Current Program Update

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- The presentation today should not be considered, in whole or in part, as statements of policy or recommendation by the US Food and Drug Administration.
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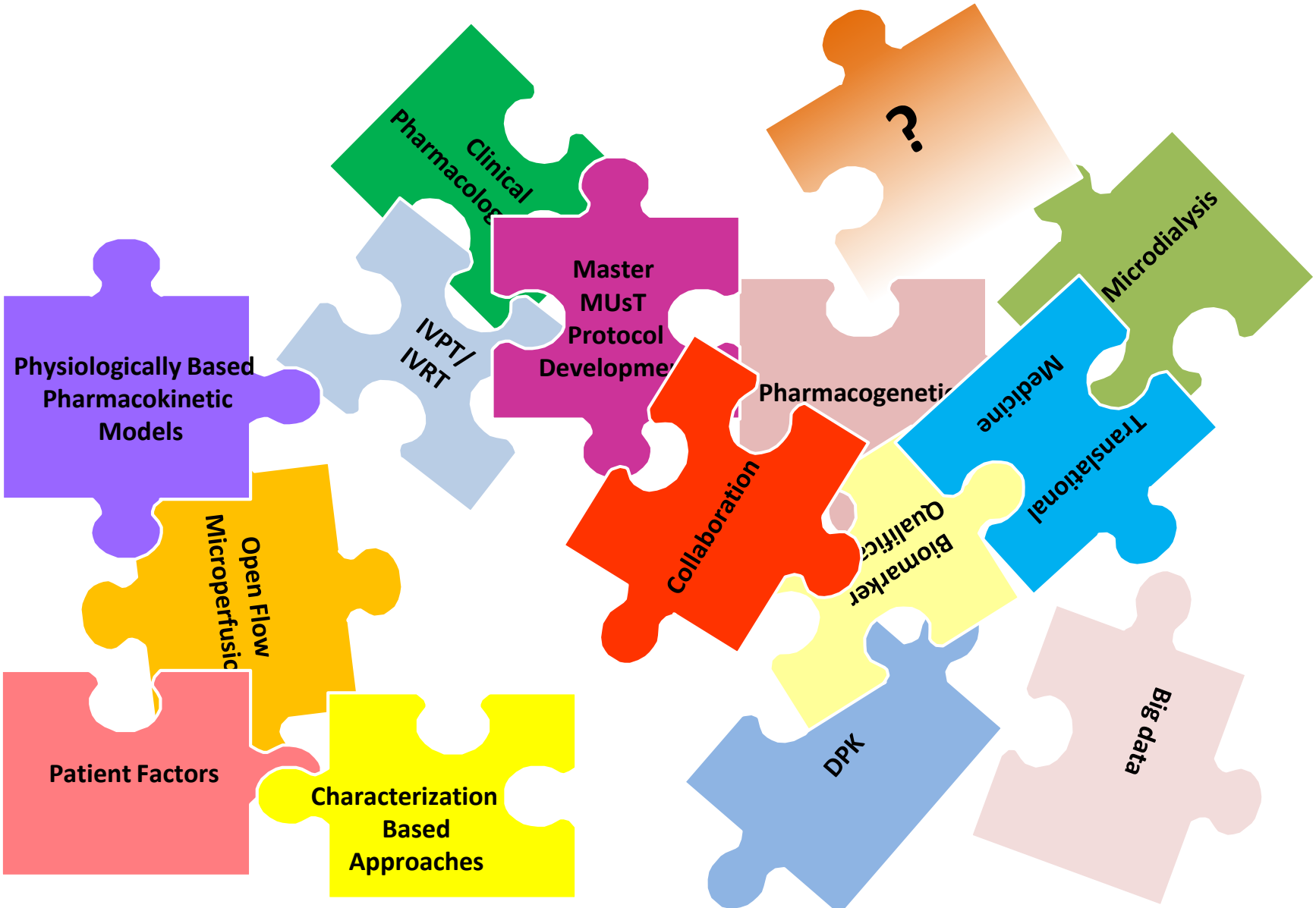
WELCOME TO THE GREAT ROOM AT THE FDA

