q and A on PK

Microsampling

- A method to collect a very small amount of blood (typically $\leq 50 \mu\text{L}$) 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 S5R3-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:

<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)

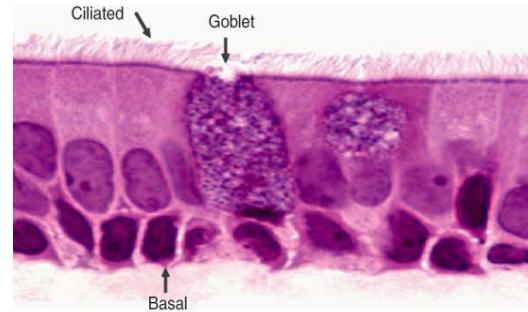
See CDRH's 2014 Device Master File (MAF) webpage:

<https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/premarketapprovalpma/ucm142714.htm>

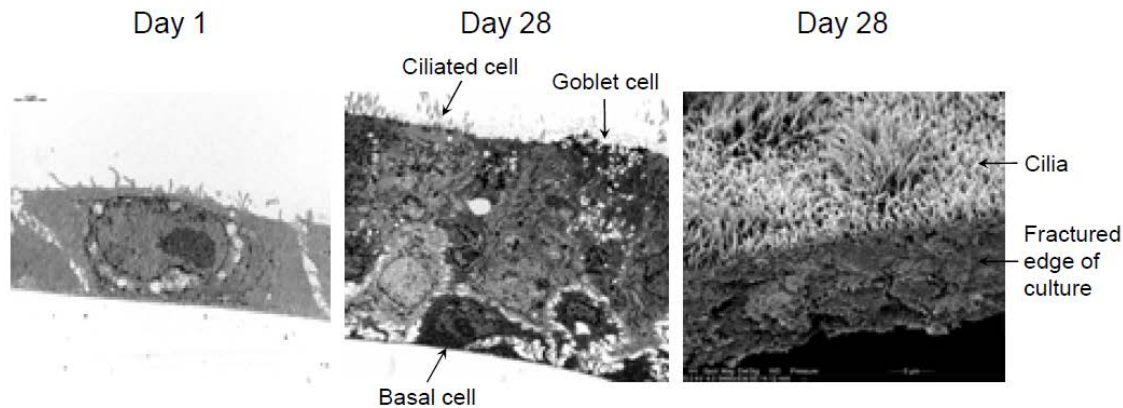
NCTR

- **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

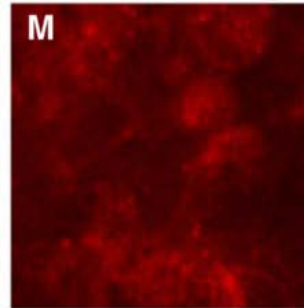
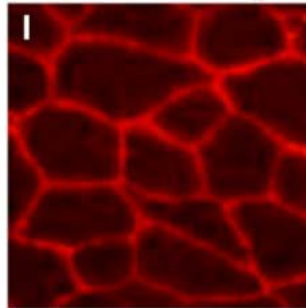
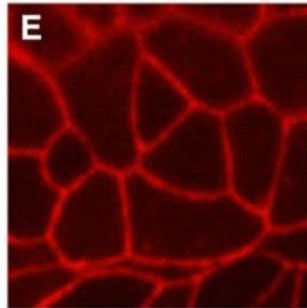
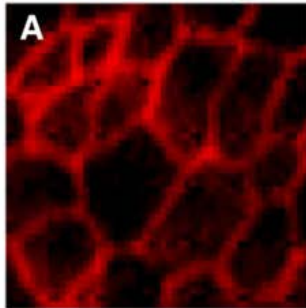
0 μM CdCl_2

30 μM CdCl_2

50 μM CdCl_2

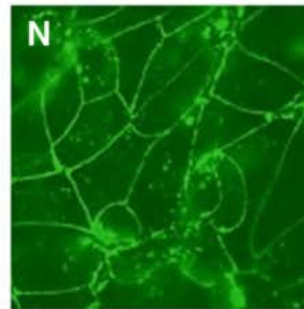
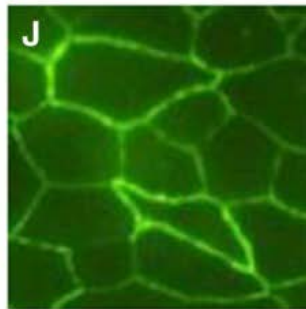
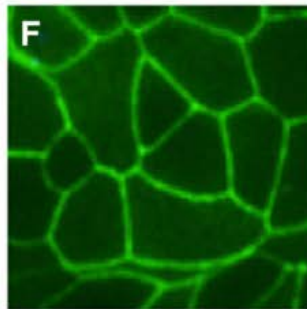
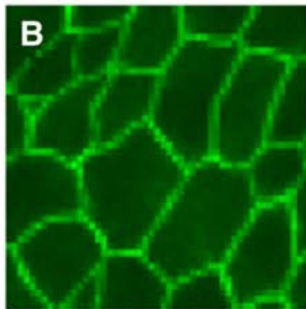
100 μM CdCl_2

ZO-1

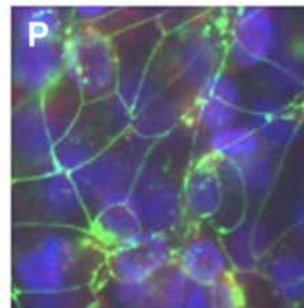
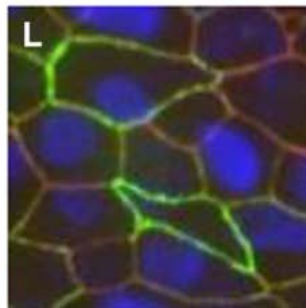
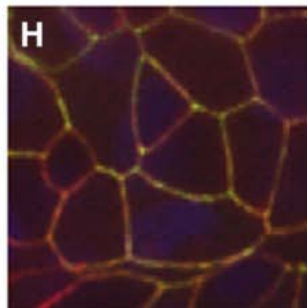
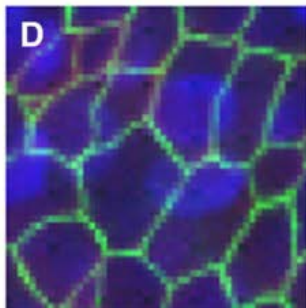


Alterations in tight junction integrity

occludin



Merged



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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