IVPT Studies with Sunscreen Products: Potential Regulatory Utility

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Disclaimer

This presentation should **not** be considered, in whole or in part as being statements of policy or recommendation by the United States Government or the US Food and Drug Administration.

This presentation is being given while I am serving as a private consultant and in my private capacity.

The views presented here are my personal views based on my experiences. Researchers are warned that prior to acting on any information presented here today that they should contact the relevant regulatory agency for guidance and concurrence before proceeding.

Throughout the presentation representative products or organizations may be used as examples to emphasize a point, no endorsement is either intended or implied.

ORIENTATION TO PRESENTATION

- I am not here representing the FDA
- I am not here presenting FDA policy
- I am not speaking for or on behalf of the FDA
- I am, however, speaking as an independent consultant with 34 yrs of FDA experience, at least one half of which was in the dermal or transdermal area.

Disclosures

Outline

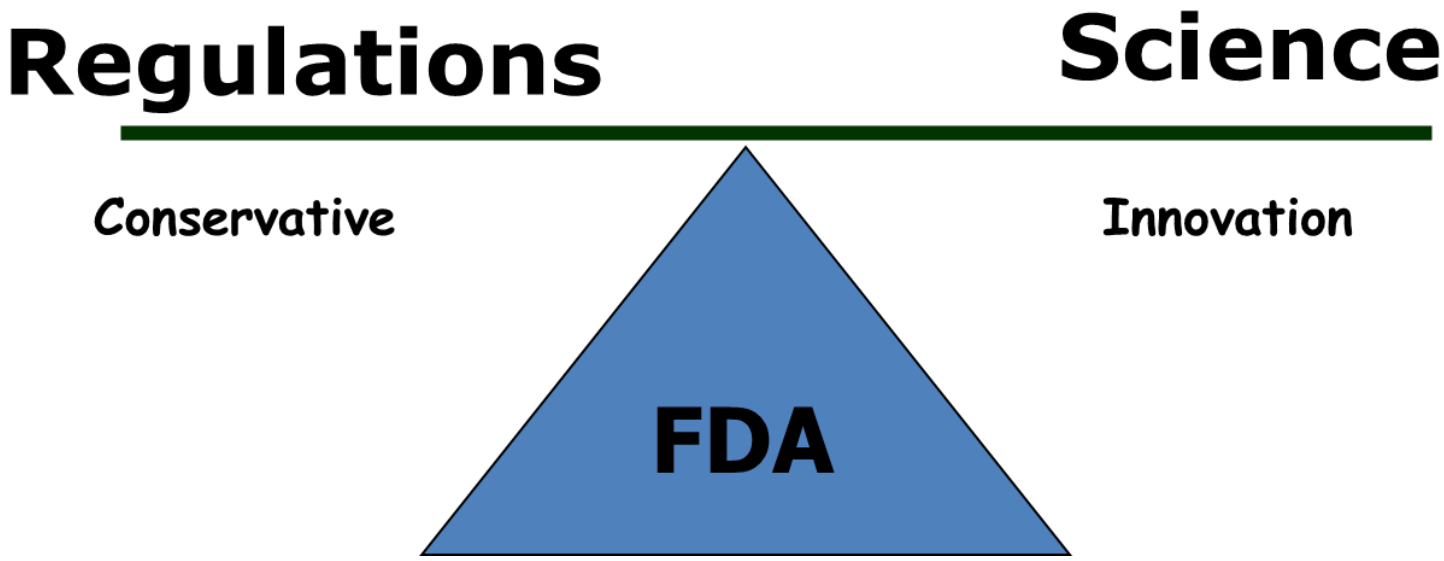
- Regulatory Utility-What is it?
- Sunscreen a “Vehicle” for Change
- IVRT/IVPT Quo Vadis

REGULATORY UTILITY

What is it?

Time to THINK Like a Regulator

The FDA's and CDER's "DUAL" Role



21 CFR 320.22 Criteria for waiver of evidence of in vivo bioavailability or bioequivalence.

- (d) For certain drug products, bioavailability may be measured or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of the drug product if the drug product meets one of the following criteria:
  - (1) [Reserved]
  - (2) The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:
    - (i) The bioavailability of this other drug product has been measured;
    - (ii) Both drug products meet an appropriate in vitro test approved by FDA; and
    - (iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

Acceptance of In Vitro Permeation Testing

General Test Characteristics

- Well defined procedures
  - Validation
  - Standardized Training
- Be reproducible
  - Run to Run
  - Site to Site
- Be predictable
- Be relevant clinically

Relevant in that it MUsT inform the development process

30

- The biggest issue facing the migration of any test from an experimental basis, to regulatory use is reproducibility and validation across different sites

Validation will be the key to acceptance

Why Hasn't IVPT Moved Into Regulatory Use?

- The science is generally well established
- Commercial IVPT single and multi-cell devices are available for use
- IVPT has use in formulation selection for scale-up and formulation development.

What is Lacking?

Why Hasn't IVPT Moved Into Regulatory Use?

- The science is generally well established
- Commercial IVPT single and multi-cell devices are available for use
- IVPT has use in formulation selection for scale-up and formulation development.