The Current State of Dermal Absorption Assessment

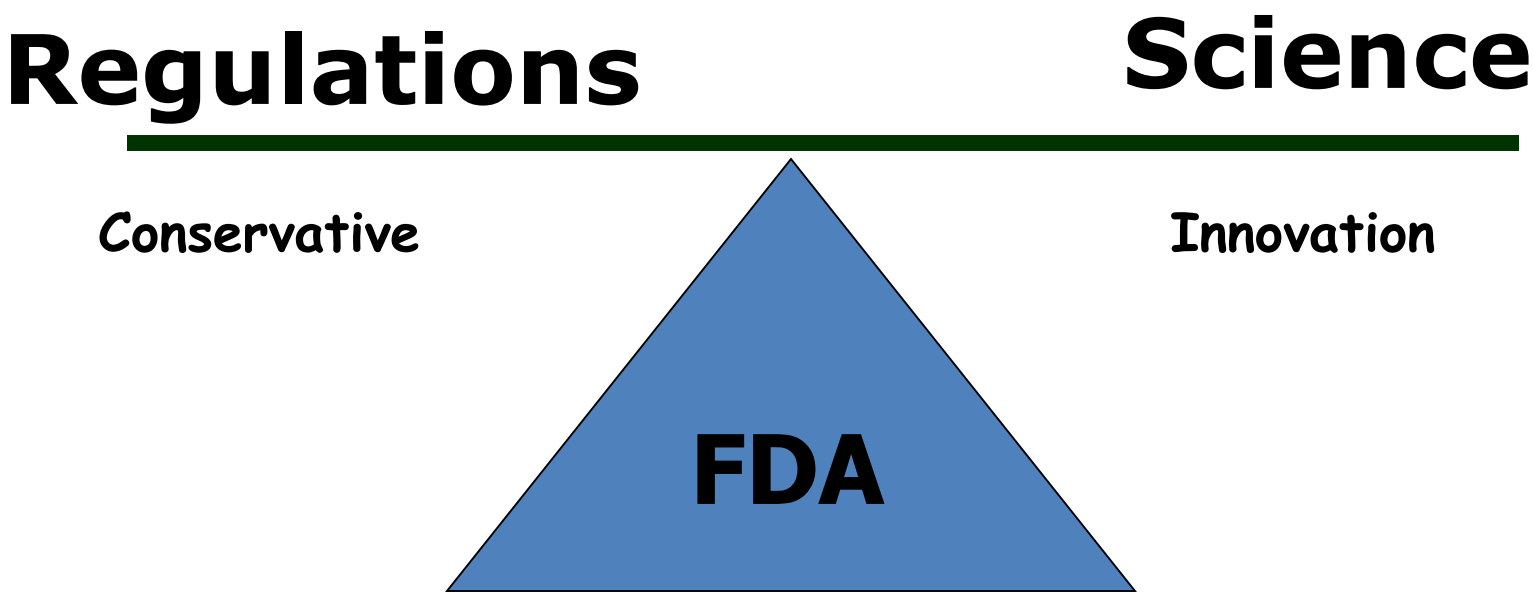


Update on Dermal Absorption Activities

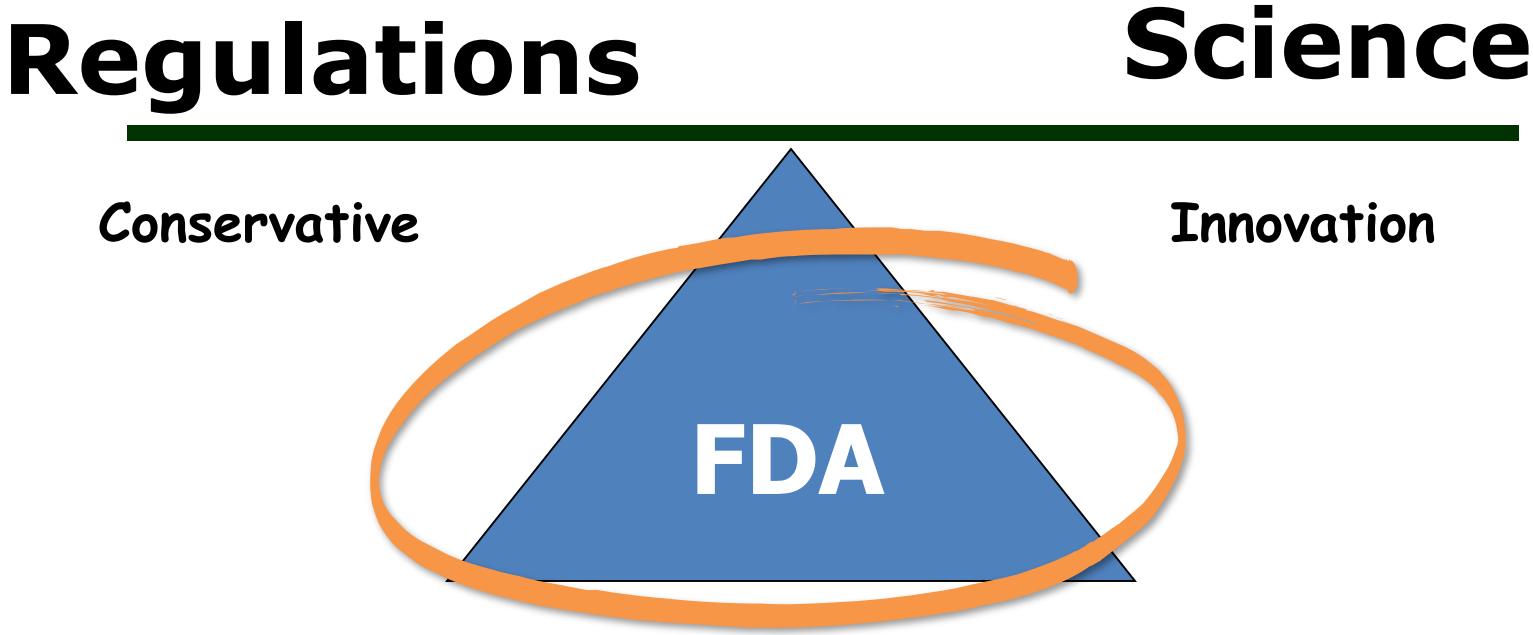
- COVID 19 has had a dramatic impact on the FDA
- The last “full staff” day at the FDA was March 16th
- Large amounts of FTE resources are being allocated regards to support of COVID-19 related priorities
  - For the Office of Clinical Pharmacology’s Monograph Group this has revolved (not surprisingly) around hand sanitizers and related issues

- Despite the difficulties in collaboration, the FDA staff working in the dermal absorption area, across all offices, have accomplished a lot that I will summarize and you will hear more about from the later speakers.

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



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



FDA Activates*

The term “Activates” is used here as often the “actions and activities” of the FDA drive other research and the science at large

*Not a typo

External Outreach

- Complicated by COVID-19
- Presentations cancelled (selected)
  - AAD
  - The Photodermatology Society
  - This workshop (twice)
  - 9th International Symposia on Microdialysis

- In early 2020 a series of talks were given at the New York Society for Cosmetic Chemists meeting at the end of January speakers included:
  - Myself
  - Dr. Raney
  - Dr. Stinchcomb
  - Dr. Yi

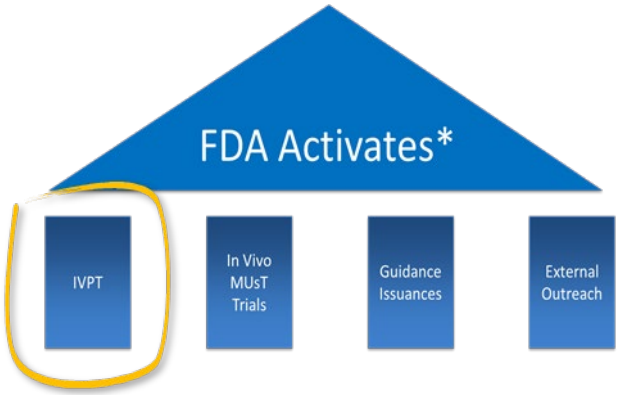
External Outreach

- In 2021 the FDA hopes to again be able to engage with the scientific community in person rather than via webex, zoom, or emails.

- For this reason, your feedback about this workshop, its pluses and minuses from an educational and scientific content delivery standpoint is very important.

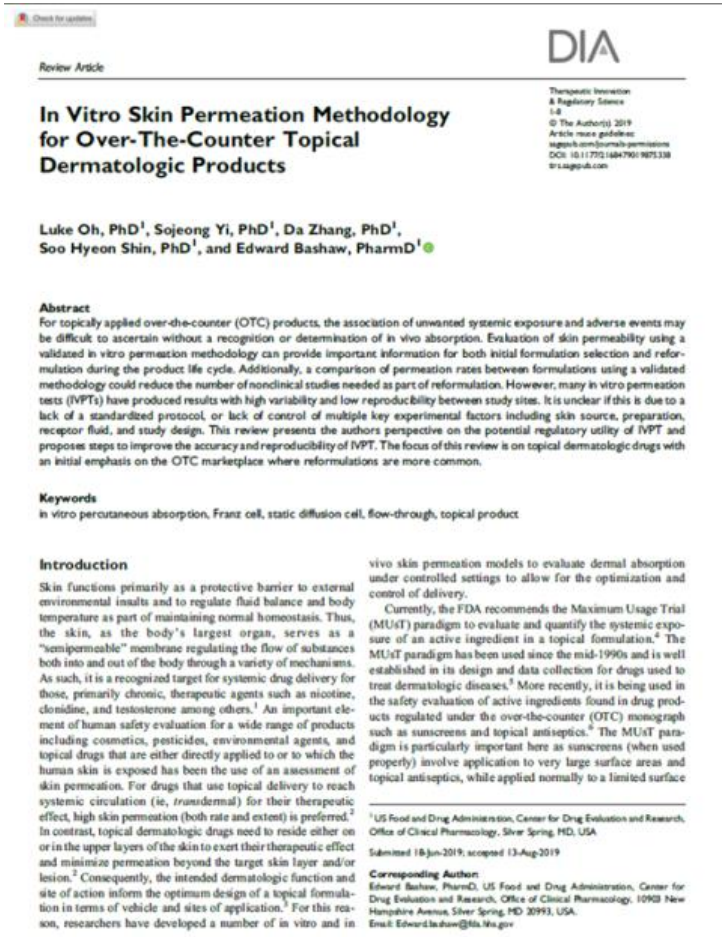
- Following the conference we will reach out and make available an opportunity for you to provide feedback and encourage you to do so.

In Vitro Permeation Testing (IVPT)



- IVPT is a key element in formulation selection but has historically had some issues with acceptance.
- Since the last workshop the FDA has published two articles on the use of IVPT in topical drug development and evaluation.
- The first article was focused as a “best practices strawman” for developing a consistent test that can be of regulatory use.
- The second article was focused on the permeation of sunscreen and the data from that article will be discussed by the lead author Dr. Yang.

