Communicating Progress in Advancing Alternative Methods for Regulatory Use at the FDA

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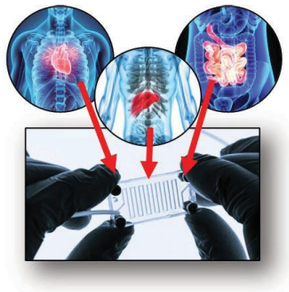
Associate Director for Pharmacology and Toxicology, Office of New Drugs, FDA/CDER

SACATM September 21, 2022



FDA's Mission

Protect and advance public health by:

- Ensuring the safety of our food supply, cosmetics, and products that emit radiation
- Ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices

- Fostering development of medical products to respond to deliberate and naturally emerging public health threats
- Regulating the manufacturing, marketing, and distribution of tobacco products

Key Point: FDA's mission is diverse, carried out by multiple Centers under different statutory authority and regulations

Fulfilling FDA's Mission

FDA reviews data submitted by product developers or obtained in other ways to establish

Under what conditions (e.g., dose, population, patient monitoring) a new medical product can be safely administered to patients (human or animal)

Whether some new medical product carries an increased risk for developmental and reproductive toxicity or an increased cancer risk

Whether a new ingredient for food is safe for consumption

The potential risks associated with tobacco products including electronic nicotine delivery systems (ENDS)

This includes evaluating endpoints that cannot be collected or ethically obtained in humans

For example:

- Histopathological evaluations
- Effects on embryofetal development
- Carcinogenic potential

Animal studies have played a critical role to meet these needs and bring safe and effective products to the market

FDA has a long-standing commitment to replace, reduce and refine ("3Rs") animal testing

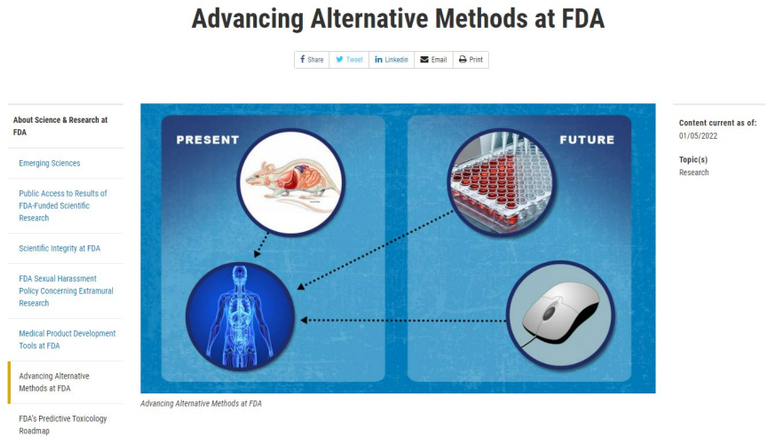
FDA has a long-standing commitment to replace, reduce and refine ("3Rs") animal testing – an incomplete timeline

ICH
harmonisation for better health

Start of ICH guidances related to nonclinical

NIH – FDA Joint Leadership Council
Advancing Regulatory Science Program
Heart-Lung Micromachine

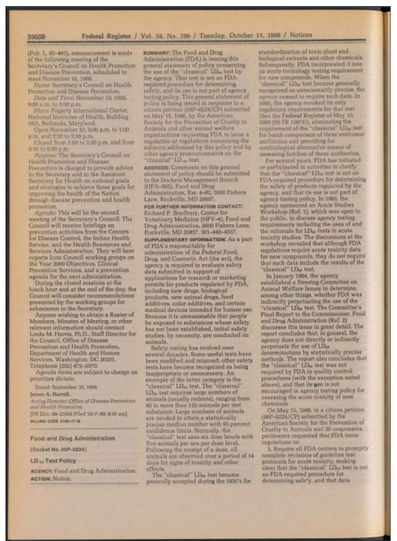
NCATS Tissue Chip Program



1988 — 1995 — 2000 — 2009 — 2010 — 2012 — 2017 — 2020

53 FR 39650

LD_{50} test is not an FDA required procedure


39630 Federal Register / Vol. 53, No. 196 / Tuesday, October 11, 1988 / Notices

(Pub. L. 92-463), announcement is made of the following meeting of the Secretary's Council on Health Promotion and Disease Prevention, scheduled to meet November 10, 1988.

Name: Secretary's Council on Health Promotion and Disease Prevention.

Date and Time: November 10, 1988, 9:00 a.m. to 5:00 p.m.

Place: Fogarty International Center, National Institutes of Health, Building 16A, Bethesda, Maryland.

Open November 10, 9:00 a.m. to 1:00 p.m. and from 2:30 to 5:00 p.m.

Closed from 1:00 to 2:30 p.m. and from 5:00 p.m.