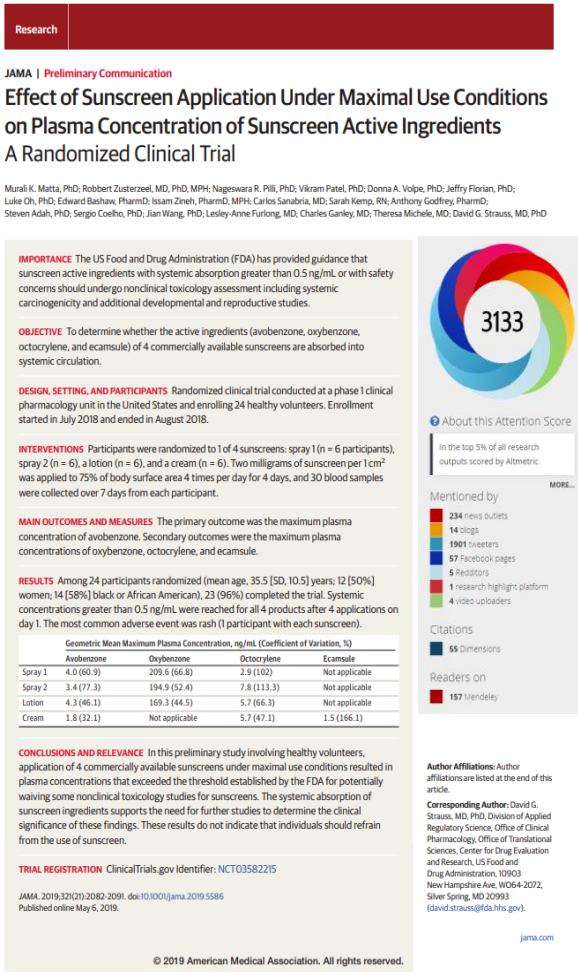
- There is a need for standardization of methods to allow for reproducibility, so as not to repeat the Dermatopharmacokinetics experience.
- Like most "new" methods, there has to be an identified need that the methodology solves.
  - In cannot be a "method in search of a problem"
  - There needs to be an unmet need that the method can fulfill

Sunscreens

A “Vehicle” For Change

FDA MUsT Publications on Sunscreen Absorption

May 2019



Research

JAMA | Preliminary Communication

Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients

A Randomized Clinical Trial

Murali K. Matta, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Jeffry Florian, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

IMPORTANCE The US Food and Drug Administration (FDA) has provided guidance that sunscreen active ingredients with systemic absorption greater than 0.5 ng/mL or with safety concerns should undergo nonclinical toxicology assessment including systemic carcinogenicity and additional developmental and reproductive studies.

OBJECTIVE To determine whether the active ingredients (avobenzone, oxybenzone, octocrylene, and ecamsule) of 4 commercially available sunscreens are absorbed into systemic circulation.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at a phase 1 clinical pharmacology unit in the United States and enrolling 24 healthy volunteers. Enrollment started in July 2018 and ended in August 2018.

INTERVENTIONS Participants were randomized to 1 of 4 sunscreens: spray 1 (n = 6 participants), spray 2 (n = 6), a lotion (n = 6), and a cream (n = 6). Two milligrams of sunscreen per 1 cm^2 was applied to 75% of body surface area 4 times per day for 4 days, and 30 blood samples were collected over 7 days from each participant.

MAIN OUTCOMES AND MEASURES The primary outcome was the maximum plasma concentration of avobenzone. Secondary outcomes were the maximum plasma concentrations of oxybenzone, octocrylene, and ecamsule.

RESULTS Among 24 participants randomized (mean age, 35.5 [SD, 10.5] years; 12 [50%] women; 14 [58%] black or African American), 23 (96%) completed the trial. Systemic concentrations greater than 0.5 ng/mL were reached for all 4 products after 4 applications on day 1. The most common adverse event was rash (1 participant with each sunscreen).

	Geometric Mean Maximum Plasma Concentration, ng/mL (Coefficient of Variation, %)			
	Avobenzone	Oxybenzone	Octocrylene	Ecamsule
Spray 1	4.0 (60.9)	209.6 (66.8)	2.9 (102)	Not applicable
Spray 2	3.4 (77.3)	194.9 (52.4)	7.8 (113.3)	Not applicable
Lotion	4.3 (46.1)	169.3 (44.5)	5.7 (66.3)	Not applicable
Cream	1.8 (32.1)	Not applicable	5.7 (47.1)	1.5 (166.1)

CONCLUSIONS AND RELEVANCE In this preliminary study involving healthy volunteers, application of 4 commercially available sunscreens under maximal use conditions resulted in plasma concentrations that exceeded the threshold established by the FDA for potentially waiving some nonclinical toxicology studies for sunscreens. The systemic absorption of sunscreen ingredients supports the need for further studies to determine the clinical significance of these findings. These results do not indicate that individuals should refrain from the use of sunscreen.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03582215

JAMA. 2019;321(21):2082-2091. doi:10.1001/jama.2019.5586
Published online May 6, 2019.