In Vitro Permeation Testing (IVPT)



Review Article

DIA

Therapeutic Innovation & Regulatory Science 1–8
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dia.sagepub.com

In Vitro Skin Permeation Methodology for Over-The-Counter Topical Dermatologic Products

Luke Oh, PhD[1], Sojeong Yi, PhD[1], Da Zhang, PhD[1], Soo Hyeon Shin, PhD[1], and Edward Bashaw, PharmD[1]

Abstract

For topically applied over-the-counter (OTC) products, the association of unwanted systemic exposure and adverse events may be difficult to ascertain without a recognition or determination of in vivo absorption. Evaluation of skin permeability using a validated in vitro permeation methodology can provide important information for both initial formulation selection and reformulation during the product life cycle. Additionally, a comparison of permeation rates between formulations using a validated methodology could reduce the number of nonclinical studies needed as part of reformulation. However, many in vitro permeation tests (IVPTs) have produced results with high variability and low reproducibility between study sites. It is unclear if this is due to a lack of a standardized protocol, or lack of control of multiple key experimental factors including skin source, preparation, receptor fluid, and study design. This review presents the authors perspective on the potential regulatory utility of IVPT and proposes steps to improve the accuracy and reproducibility of IVPT. The focus of this review is on topical dermatologic drugs with an initial emphasis on the OTC marketplace where reformulations are more common.

Keywords

in vitro percutaneous absorption, Franz cell, static diffusion cell, flow-through, topical product

Introduction

Skin functions primarily as a protective barrier to external environmental insults and to regulate fluid balance and body temperature as part of maintaining normal homeostasis. Thus, the skin, as the body's largest organ, serves as a "semipermeable" membrane regulating the flow of substances both into and out of the body through a variety of mechanisms. As such, it is a recognized target for systemic drug delivery for those, primarily chronic, therapeutic agents such as nicotine, clonidine, and testosterone among others.[1] An important element of human safety evaluation for a wide range of products including cosmetics, pesticides, environmental agents, and topical drugs that are either directly applied to or to which the human skin is exposed has been the use of an assessment of skin permeation. For drugs that use topical delivery to reach systemic circulation (ie, *trans*dermal) for their therapeutic effect, high skin permeation (both rate and extent) is preferred.[2] In contrast, topical dermatologic drugs need to reside either on or in the upper layers of the skin to exert their therapeutic effect and minimize permeation beyond the target skin layer and/or lesion.[2] Consequently, the intended dermatologic function and site of action inform the optimum design of a topical formulation in terms of vehicle and sites of application.[3] For this reason, researchers have developed a number of in vitro and in vivo skin permeation models to evaluate dermal absorption under controlled settings to allow for the optimization and control of delivery.

Currently, the FDA recommends the Maximum Usage Trial (MUsT) paradigm to evaluate and quantify the systemic exposure of an active ingredient in a topical formulation.[4] The MUsT paradigm has been used since the mid-1990s and is well established in its design and data collection for drugs used to treat dermatologic diseases.[5] More recently, it is being used in the safety evaluation of active ingredients found in drug products regulated under the over-the-counter (OTC) monograph such as sunscreens and topical antiseptics.[6] The MUsT paradigm is particularly important here as sunscreens (when used properly) involve application to very large surface areas and topical antiseptics, while applied normally to a limited surface

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- Topics covered include
  - System selection
    - Static vs Flow-Thru
  - Skin selection for use
    - Donor
    - Skin site
    - Skin Integrity
    - Thickness
    - Preparation and storage
  - Receptor fluid
    - Temperature
    - Agitation
    - Duration
  - Study Design
    - Duration
    - Sampling time intervals
    - Replicates

https://doi.org/10.1177/2168479019875338

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

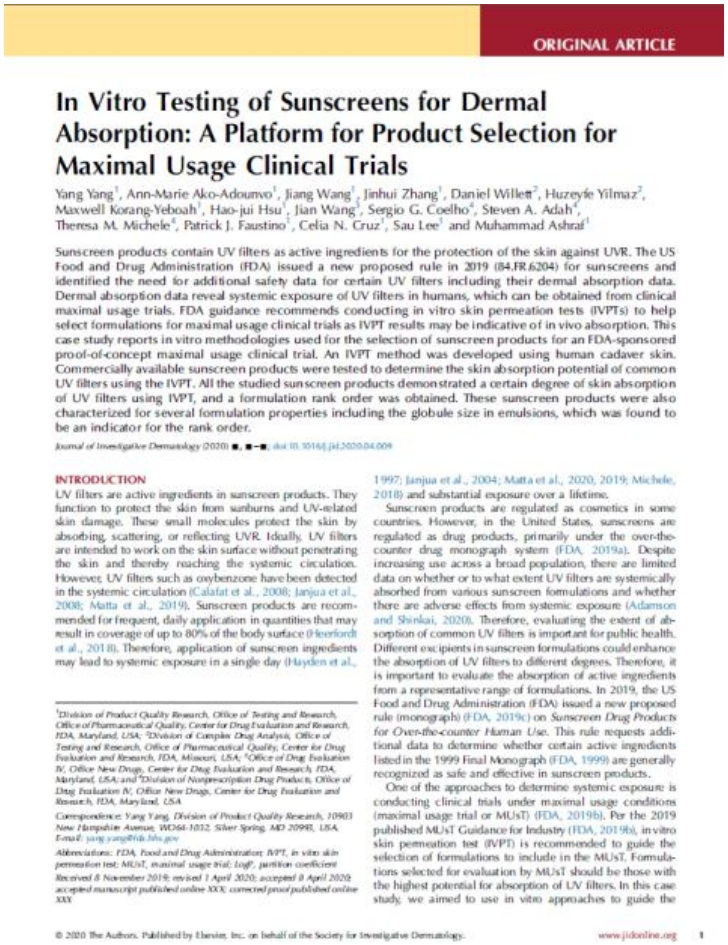
Relevant in that it MUsT inform the development process

30

- The purpose of the paper was to be a true “strawman” to advance the conversation to begin to move a laboratory test into a regulatory test.
- 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

In Vitro Permeation Testing (IVPT)



ORIGINAL ARTICLE

In Vitro Testing of Sunscreens for Dermal Absorption: A Platform for Product Selection for Maximal Usage Clinical Trials

Yang Yang[1], Ann-Marie Ako-Adounvo[1], Jiang Wang[1], Jinhui Zhang[1], Daniel Willett[2], Huzeyfe Yilmaz[2], Maxwell Korang-Yeboah[1], Hao-jui Hsu[1], Jian Wang[3], Sergio G. Coelho[4], Steven A. Adah[4], Theresa M. Michele[5], Patrick J. Faustino[1], Celia N. Cruz[1], Sau Lee[1] and Muhammad Ashraf[1]

Sunscreen products contain UV filters as active ingredients for the protection of the skin against UVR. The US Food and Drug Administration (FDA) issued a new proposed rule in 2019 (84.FR.6204) for sunscreens and identified the need for additional safety data for certain UV filters including their dermal absorption data. Dermal absorption data reveal systemic exposure of UV filters in humans, which can be obtained from clinical maximal usage trials. FDA guidance recommends conducting in vitro skin permeation tests (IVPTs) to help select formulations for maximal usage clinical trials as IVPT results may be indicative of in vivo absorption. This case study reports in vitro methodologies used for the selection of sunscreen products for an FDA-sponsored proof-of-concept maximal usage clinical trial. An IVPT method was developed using human cadaver skin. Commercially available sunscreen products were tested to determine the skin absorption potential of common UV filters using the IVPT. All the studied sunscreen products demonstrated a certain degree of skin absorption of UV filters using IVPT, and a formulation rank order was obtained. These sunscreen products were also characterized for several formulation properties including the globule size in emulsions, which was found to be an indicator for the rank order.