Purpose: The Secretary's Council on Health Promotion and Disease Prevention is charged to provide advice to the Secretary and to the Assistant Secretary for Health on national goals and strategies to achieve those goals for improving the health of the Nation through disease prevention and health promotion.

Agenda: This will be the second meeting of the Secretary's Council. The Council will receive briefings on prevention activities from the Centers for Disease Control, the Indian Health Service, and the Health Resources and Services Administration. They will hear reports from Council working groups on the Year 2000 Objectives, Clinical Preventive Services, and a prevention agenda for the next administration.

During the closed session of the meeting on November 10th day, the Council will consider recommendations presented by the working groups for submission to the Secretary.

Anyone wishing to obtain a Roster of Members, Minutes of Meeting, or other relevant information should contact Linda M. Harris, Ph.D., Staff Director for the Council, Office of Disease Prevention and Health Promotion, Department of Health and Human Services, Washington, DC 20201. Telephone (202) 472-5370.

Agenda items are subject to change as priorities dictate.

Dated: September 30, 1988.

James A. Harrell,

Acting Director, Office of Disease Prevention and Health Promotion.

[FR Doc. 88-23584 Filed 10-7-88; 8:45 am]

BILLING CODE 4160-17-M

Food and Drug Administration

[Docket No. 88P-0324]

LD_{50} Test Policy

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing this statement of policy concerning the use of the "classical" LD_{50} test by the agency. That test is not an FDA-required procedure for determining safety, and its use is not part of agency testing policy. This general statement of policy is being issued in response to a citizen petition (88P-0324/CP) submitted on May 18, 1988, by the American Anti-Vivisection Society and Jamie Whitten Animal and other animal welfare organizations requesting FDA to issue a regulation or regulations concerning the subjects addressed by this policy and by other agency pronouncements on the "classical" LD_{50} test.

ADDRESS: Comments on this general statement of policy should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Richard P. Hill, Advisory Center for Toxicology (HFV-4), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4857.

SUPPLEMENTARY INFORMATION: As a part of FDA's responsibility for administration of the Federal Food, Drug, and Cosmetic Act (the act), the agency is required to evaluate safety data submitted in support of applications for research or marketing permits for products regulated by FDA, including new drugs, biological products, new animal drugs, food additives, and color additives, and certain medical devices intended for human use. Because it is unreasonable that people be exposed to substances whose safety has not been established, initial safety studies, by necessity, are conducted in animals.

Safety testing has evolved over several decades. Some useful tests have been modified and retained; other safety tests have become recognized as being inappropriate or unnecessary. An example of the latter category is the "classical" LD_{50} test. The "classical" LD_{50} test requires large numbers of animals (usually rodents), ranging from 50 to more than 120 animals per test substance. Large numbers of animals are needed to attain a statistically precise median number with 95 percent confidence limits. Normally, the "classical" test uses six dose levels with approximately 10 animals per dose. Following the receipt of a dose, all animals are observed over a period of 14 days for signs of toxicity and other effects.

The "classical" LD_{50} test became generally accepted during the 1930's for standardization of toxic plant and biological extracts and other chemicals. Subsequently, FDA incorporated it into its acute toxicology testing requirement for new compounds. When the "classical" LD_{50} test became generally recognized as unnecessarily precise, the agency ceased to require such data. In 1986, the agency revoked its only regulatory requirements for that test (See the Federal Register of May 30, 1986 (51 FR 19526)). Subsequent to the retirement of the "classical" LD_{50} test for batch comparison of three antitumor antibiotics and providing for nonbiological alternative means of assessing batches of these antibiotics.

For several years, FDA has initiated or participated in activities to clarify that the "classical" LD_{50} test is not an FDA-required procedure for determining the safety of products regulated by the agency, and that its use is not part of agency testing policy. At 1985 Bal Harbour Workshop (Ref. 1) and the Bal Harbour Workshop (Ref. 1) which was open to the public, to discuss agency testing requirements including the uses of and the rationale for LD_{50} tests in acute toxicity studies. The discussions at the workshop revealed that although FDA regulations require acute toxicity data for new compounds, they do not require that such data include the results of the "classical" LD_{50} test.

