Policy for Science: How policies affect the use of New Approach Methodologies

Kristie Sullivan, MPH
Elizabeth Baker, Esq.
June 27, 2022

ESTIV ASCCT

Physicians Committee for Responsible Medicine

- *In vivo* tests are resource- and animal-intensive
- Faster, more species-relevant decision-making tools are needed
- *In vivo* tests don't usually adequately capture diversity, sensitivities, emerging concerns

“Policy” in broad terms

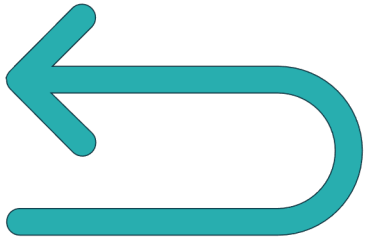
- Laws, legislative directives
- Corporate or institutional policies or practices
- Regulations, guidance, guidelines, or requirements
- Agency policies, practices, or statements

Policies

INSPIRE

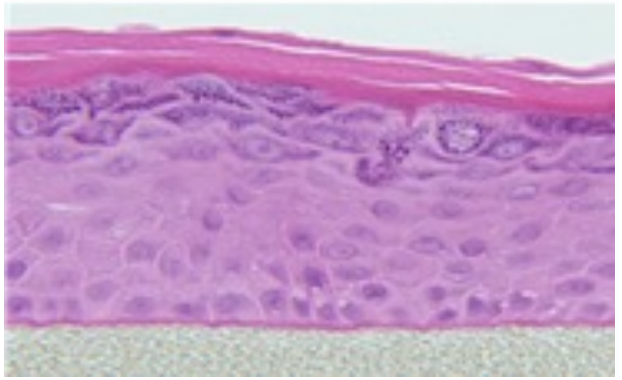
SIGNAL

STIFLE



Policies Inspire New Science

European Union Cosmetics Directive



Banned animal testing while requiring safety for products be demonstrated

Led to $M of public and private investment in alternatives development

Images: MatTek, Inc., IPTC Photo

Lautenberg Chemical Safety Act facilitates implementation of 21st-century vision of toxicology

- Mandates reduction and replacement of animal-based tests, while
- Allowing and incentivizing development and implementation of alternative methods and approaches
- Requires EPA to publish strategic plan and list of NAMs

Strategic Plan to Reduce the Use of Vertebrate Animals in Chemical Testing

EPA New Approach Methods Work Plan: Reducing Use of Vertebrate Animals in Chemical Testing

New Chemicals Collaborative Research Program

List of Alternative Test Methods and Strategies (or New Approach Methodologies [NAMs])

- Provides starting point for potential NAMs to use for TSCA submissions (OECD, EPA TGs, etc.)
- Suggests other tools and approaches
- Clarifies that EPA will accept other NAMs not on this list, and that the list will change to accommodate new science
- Provides criteria for evaluating other NAMs

https://www.epa.gov/sites/default/files/2021-02/documents/nams_list_second_update_2-4-21_final.pdf

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CORRESPONDENCE | 30 November 2021

Animal experiments: EU is pu to find substitutes fast

Stefan Hippenstiel, Christa Thöne-Reineke & Jens Kurreck

Parliament votes through demand for faster phase out of animal testing in research

16 Sep 2021 | News

Resolution adopted with 667 votes to 4, but research lobbies say not enough alternatives exist to set out a step-by-step plan

By Goda Naujokaitytė

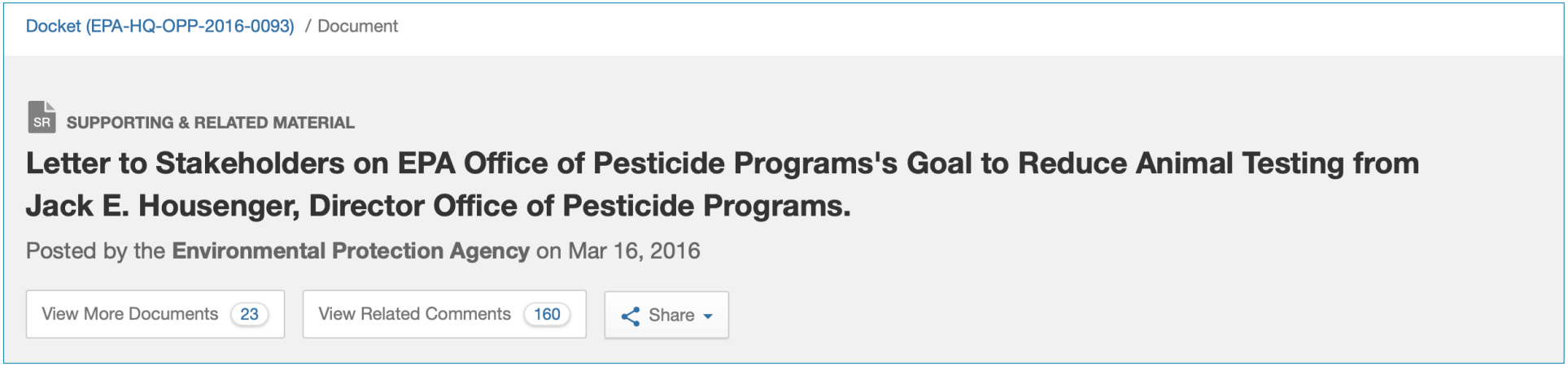
Tilly Metz, Member of the European Parliament. Photo : European Union