Journal of Investigative Dermatology (2020) ■, ■–■; doi:10.1016/j.jid.2020.04.009

INTRODUCTION

UV filters are active ingredients in sunscreen products. They function to protect the skin from sunburns and UV-related skin damage. These small molecules protect the skin by absorbing, scattering, or reflecting UVR. Ideally, UV filters are intended to work on the skin surface without penetrating the skin and thereby reaching the systemic circulation. However, UV filters such as oxybenzone have been detected in the systemic circulation (Calafat et al., 2008; Janjua et al., 2008; Matta et al., 2019). Sunscreen products are recommended for frequent, daily application in quantities that may result in coverage of up to 80% of the body surface (Heerfordt et al., 2018). Therefore, application of sunscreen ingredients may lead to systemic exposure in a single day (Hayden et al., 1997; Janjua et al., 2004; Matta et al., 2020, 2019; Michele, 2018) and substantial exposure over a lifetime.

Sunscreen products are regulated as cosmetics in some countries. However, in the United States, sunscreens are regulated as drug products, primarily under the over-the-counter drug monograph system (FDA, 2019a). Despite increasing use across a broad population, there are limited data on whether or to what extent UV filters are systemically absorbed from various sunscreen formulations and whether there are adverse effects from systemic exposure (Adamson and Shinkai, 2020). Therefore, evaluating the extent of absorption of common UV filters is important for public health. Different excipients in sunscreen formulations could enhance the absorption of UV filters to different degrees. Therefore, it is important to evaluate the absorption of active ingredients from a representative range of formulations. In 2019, the US Food and Drug Administration (FDA) issued a new proposed rule (monograph) (FDA, 2019c) on *Sunscreen Drug Products for Over-the-counter Human Use*. This rule requests additional data to determine whether certain active ingredients listed in the 1999 Final Monograph (FDA, 1999) are generally recognized as safe and effective in sunscreen products.

One of the approaches to determine systemic exposure is conducting clinical trials under maximal usage conditions (maximal usage trial or MUsT) (FDA, 2019b). Per the 2019 published MUsT Guidance for Industry (FDA, 2019b), in vitro skin permeation test (IVPT) is recommended to guide the selection of formulations to include in the MUsT. Formulations selected for evaluation by MUsT should be those with the highest potential for absorption of UV filters. In this case study, we aimed to use in vitro approaches to guide the

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Abbreviations: FDA, Food and Drug Administration; IVPT, in vitro skin permeation test; MUsT, maximal usage trial; LogP, partition coefficient

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https://doi.org/10.1016/j.jid.2020.04.009

FDA In Vivo MUsT Study #2

THE WALL STREET JOURNAL.

ARTICLES

THE NUMBERS

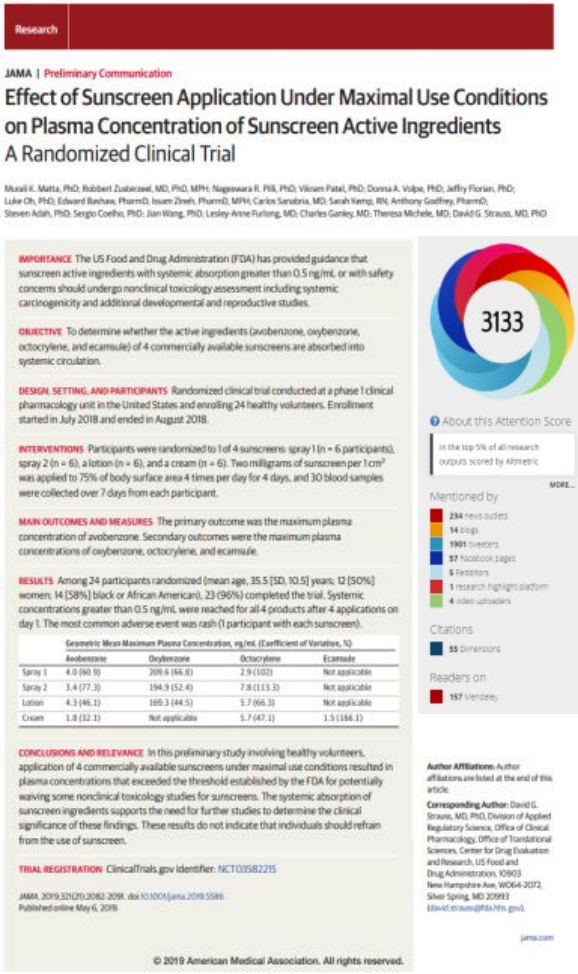
Sunscreen Chemicals Accumulate in Body at High Levels

July 17, 2020 05:30 am ET

For the second time in less than a year, a study of common sunscreen ingredients has established that the chemicals are absorbed into the bloodstream at concentrations far greater than the Food and Drug Administration's safety threshold.

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 toxicities.

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 I 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.

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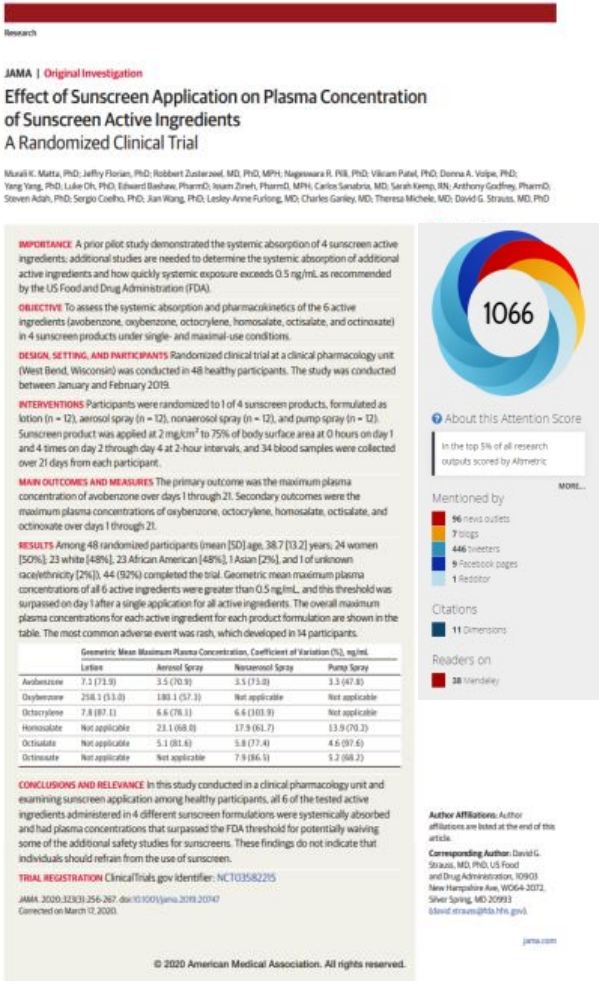
March 2020



