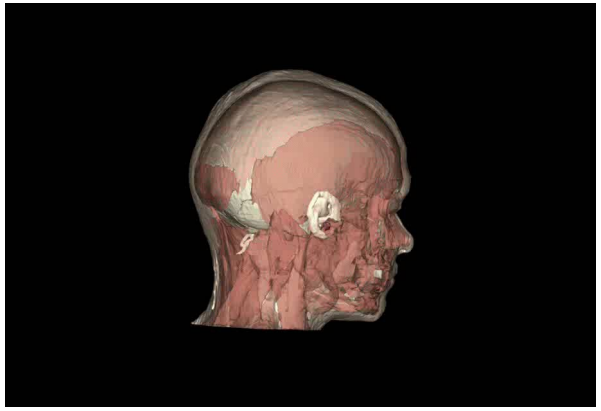


U.S. FOOD & DRUG ADMINISTRATION

# Regulatory Science Tools for accelerating innovation in Toxicology Reviews

Ed Margerrison PhD

Director, Office of Science and Engineering Labs

CDRH, US FDA

# CDRH's Office of Science and Engineering Labs

**165**
FEDERAL EMPLOYEES
Up to 180 visiting scientists

**140 Research Projects**
In 20 Program Areas

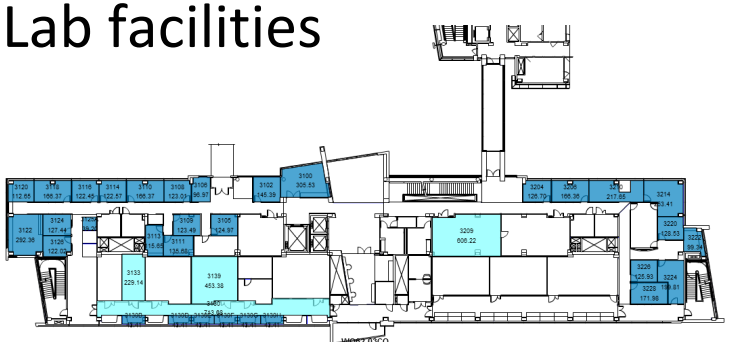
**400/year**
Peer-reviewed presentations, articles, and other public disclosures

**> 3,000/year**
Premarket regulatory reviews

**75**
Standards and conformity assessment committees

**70%**
Staff with a graduate degree

**55,000 ft²**
Lab facilities



# The Family of Evaluation Tools

- Reg Science Tools
  - May be developed in parallel with novel technology
- Medical Device Development Tools
  - Qualified for regulatory use within a specific and defined Context of Use (CoU)
  - Voluntary
  - If used within CoU, methodology prequalified for regulatory pathway use
- Recognized Consensus Standards
  - Quite burdensome to come to consensus
  - Heavy lifting often done by innovators

# Regulatory Science Tools

- Innovative, peer reviewed approach or methodology to help assess the safety or effectiveness of a medical device or emerging technology
  - Brought into the public domain as early as possible before other standards may be available
- We have identified a number of types
  - Virtual and physical phantoms eg PAI phantoms
  - CM&S and related datasets eg in silico clinicals
  - Lab methodologies eg E/L testing methods
  - Best practices eg application specific material selection

# Medical Device Development Tools

- If used within CoU, methodology prequalified for regulatory pathway use

- Guidance Available https://www.fda.gov/media/87134/download
  - Process being updated following 5 years of CDRH experience to 2 steps:

  - Qualification Plan
    - What does the tool measure/ how does it evaluate the safety/ effectiveness of a device?
    - What is the Context of Use?
    - What are the success criteria for the tool?