3133

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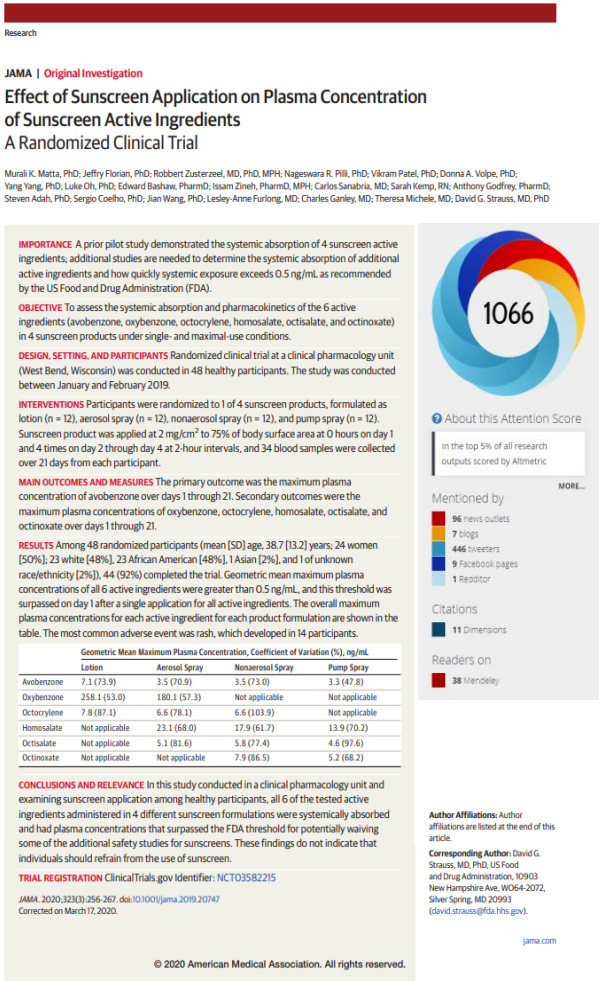
Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: David G. Strauss, MD, PhD, Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, WO64-2072, Silver Spring, MD 20993 (david.strauss@fda.hhs.gov).

March 2020



Research

JAMA | Original Investigation

Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients

A Randomized Clinical Trial

Murali K. Matta, PhD; Jeffry Florian, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Yang Yang, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

IMPORTANCE A prior pilot study demonstrated the systemic absorption of 4 sunscreen active ingredients; additional studies are needed to determine the systemic absorption of additional active ingredients and how quickly systemic exposure exceeds 0.5 ng/mL as recommended by the US Food and Drug Administration (FDA).

OBJECTIVE To assess the systemic absorption and pharmacokinetics of the 6 active ingredients (avobenzone, oxybenzone, octocrylene, homosalate, octisalate, and octinoxate) in 4 sunscreen products under single- and maximal-use conditions.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial at a clinical pharmacology unit (West Bend, Wisconsin) was conducted in 48 healthy participants. The study was conducted between January and February 2019.

INTERVENTIONS Participants were randomized to 1 of 4 sunscreen products, formulated as lotion (n = 12), aerosol spray (n = 12), nonaerosol spray (n = 12), and pump spray (n = 12). Sunscreen product was applied at 2 mg/cm^2 to 75% of body surface area at 0 hours on day 1 and 4 times on day 2 through day 4 at 2-hour intervals, and 34 blood samples were collected over 21 days from each participant.

MAIN OUTCOMES AND MEASURES The primary outcome was the maximum plasma concentration of avobenzone over days 1 through 21. Secondary outcomes were the maximum plasma concentrations of oxybenzone, octocrylene, homosalate, octisalate, and octinoxate over days 1 through 21.

RESULTS Among 48 randomized participants (mean [SD] age, 38.7 [13.2] years; 24 women [50%]; 23 white [48%], 23 African American [48%], 1 Asian [2%], and 1 of unknown race/ethnicity [2%]), 44 (92%) completed the trial. Geometric mean maximum plasma concentrations of all 6 active ingredients were greater than 0.5 ng/mL, and this threshold was surpassed on day 1 after a single application for all active ingredients. The overall maximum plasma concentrations for each active ingredient for each product formulation are shown in the table. The most common adverse event was rash, which developed in 14 participants.

	Geometric Mean Maximum Plasma Concentration, Coefficient of Variation (%), ng/mL			
	Lotion	Aerosol Spray	Nonaerosol Spray	Pump Spray
Avobenzone	7.1 (73.9)	3.5 (70.9)	3.5 (73.0)	3.3 (47.8)
Oxybenzone	258.1 (53.0)	180.1 (57.3)	Not applicable	Not applicable
Octocrylene	7.8 (87.1)	6.6 (78.1)	6.6 (103.9)	Not applicable
Homosalate	Not applicable	23.1 (68.0)	17.9 (61.7)	13.9 (70.2)
Octisalate	Not applicable	5.1 (81.6)	5.8 (77.4)	4.6 (97.6)
Octinoxate	Not applicable	Not applicable	7.9 (86.5)	5.2 (68.2)

CONCLUSIONS AND RELEVANCE In this study conducted in a clinical pharmacology unit and examining sunscreen application among healthy participants, all 6 of the tested active ingredients administered in 4 different sunscreen formulations were systemically absorbed and had plasma concentrations that surpassed the FDA threshold for potentially waiving some of the additional safety studies for sunscreens. These findings do not indicate that individuals should refrain from the use of sunscreen.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03582215

JAMA. 2020;323(3):256-267. doi:10.1001/jama.2019.20747
Corrected on March 17, 2020.