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 (73.3)	3.5 (70.9)	3.5 (73.0)	3.3 (47.8)
Oxybenzone	258.1 (53.0)	180.1 (57.1)	Not applicable	Not applicable
Octocrylene	7.8 (87.1)	6.6 (76.1)	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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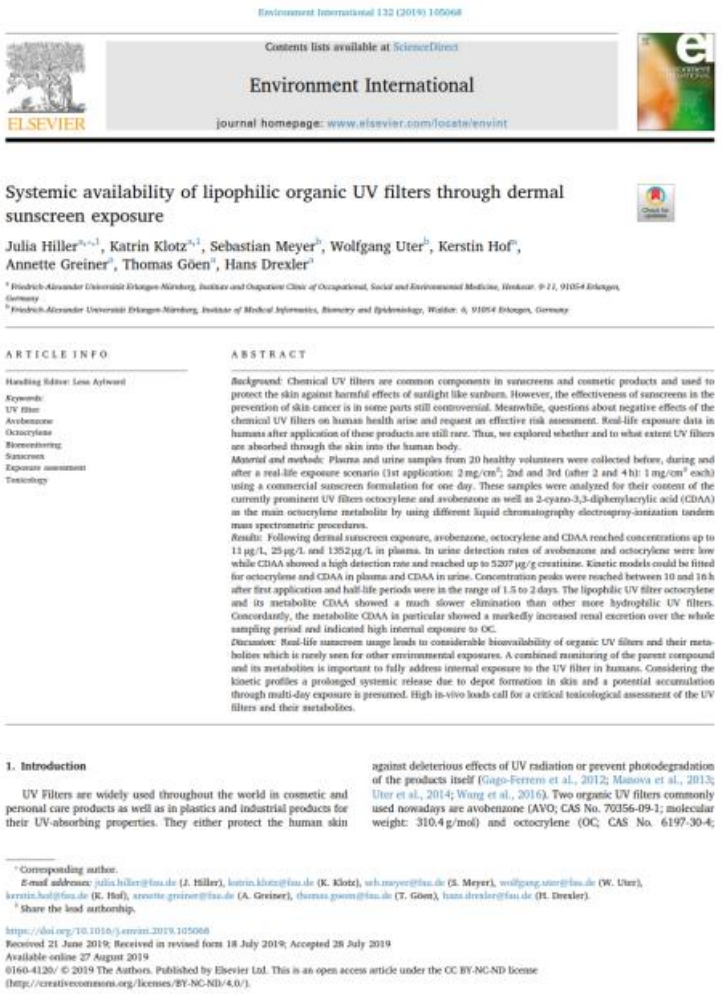
Non-FDA MUsT Sunscreen Absorption

- Article published August 2019 from Friedrich-Alexander Universität Erlangen-Nürnberg
- 20 subjects received topical application of a commercially available sunscreen containing avobenzone and octocrylene
- Dosing was for 1 day with an initial dose of 2mg/cm^2 followed by 1mg/cm^2 reapplied at 2 and 4 hours to approximately 75-80% BSA.
- Subjects were exposed to the sun for 9hrs.



Environment International 132 (2019) 105068

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Systemic availability of lipophilic organic UV filters through dermal sunscreen exposure

Julia Hiller[a,*,1], Katrin Klotz[a,1], Sebastian Meyer[b], Wolfgang Uter[b], Kerstin Hof[c], Annette Greiner[a], Thomas Göen[a], Hans Drexler[a]

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ARTICLE INFO

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Avobenzone
Octocrylene
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Exposure assessment
Toxicology

ABSTRACT

Background: Chemical UV filters are common components in sunscreens and cosmetic products and used to protect the skin against harmful effects of sunlight like sunburn. However, the effectiveness of sunscreens in the prevention of skin cancer is in some parts still controversial. Meanwhile, questions about negative effects of the chemical UV filters on human health arise and request an effective risk assessment. Real-life exposure data in humans after application of these products are still rare. Thus, we explored whether and to what extent UV filters are absorbed through the skin into the human body.

Material and methods: Plasma and urine samples from 20 healthy volunteers were collected before, during and after a real-life exposure scenario (1st application: 2 mg/cm^2; 2nd and 3rd (after 2 and 4 h): 1 mg/cm^2 each) using a commercial sunscreen formulation for one day. These samples were analyzed for their content of the currently prominent UV filters octocrylene and avobenzone as well as 2-cyano-3,3-diphenylacrylic acid (CDAA) as the main octocrylene metabolite by using different liquid chromatography electrospray-ionization tandem mass spectrometric procedures.

Results: Following dermal sunscreen exposure, avobenzone, octocrylene and CDAA reached concentrations up to 11 µg/L, 25 µg/L and 1352 µg/L in plasma. In urine detection rates of avobenzone and octocrylene were low while CDAA showed a high detection rate and reached up to 5207 µg/g creatinine. Kinetic models could be fitted for octocrylene and CDAA in plasma and CDAA in urine. Concentration peaks were reached between 10 and 16 h after first application and half-life periods were in the range of 1.5 to 2 days. The lipophilic UV filter octocrylene and its metabolite CDAA showed a much slower elimination than other more hydrophilic UV filters. Concordantly, the metabolite CDAA in particular showed a markedly increased renal excretion over the whole sampling period and indicated high internal exposure to OC.

Discussion: Real-life sunscreen usage leads to considerable bioavailability of organic UV filters and their metabolites which is rarely seen for other environmental exposures. A combined monitoring of the parent compound and its metabolites is important to fully address internal exposure to the UV filter in humans. Considering the kinetic profiles a prolonged systemic release due to depot formation in skin and a potential accumulation through multi-day exposure is presumed. High in-vivo loads call for a critical toxicological assessment of the UV filters and their metabolites.

1. Introduction

UV Filters are widely used throughout the world in cosmetic and personal care products as well as in plastics and industrial products for their UV-absorbing properties. They either protect the human skin against deleterious effects of UV radiation or prevent photodegradation of the products itself (Gago-Ferrero et al., 2012; Manova et al., 2013; Uter et al., 2014; Wang et al., 2016). Two organic UV filters commonly used nowadays are avobenzone (AVO; CAS No. 70356-09-1; molecular weight: 310.4 g/mol) and octocrylene (OC; CAS No. 6197-30-4;

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[1] Share the lead authorship.

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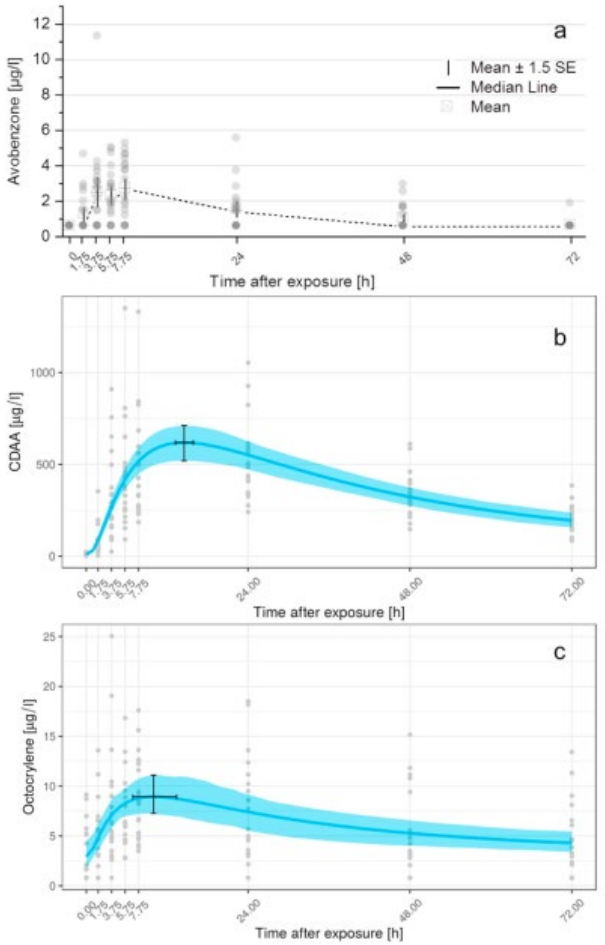
Non-FDA MUsT Sunscreen Absorption

- Even though the study was only a one day study and was dosed at a lower level than in the FDA studies, significant levels of avobenzone, octocrylene, and octocrylene's primary metabolite (CDAA) were seen in the plasma and urine



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Non-FDA MUsT Sunscreen Absorption

Table 2
Key figures and toxicokinetic parameters for plasma data.