US FDA Launches iSTAND Qualification Program

A key part of this effort has been our robust support for the development of new regulatory tools that can help improve predictivity and potentially replace, reduce, and/or refine animal testing. I am proud to highlight in this report some of the activities in which FDA is engaged that are moving us closer to the goal of replacing, reducing, and refining the use of animals in medical product development while continuing to advance disease modeling, toxicology, and pharmacology in support of FDA's mission.

Stephen M. Hahn, M.D.
Commissioner of Food and Drugs

Policies Signal Acceptance of Advancing Science



- 2012: Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products
- 2015: Use of an Alt. Testing Framework for Classification of Eye Irritation Potential of EPA Pesticide Products
- 2016: Waiving Acute Dermal Toxicity Tests for Pesticide Formulations
- 2018: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing
- 2020: Waiving Acute Dermal Toxicity Tests for single chemicals

Policies Signal Acceptance of Advancing Science

Acute Dermal Retrospective Waiver Request Metrics

Waivers granted under the 2016 Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations & Supporting Retrospective Analysis.

Fiscal Year	Waivers Granted	Animal Reduction	Cost Savings*
2018	31	310-930	$201,500
2019	37	370-1110	$240,500
2020	30	300-900	$195,000
2021	56	560-1680	$364,000

**** Cost savings is based on the number of studies and/or waivers granted.***

https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-0

Policies Signal Acceptance of Advancing Science

In Vitro Assay Metrics

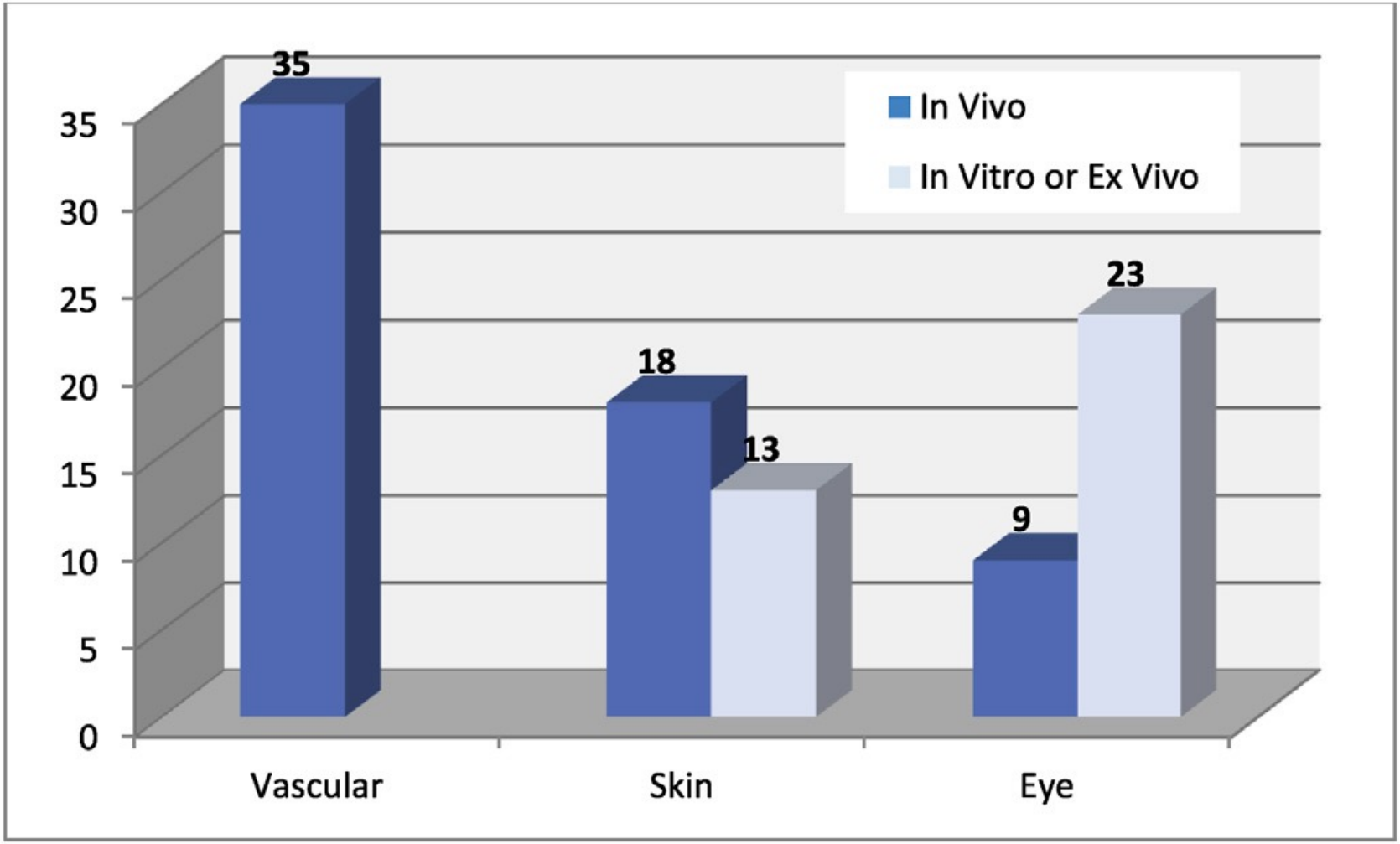
The number of in vitro assays that were submitted to address the acute toxicity data requirements and support the registration of new pesticide products and the registration review of currently registered pesticides.