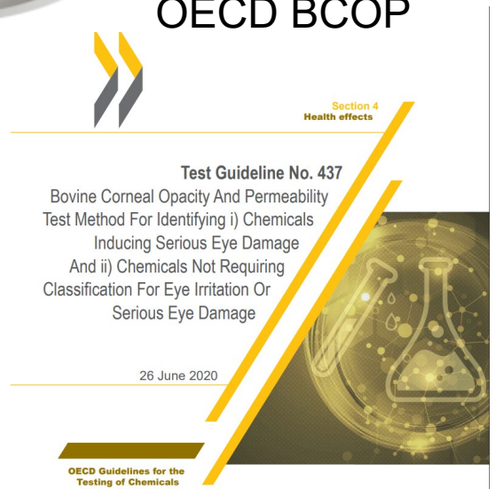
In 1987, the agency established a Steering Committee on Animal Welfare Issues to determine, among other things, whether FDA was indirectly perpetuating the use of the "classical" LD_{50} test. The Committee's Final Report to the Commissioner, Food and Drug Administration (Ref. 2) discusses this issue in great detail. The report concludes that, in general, the agency does not directly or indirectly perpetuate the use of the "classical" LD_{50} test for statistically precise determinations. The report also concludes that the "classical" LD_{50} test was not required by FDA in quality control procedures (with the exception noted above), and that the test is not encouraged in agency testing policy for assessing the acute toxicity of new chemicals.

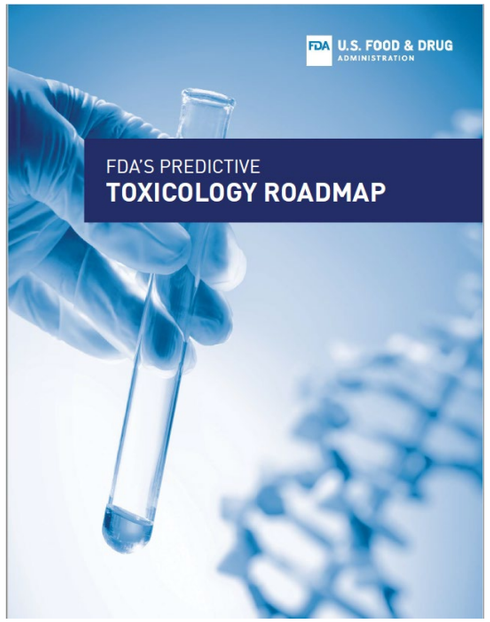
On May 15, 1986, in a citizen petition (86P-0226/CP) submitted by the American Society for the Prevention of Cruelty to Animals and 20 cosponsors, petitioners requested that FDA issue regulations to:

1. Require all FDA centers to promptly complete revisions of guideline test protocols for acute toxicity, making clear that the "classical" LD_{50} test is not an FDA-required procedure for determining safety, and that data

UNITED STATES ICCVAM
Advancing Alternatives to Animal Testing

OECD BCOP

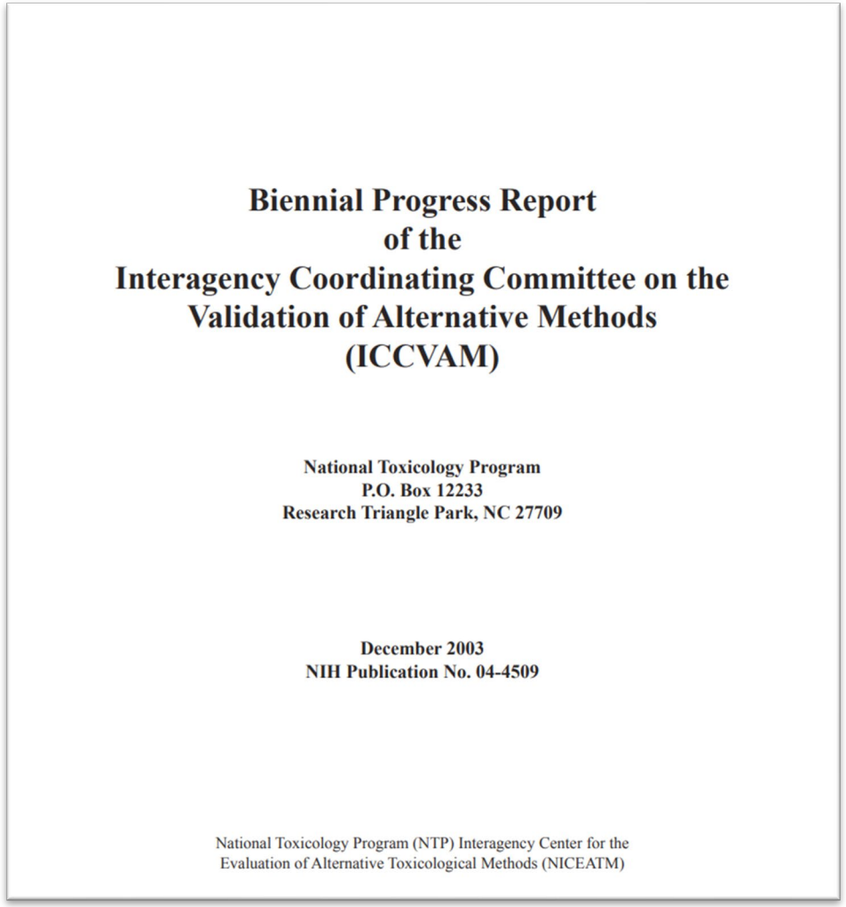




How can FDA demonstrate contribution to 3Rs and implementation of alternative methods?