	AVO		OC		CDAA	
	Median	Max.	Median	Max.	Median	Max.
Concentration at t_0 [µg/L]	< LOD	< LOD	1.7	9.1	7.8	21.9
Max. observed concentration [µg/L]	4.0	11.3	11.7	25.0	570.2	1351.7
Concentration at 72 h [µg/L]	< LOD	1.8	3.1	13.4	198.9	385.5
t_{max} [h]	n.d.		10.0 (95% CI: 6.9–13.4)		14.5 (95% CI: 13.2–15.9)	
k_{el} [h^{-1}]	n.d.		0.016 (95% CI: 0.007–0.025)		0.019 (95% CI: 0.016–0.022)	
Half-life $t_{1/2}$ [h]	n.d.		43.9 (95% CI: 19.0–68.7)		36.1 (95% CI: 31.0–41.2)	
Subjects with analyte detected [%]	85		100		100	
Samples below LOD [%]	57		17		6	
LOD [µg/L]	1.1		1.6		6.5	

n.d. = not determined, LOD = limit of detection, Max. = maximum; t_{max} = time of peak concentration after first application.

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Discussion: Real-life sunscreen usage leads to considerable bioavailability of organic UV filters and their metabolites which is rarely seen for other environmental exposures. A combined monitoring of the parent compound and its metabolites is important to fully address internal exposure to the UV filter in humans. Considering the kinetic profiles a prolonged systemic release due to depot formation in skin and a potential accumulation through multi-day exposure is presumed. High in-vivo loads call for a critical toxicological assessment of the UV filters and their metabolites.

Guidance Issuance

FDA Pilot Guidance Snapshot

Guidance Snapshots are a communication tool that provide highlights from guidance documents using visuals and plain language to support transparent communication and dissemination of FDA guidance documents. During the Pilot, Guidance Snapshots will contain a *subset* of the following key features:

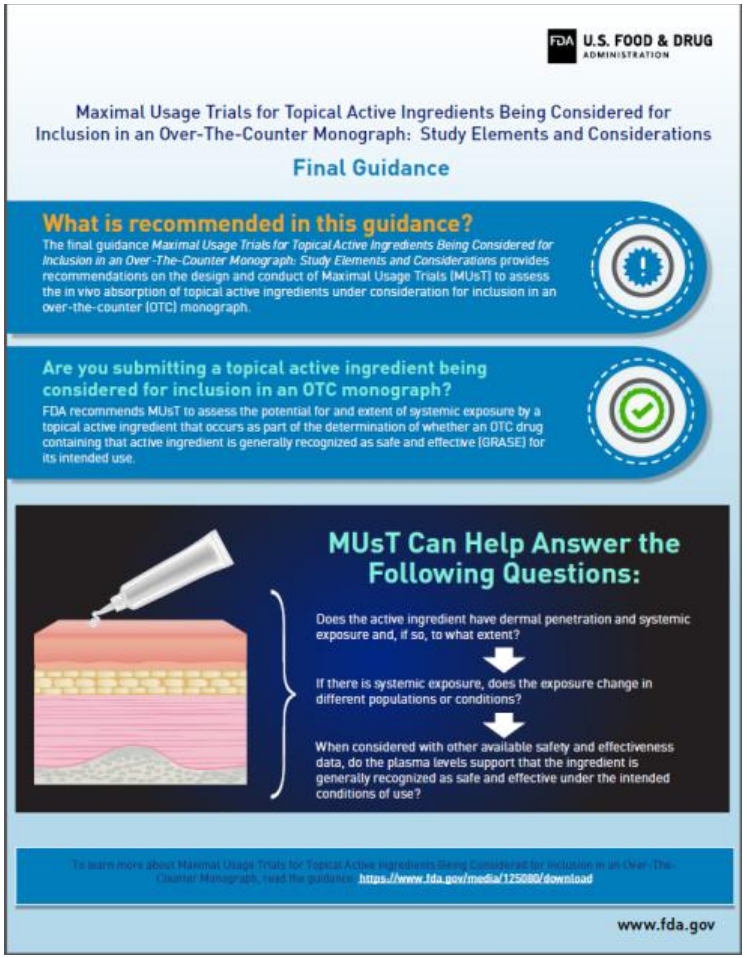
- Explanation of why the guidance document is important
- Highlights from the guidance document
- Educational background about the guidance topic
- Link to the full guidance document
- Drug development timeline for when to apply the guidance recommendations
- Guidance Recap Podcast that describes highlights and background the guidance document explained directly from the authors
- Twitter hashtags to create a platform for discussing views on the guidance
- Link to the FDA docket for providing official comments to the Agency (for applicable draft guidances)

https://www.fda.gov/drugs/guidances-drugs/guidance-snapshot-pilot

MUsT Snapshot

- The MUsT Snapshot is the fourth one prepared as part of the FDA pilot program.
- Previous snapshots have been issued for:

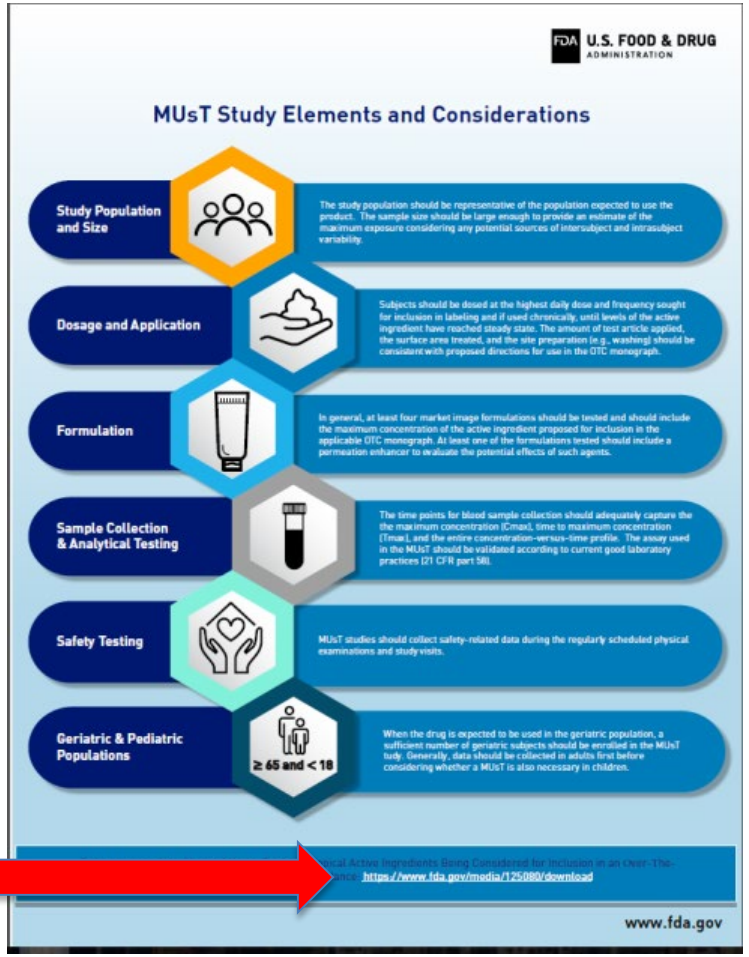
Guidance Document	Guidance Snapshot
In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions Final Guidance	In Vitro DDI Guidance Snapshot
Clinical Drug Interaction Studies - Cytochrome P450 Enzyme-and Transporter-Mediated Drug Interactions Final Guidance	Clinical DDI Guidance Snapshot
Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease Final Guidance	Targeted Therapies Guidance Snapshot