  - Qualification Phase
    - Collect the data described in the plan

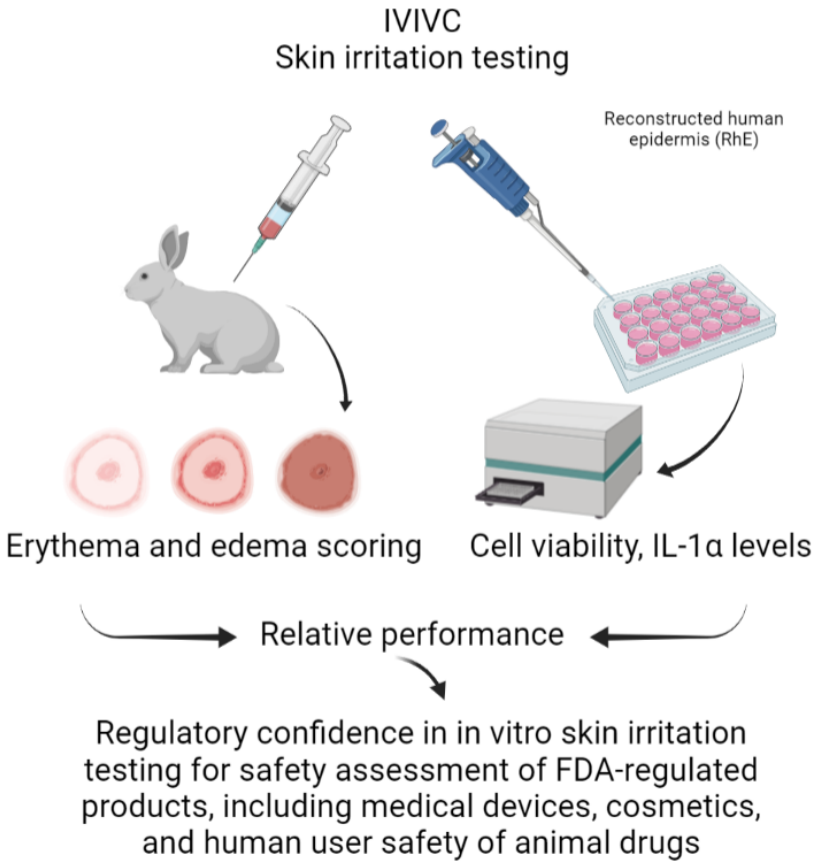
# An Evaluation Tool for All Seasons

(with apologies to Robert Bolt and Sir Thomas More)

- Early de-risking of technology and product development
  - Focus on how good an innovation is and not just how well it is tested
  - More efficient use of scarce resources
- Breadth of technology increasing from other industries
  - E.g. Augmented/ virtual/ extended reality being adapted from gaming
  - Is it sufficiently robust for medical applications?
- Common methodologies drive predictability and premarket review

# In Vitro Alternative to Irritation

- Qualification of the in vitro human skin irritation test for safety assessment of FDA-regulated products
  - Biocomp remains one of the largest areas for deficiencies for device premarket applications
  - Provision of standardized methods will make a massive difference to product development and clearance/ approvals
  - New methods don't need to give exactly the same answer, they need to give the same regulatory decision



# FDA's Color Hazard and RISk Calculator

## 1. Color Additive

Identity: Titanium dioxide (CAS#:13463-67-7)
Molecular weight (g/mol): 1100
Amount (mg): 1.0

## 2. Polymer Matrix

Matrix: Silicone
Mass (g): 1.0
Density (g/cm$^3$): 1.0

## 3. Device Characteristics

Exposed surface area (cm$^2$): 5.0
Exposure type: long-term prolonged limited

## 4. Assumptions

Check all statements below that are applicable to your color additive containing component:

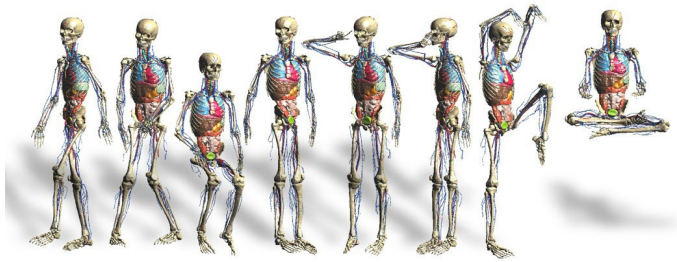
- The clinical use environment does not cause the polymer matrix to swell or degrade.
- Color additive particles/aggregates present in the polymer are much smaller than the smallest component dimension (≤ 50x).
- The color additive is homogeneously distributed throughout the polymer.
- The total amount of color additive is present in dilute concentrations (≤ 2 m/v %).
- Manufacturing processes do not impact the stability of the polymer.