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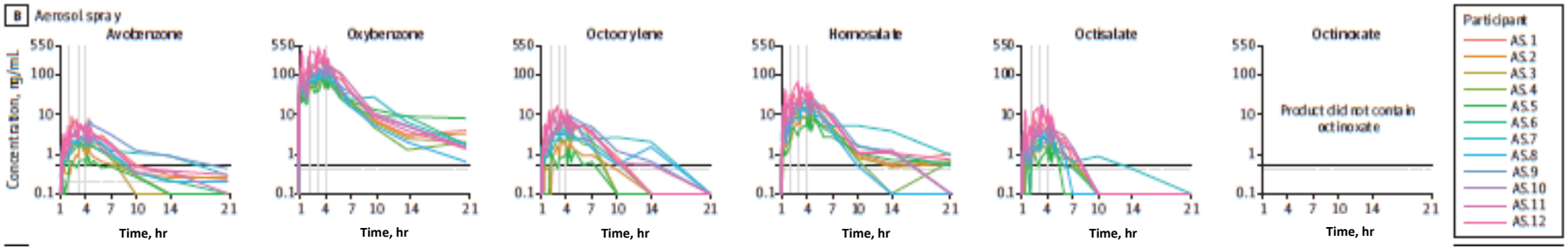
Representative Single Dose Absorption Data



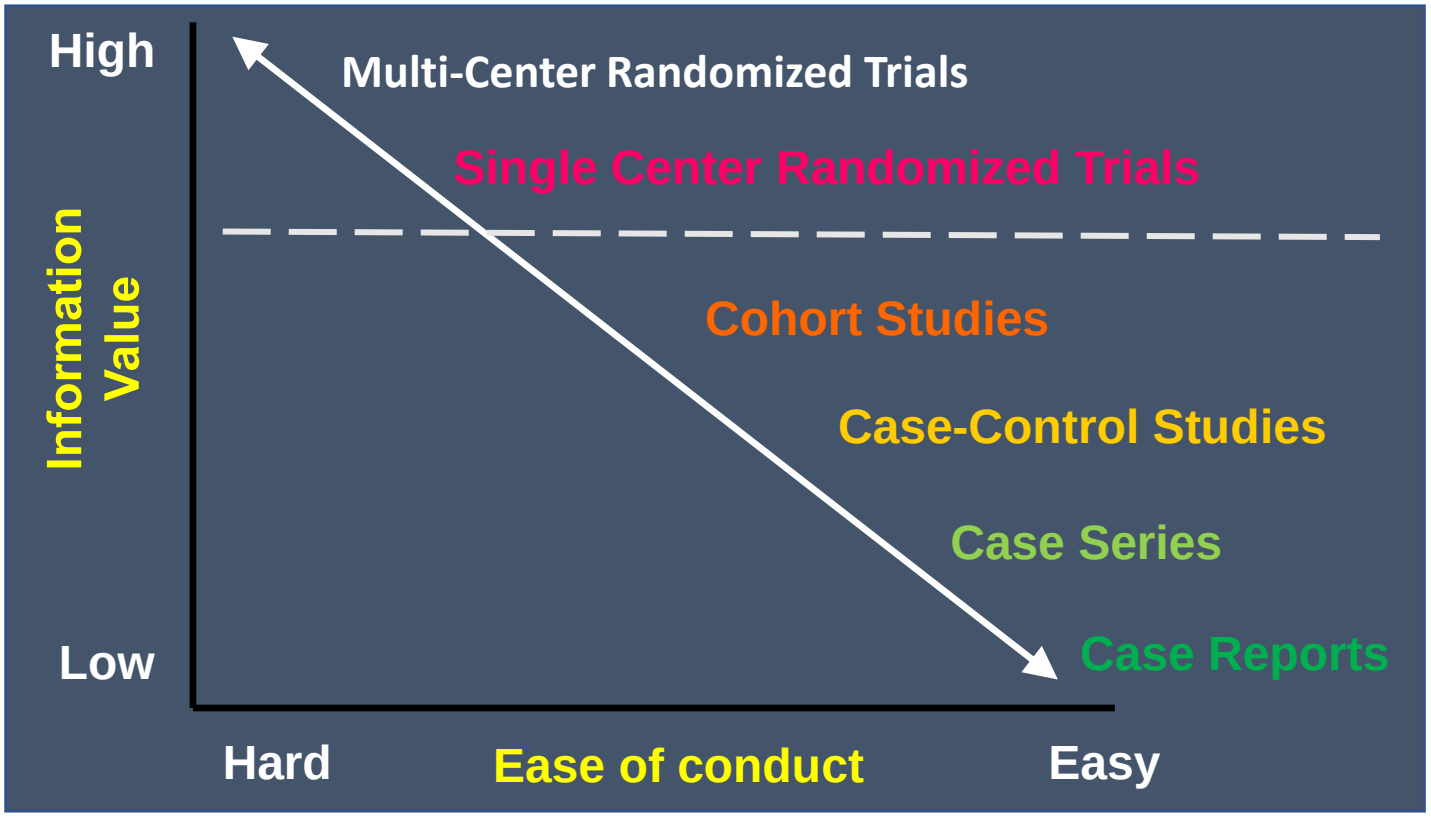
- One of the key findings of this study was that all of the tested sunscreen produced in vivo plasma levels following a single dose (2mg/cm^2 applied to 75%BSA)
- The original figure had the wrong x-axis units, this figure has been corrected *(see JAMA. 2020;323(11):1098. doi:10.1001/jama.2020.1950)*