https://www.fda.gov/media/140321/download

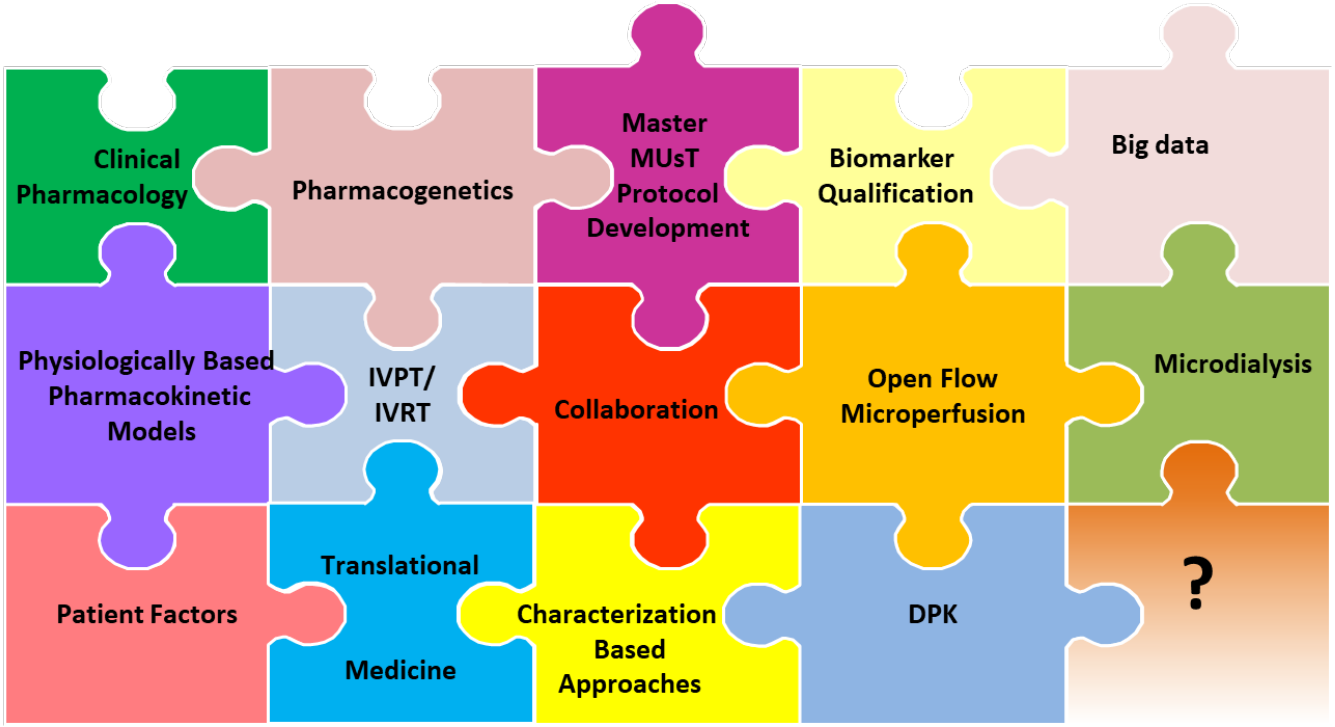
MUsT Snapshot

- In comparison, in the actual Guidance document, the MUsT Study Elements and Consideration section is over 5 pages and has specific verbiage on these elements and how to address them.
- The snapshot provides a concise overview of the issues and why it is an element to be evaluated.
- Each page of the snapshot also contains the weblink to the actual guidance



MUsT Snapshot

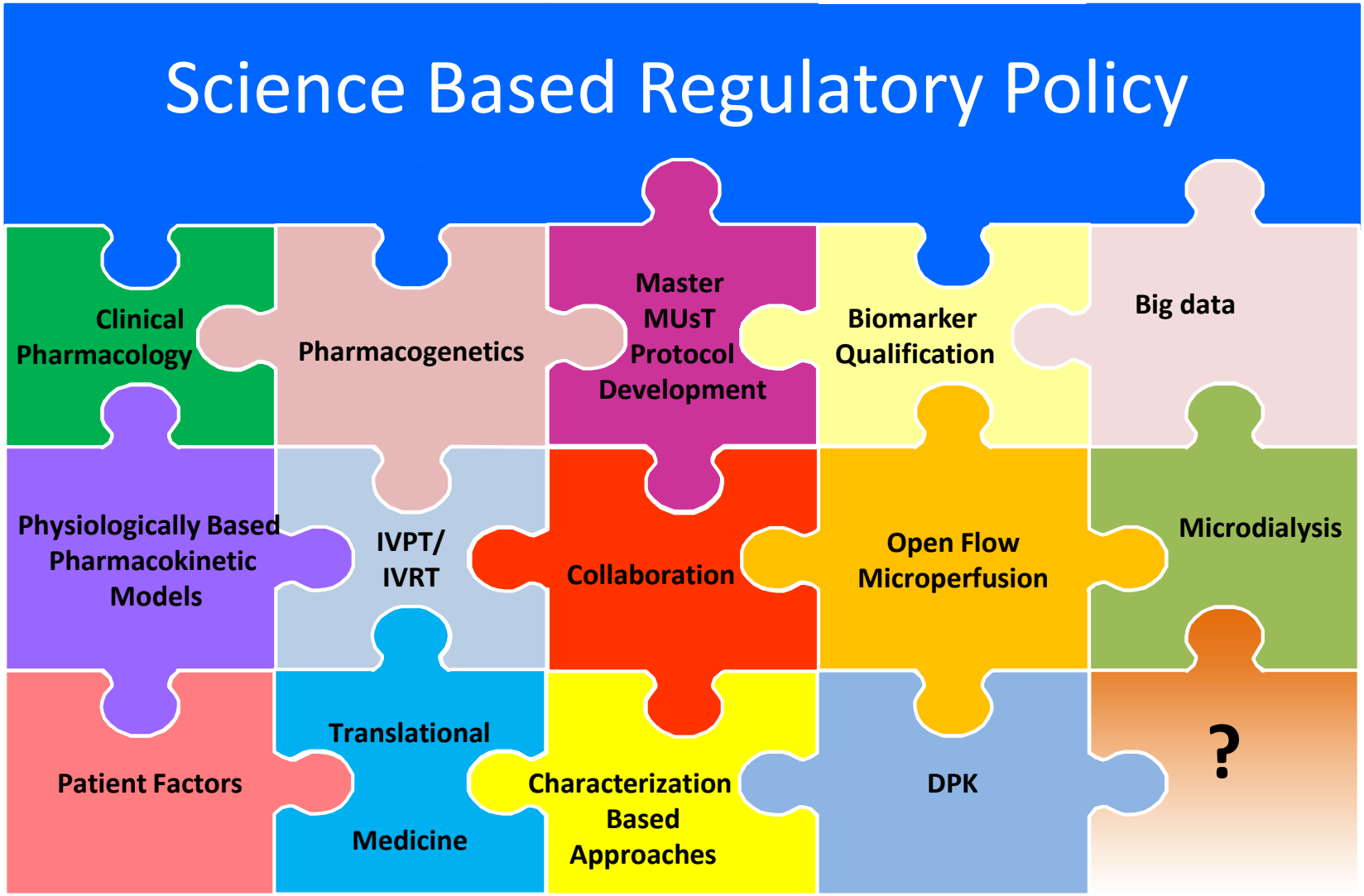
- A short background is included along with an explanation, and an example as to why the guidance is important.
- This information is provided to put the document into the context of drug development (in this case dermal drug development).
- As noted this is the fourth snapshot to be issued in the pilot program and it was posted at the FDA on July 21st, 2020.