## 5. Exposure Assessment

Click Here

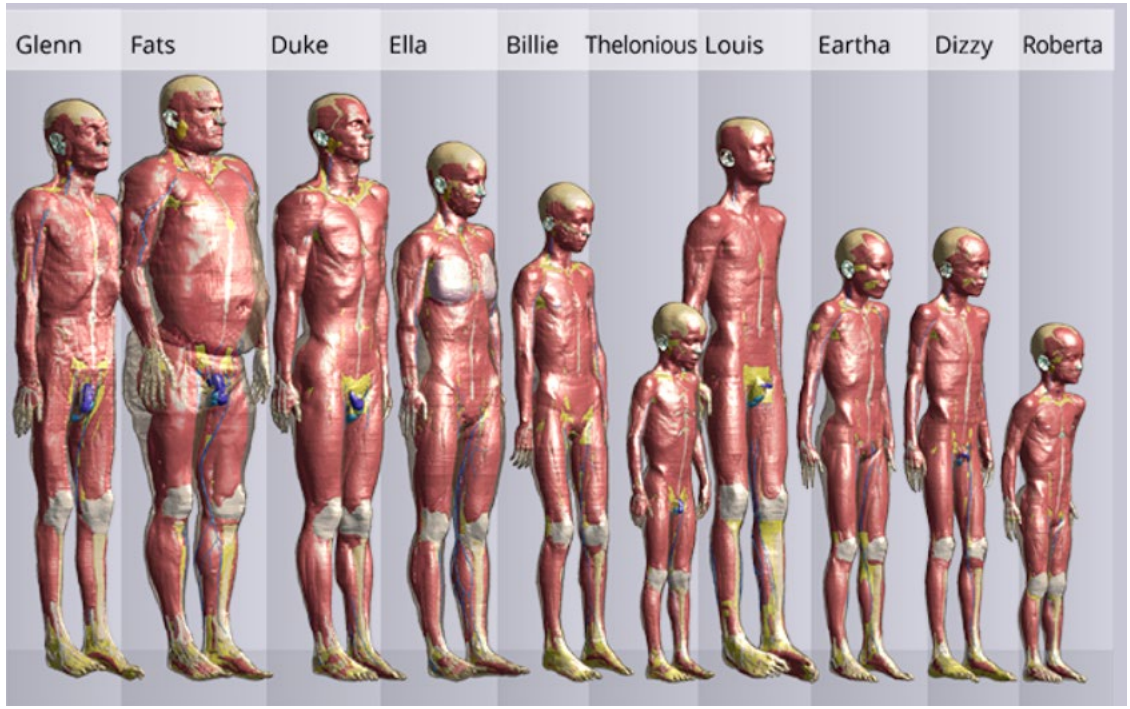
**Disclaimer: CHRIS only addresses risk associated with the presence of color additives and additives and impurities associated with the color additive. Therefore, a favorable outcome by CHRIS does not imply acceptable biological risk for a finished, sterilized device. Further, a successful CHRIS evaluation does not address local biocompatibility endpoints, and therefore additional testing may be needed despite a positive outcome from CHRIS.**

For details on how to use CHRIS, please read the instructions. and context of use (COU). Answers to frequently asked questions can be found here.



# IT'IS and FDA's Virtual Family

- Aset of anatomically correct whole body models for thermal, EM and fluid dynamic simulations
  - Models have been downloaded 000s of times
  - The models have been used in over 200 premarket submissions…
  - Including the world's first 7T MRI without needing a clinical trial




# Public Availability of RSTs and MDDTs

| Phantom Name | Description | Type | Areas | Reference |
|---|---|---|---|---|
| 3D printed phantom material and design with tissue-relevant Raman signature | A tool for performing Raman spectroscopy measurements on a well-characterized 3D printed sample that has tissue-simulating optical properties | Physical | Medical imaging and diagnostics | Article |
| Blood Mimicking Fluid for High Intensity Focused Ultrasound | A blood mimicking fluid (BMF) for the acoustic and thermal characterizations of high intensity focused ultrasound (HIFU) ablation devices | Physical | Therapeutic ultrasound | Article |
| Digital models of retinal vasculature based on a clinical fundus camera image | Digital model available on NIH's 3D Print Exchange site that can be used to fabricate tissue simulating phantoms with biomimetic vascular structures derived from a clinical image | Physical | Medical imaging and diagnostics | Article<br>Article<br>Assembly |
| Microcalcification templates | Templates containing clusters of microcalcifications that can be inserted into physical breast phantoms | Physical | Evaluation of 3D breast imaging systems | Article |
| Nanostructured Virus-simulating Phantoms for Evaluating Optical Biosensing Methods | A shelf-stable, biohazard-free viral particle phantom for evaluation of optical biosensing methods | Physical | Medical imaging and diagnostics | Article |
| Parchment breast phantom | A physical breast phantom fabricated from inkjet printing onto parchment paper that can be pendant, compressed, or contain masses | Physical | Evaluation of 3D breast imaging systems | Article |
| Phantom for assessing performance of near-infrared hematoma detectors | A modular, polymer phantom approach that enables evaluation of the performance of hematoma detectors using wavelengths close to the 805 nm isosbestic point of hemoglobin | Physical | Medical imaging and diagnostics | Article |

https://www.fda.gov/medical-devices/science-and-research-medical-devices/catalog-regulatory-science-tools-help-assess-new-medical-devices

# Some Thoughts and Hypotheses

- Development of methods is the easy part, screening and qualification are hard
  - Every lab in the world has developed methods
- There are many common mistakes
  - “Here’s our plan and our validation data”
  - “Our tool is applicable for all devices”
  - “I published a paper so it’s validated”
- It takes significant resources to qualify tools
  - Often lower priority than premarket review
  - Qualification process capacity is key

# Future Plans

- Expand Reg Science Tools/ Product Catalogue
  - Towards a RST library that is the go to place for evaluations
  - Expand “Owners’ Manuals”
    - Playbook for conducting in silico clinical trials etc
    - CM&S tools are already a valuable scientific tool, but we need to make them a regulatory tool
- Acceleration in the precompetitive space is a team sport
  - Useful methodologies have an intrinsic and tangible value
  - We need programmatic partners to increase capacity 2 orders of magnitude
- Success measured by the number of tools used in premarket applications


# U.S. FOOD & DRUG ADMINISTRATION (& Devices)