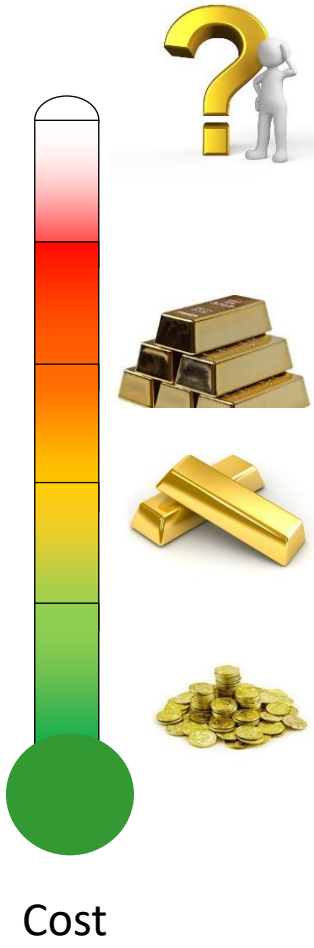
Note: The identities and formulations of the test products are contained in the Supplemental Materials section, supplement 1 pages 39-40

Why Are Sunscreens a “Vehicle” for IVPT

- Sunscreens are marketed by many manufacturers in a variety of dosage forms
- Sunscreens undergo significant reformulations over time
  - The sunscreens of the 1960s or 1980s (as formulated) are not marketed today
  - Reformulations of existing products are to be expected
- The use of sunscreen active ingredients in cosmetic and other consumer products has proliferated in parallel to the concern over solar skin damage and subsequent premature aging
- Maximum Usage Trials or MUsT’s can answer the absorption question but they are complicated and are not (generally) considered a routine test in this setting