PUTTING THE PIECES TOGETHER

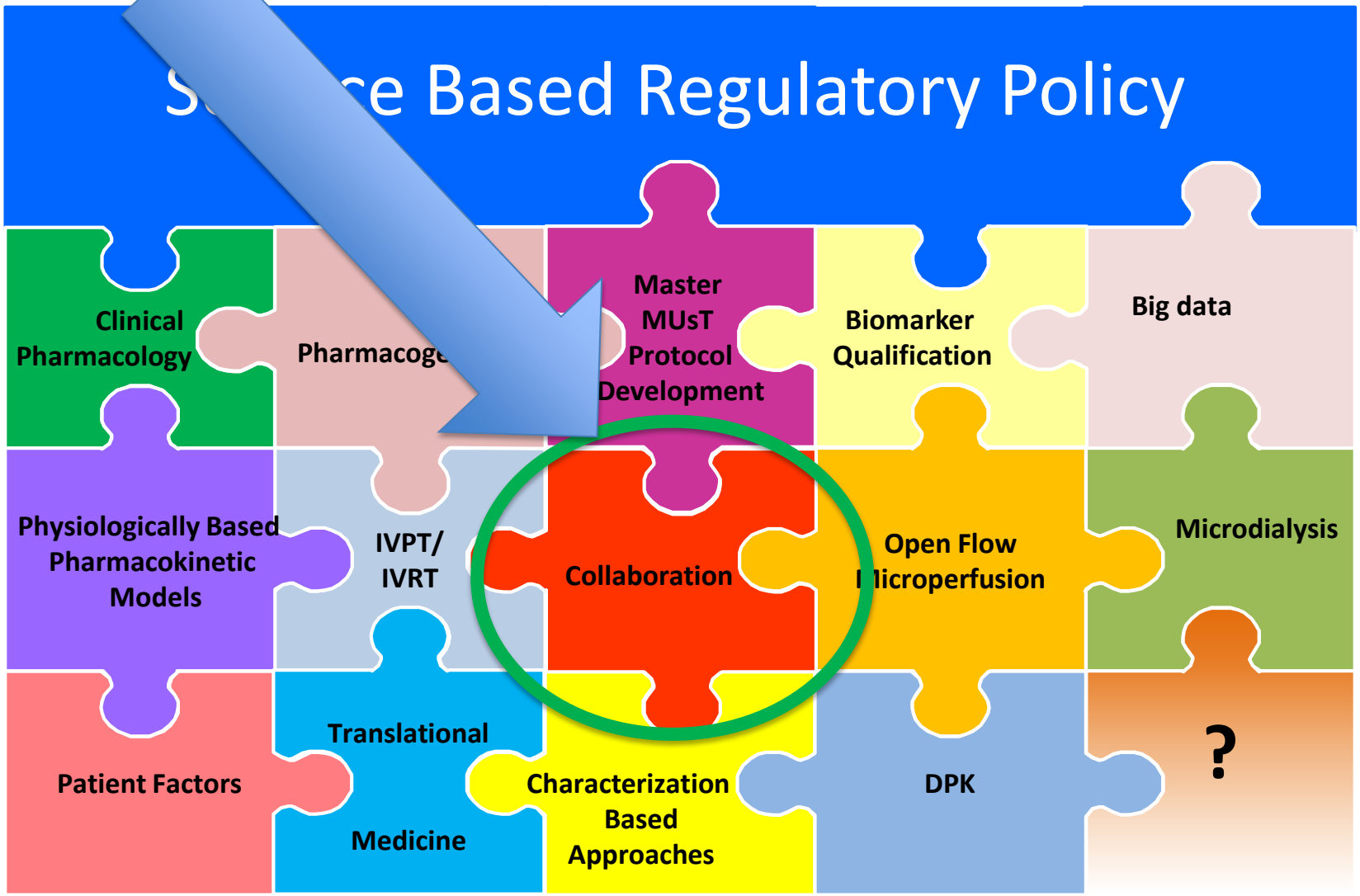
- COVID-19 has impacted the FDA and regulated industry in ways that could not have been imagined at the end of the workshop last August
- Even so the FDA has continued to move forward in developing the science and in communicating with industry using the tools we have available to us
- The development of the tests and the standards has moved on and will continue to do so

The Goal


Science Based Regulatory Policy
Clinical Pharmacology
Pharmacogenetics
Master MUsT Protocol Development
Biomarker Qualification
Big data
Physiologically Based Pharmacokinetic Models
IVPT/ IVRT
Collaboration
Open Flow Microperfusion
Microdialysis
Patient Factors
Translational Medicine
Characterization Based Approaches
DPK
?

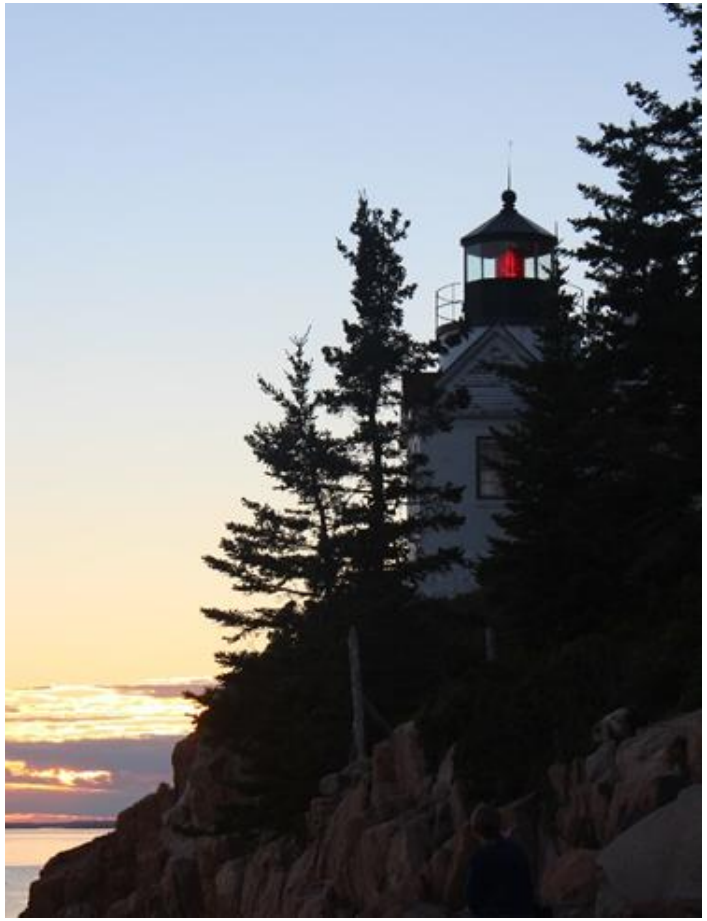
Collaboration is the KEY
To success

The Goal



- Developing a Science Based Regulatory Policy can only be done with the input of all stakeholders.
  - The FDA cannot do it alone
  - The Industry cannot do it alone
  - Academia, Clinicians, and the Public cannot do it alone.

Contact Info



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