Fiscal Year	*in vitro* eye irritation assays	*in vitro* skin irritation assays	*in vitro* skin sensitization assays
2018	19	11	1
2019	12	7	0
2020	13	7	3
2021	32	28	12

https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-0

FDA New Drug Applications 2015-2018

Number of irritation studies



Manuppello et al 2020; https://doi.org/10.1016/j.yrtph.2020.104666

Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route, FDA Center for Drug Evaluation and Research, Oct. 2015

> If the new formulation contains a drug substance that has not been evaluated for ocular irritation, then the potential of the topical drug product to induce irritation of the eyes if the eyes were inadvertently exposed to the product should be appropriately addressed. The topical drug product's ocular irritation potential should be evaluated through the use of appropriate in vitro or ex vivo methods. The in vivo rabbit ocular irritation test method is no longer recommended for topical drug products.

https://www.fda.gov/files/drugs/published/Nonclinical-Safety-Evaluation-of-Reformulated-Drug-Products-and-Products-Intended-for-Administration-by-an-Alternate-Route.pdfDrug-Products-and-Products-Intended-for-Administration-by-an-Alternate-Route.pdf

Policies Stifle Advancing Science

US FDA Regulations

21 C.F.R. § 312.23(a)(5)(ii)

Current Regulatory Text:

"A summary of the pharmacological and toxicological effects of the drug in **animals**, and, to the extent known, in humans."

Proposed Regulatory Text:

"A summary of the pharmacological and toxicological effects of the drug in **nonclinical approaches**, and, to the extent known, in humans."

Guidance: ICH M3R2 / FDA implementation

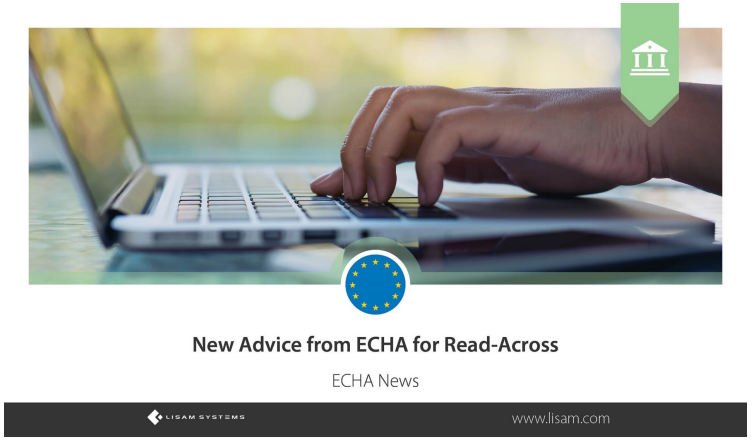
development resources. Although not discussed in this guidance, consideration should be given to use of new in vitro alternative methods for safety evaluation. These methods, if validated and accepted by all ICH regulatory authorities, can be used to replace current standard methods. This guidance promotes safe, ethical development and availability of new pharmaceuticals.

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Source: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization

EU REACH, CLP Legislation

- Advanced QSAR Toolbox, inspired a lot of activity
- Strict data requirements erect a high barrier for using new methods or flexibility



Conclusions

- Policies should reflect societal values
- Updating and strengthening policies can inspire and facilitate scientific progress
- Updating and strengthening policies is required to ensure application of new science
- Statements are not enough—need to be supported by funding, actions, changes

Modern policies = modern science

ksullivan@pcrm.org

www.pcrm.org/NURA | www.ascctox.org

@KristiePCRM

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