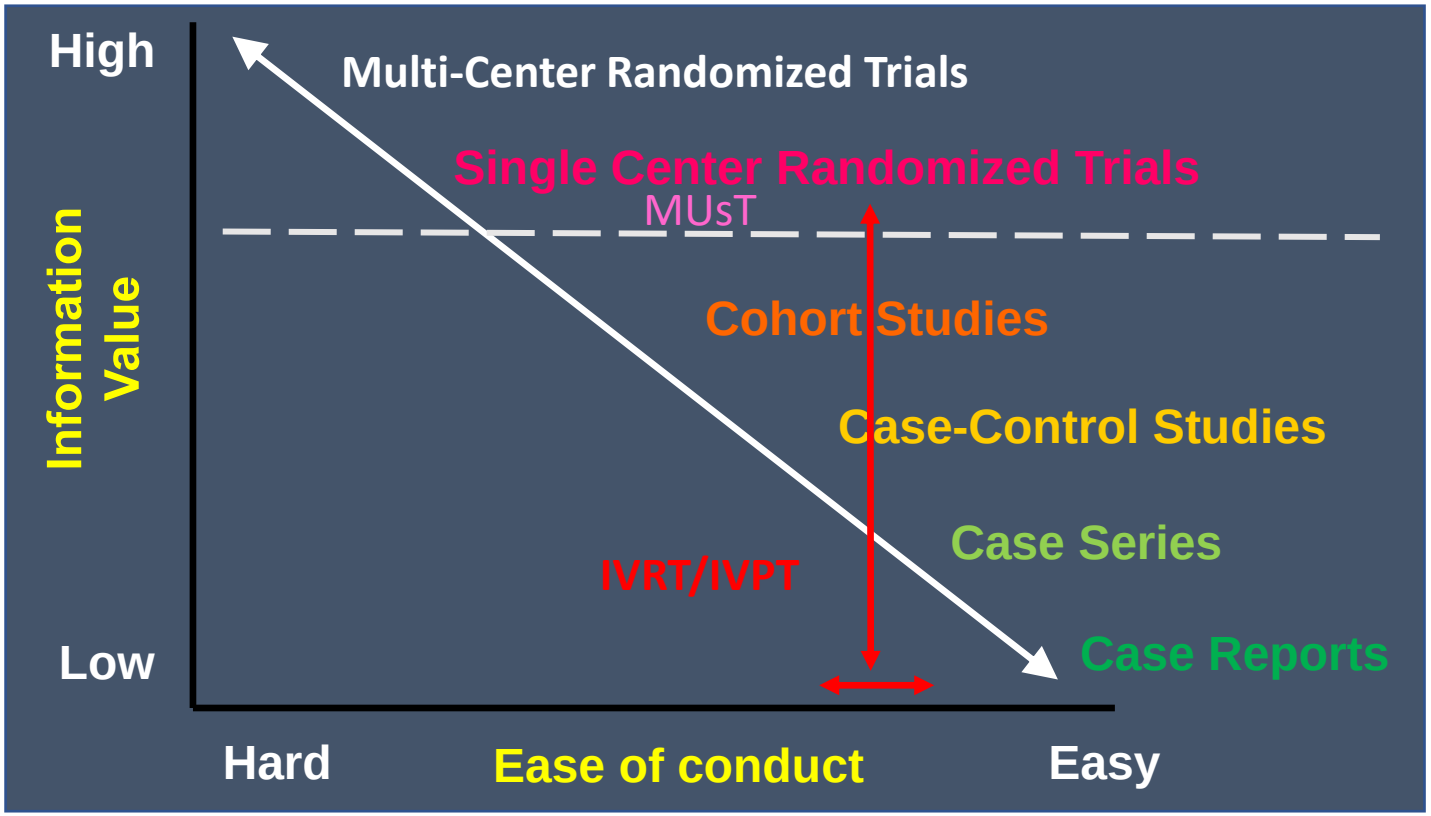
The Cost of Research vs Ease of Conduct

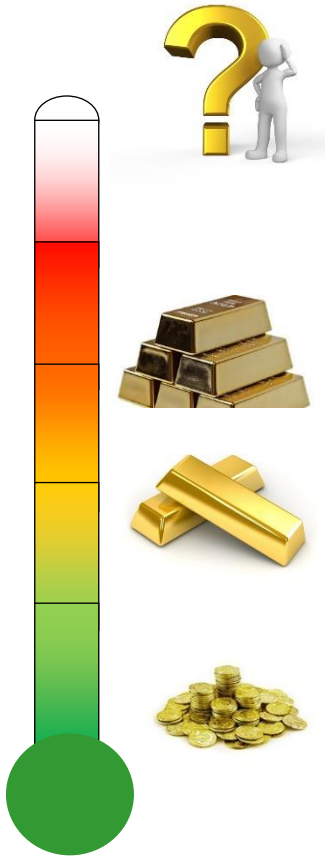




Normally, the ease of conduct is directly related to cost and inversely related to the relative informational value of the study.

The Cost of Research vs Ease of Conduct





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Advancing the Use/Standardization of In Vitro Permeation Testing (IVPT)

- IVPT is a key element in formulation selection but has historically had some issues with acceptance due to issues of reproducibility.
- OGD research led by Dr. Raney's group has developed a Q3 paradigm that resulted in the approval of a generic for acyclovir ointment
- In the last few years the FDA has published two articles on the use of IVPT in topical drug development and evaluation, primarily focusing on sunscreens.
  - The first article was focused as a "best practices strawman" for developing a consistent test that can be of regulatory use.
    - https://doi.org/10.1177/2168479019875338
  - The second article was focused on the permeation of sunscreen from the FDA labs led by Dr. Yang.
    - https://doi.org/10.1016/j.jid.2020.04.009

IVPT Acceptance Scorecard

In Hand Elements

- ✓We have a defined need to assess formulation changes in an in vitro setting that can be used to maintain the currency of pre-clinical safety findings
- ✓We have a methodology that is probably as close to the biological system as we can get (short of microdialysis) at this time
- ✓We have a regulatory need and interest in the methodology

Missing Elements

- ❑Standardization of Methods
  - ❑Proliferation of differential methods is not to be preferred
- ❑Validation of Methods
  - ❑To include cross-lab reproducibility (DPK experience)

IVRT/IVPT Quo Vadis

We have had a methodology, but have not used it to its full potential because of a lack of driving force

We now have a need, in the case of sunscreens where this methodology can potentially lessen a regulatory burden, and to be clear the burden is on both sides

What is holding us back is inertia in the system, fear of the unknown

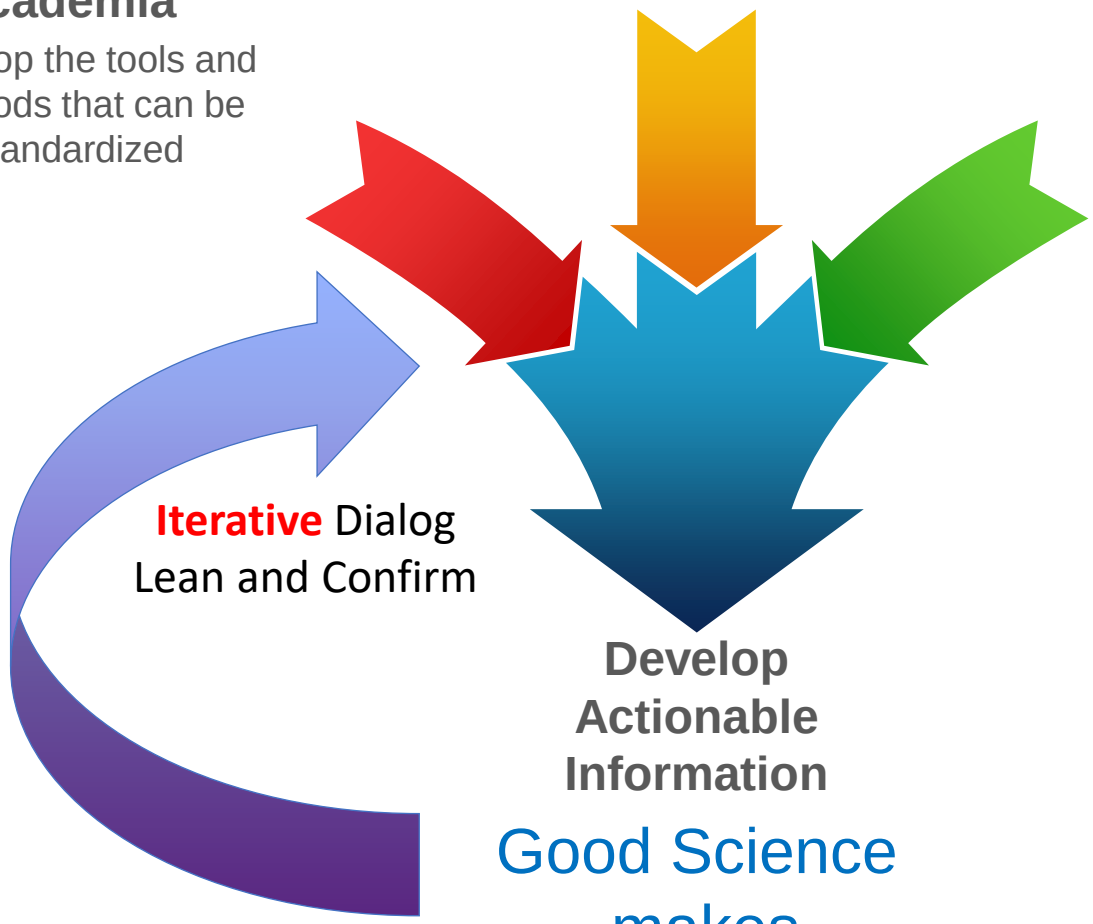
IVPT Adoption as a Regulatory Method (NDA/ANDA/Other)

- The question is often asked “When will the FDA accept “X” data or method for approval?” The answer is “When will YOU do it?”
- Science and regulatory policy does not exits in a vacuum. All of us, those at the FDA and those in academia or industry have a role to play.
- For IVPT, Sunscreens and the issues surrounding their absorption provide an impetus for the development of IVPT methods that can be validated.

Industry
Support and adopt the methodologies

Academia
Develop the tools and methods that can be standardized

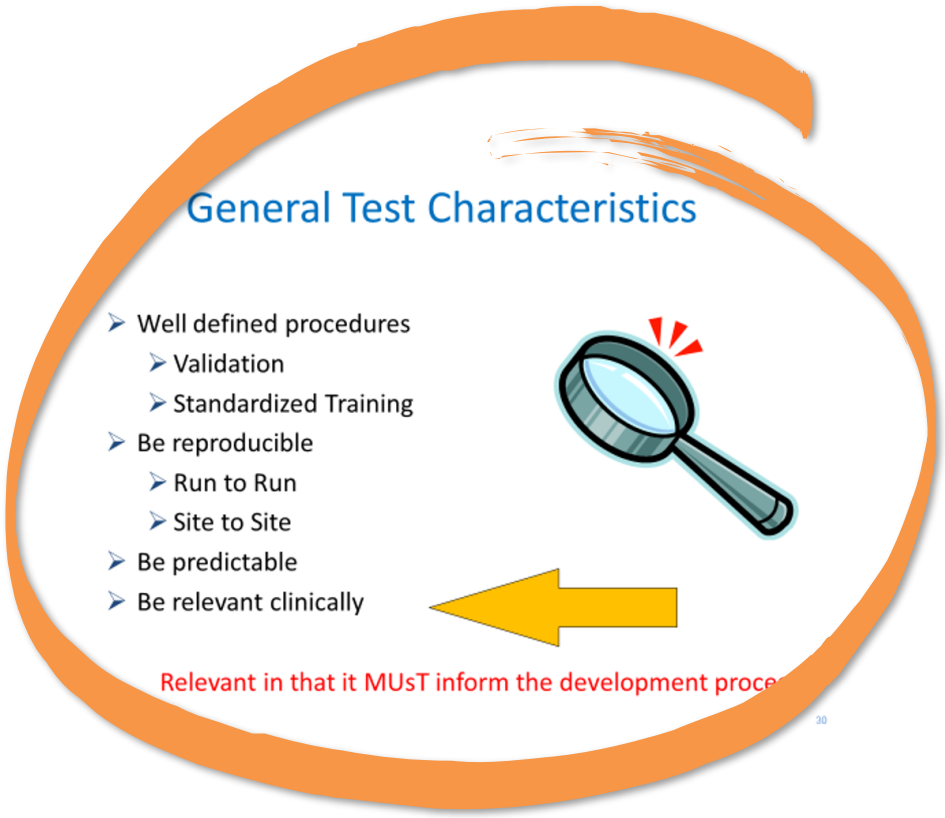
Regulators
Communicate clearly expectations and the benefit to a paradigm shift to stakeholders



Develop Actionable Information

Good Science makes Good Policy

Acceptance of In Vitro Permeation Testing



- The biggest issue facing the migration of any test from an experimental basis, to regulatory use is reproducibility and validation across different sites

Validation will be the key to acceptance

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Regulatory Approaches for New Drugs: BA/BE of Topical Drug Products

CAPT E. Dennis Bashaw, Pharm.D
Director, Division of Clinical Pharmacology-3
Office of Clinical Pharmacology
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General Test Characteristics

- Well defined procedures
  - Validation
  - Standardized Training
- Be reproducible
  - Run to Run
  - Site to Site
- Be predictable
- Be relevant clinically

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Dir. Div. of Clincal Pharmacology-3
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General Test Characteristics

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  - Validation
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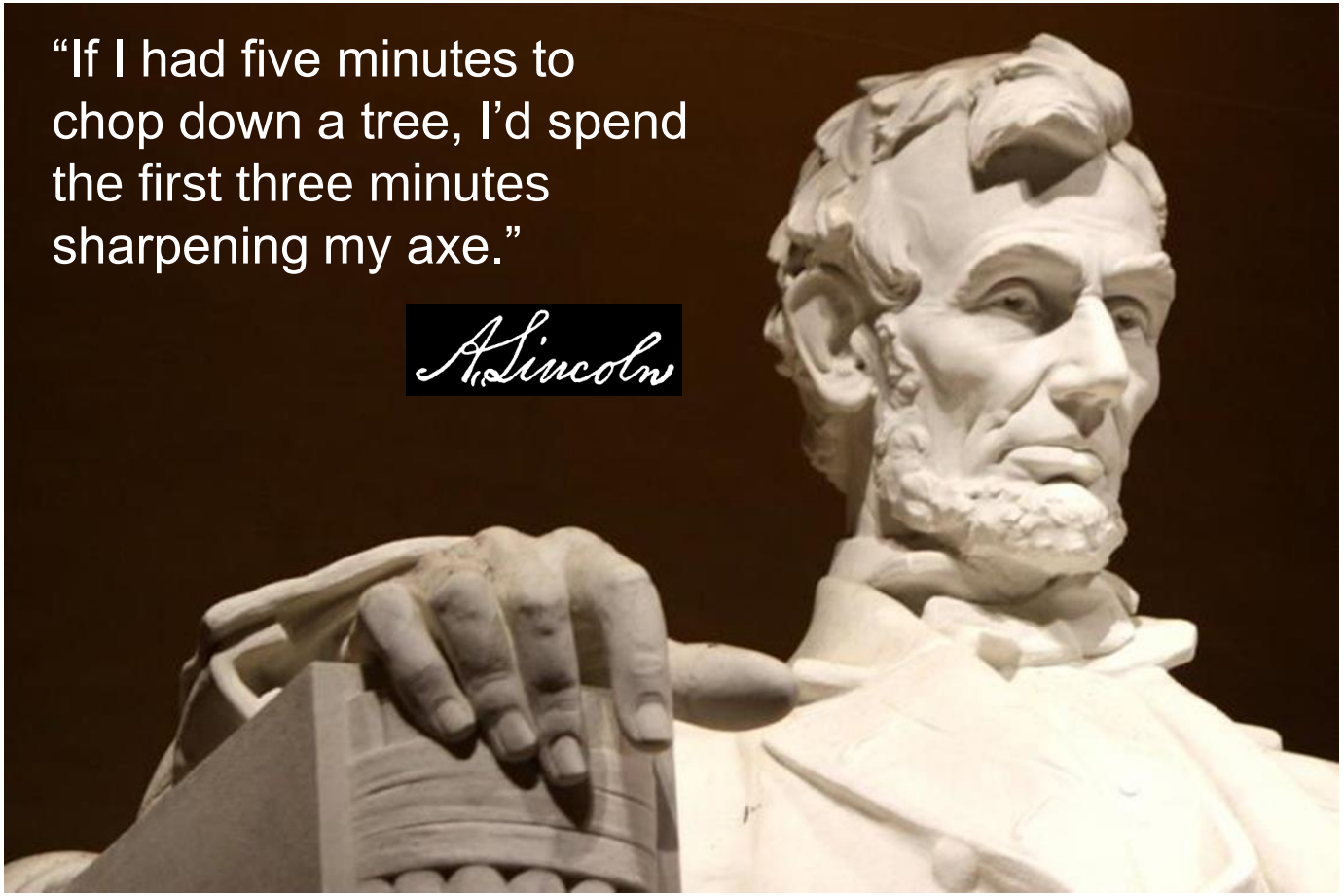
Is 2021 IVPT's Time? If NOT, then WHEN?



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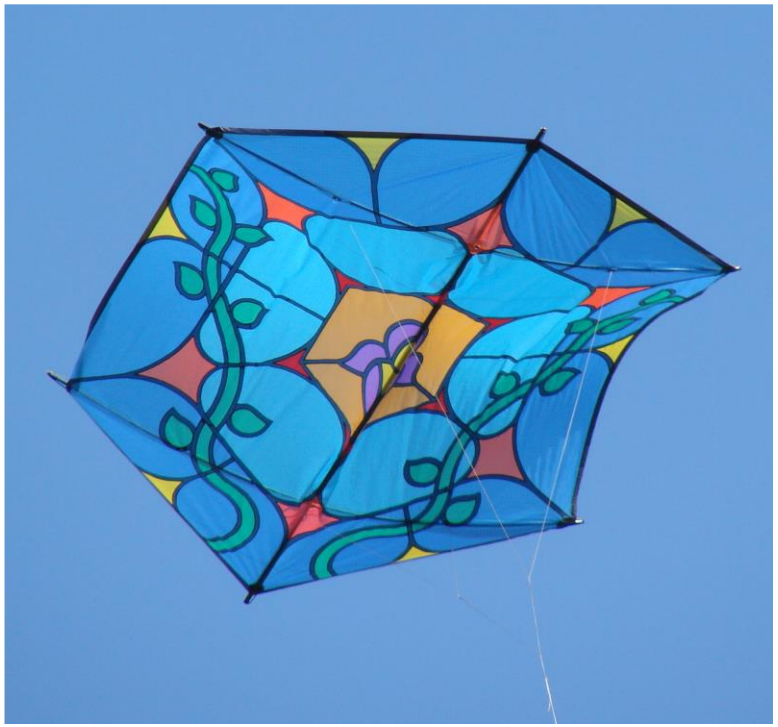

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