- Collate and provide a list of FDA research, policy, guidance and qualified methods related to 3Rs and alternative methods
- Communicate how these efforts impact 3Rs and alternative methods
- Provide and track training in these efforts

Collate FDA research, policy and guidance related to 3Rs and alternative methods *and* Communicate



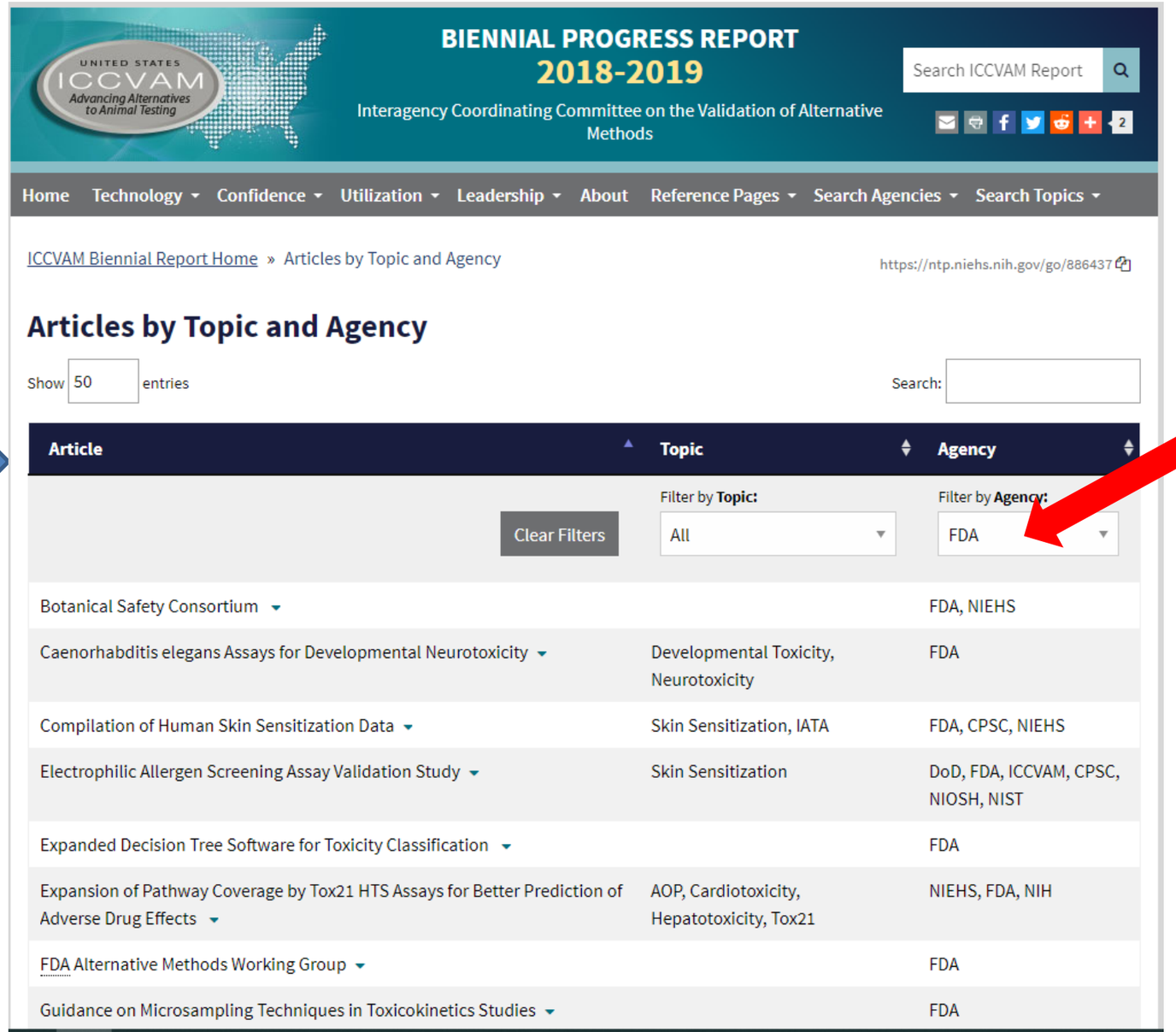
Biennial Progress Report
of the
Interagency Coordinating Committee on the
Validation of Alternative Methods
(ICCVAM)

National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709

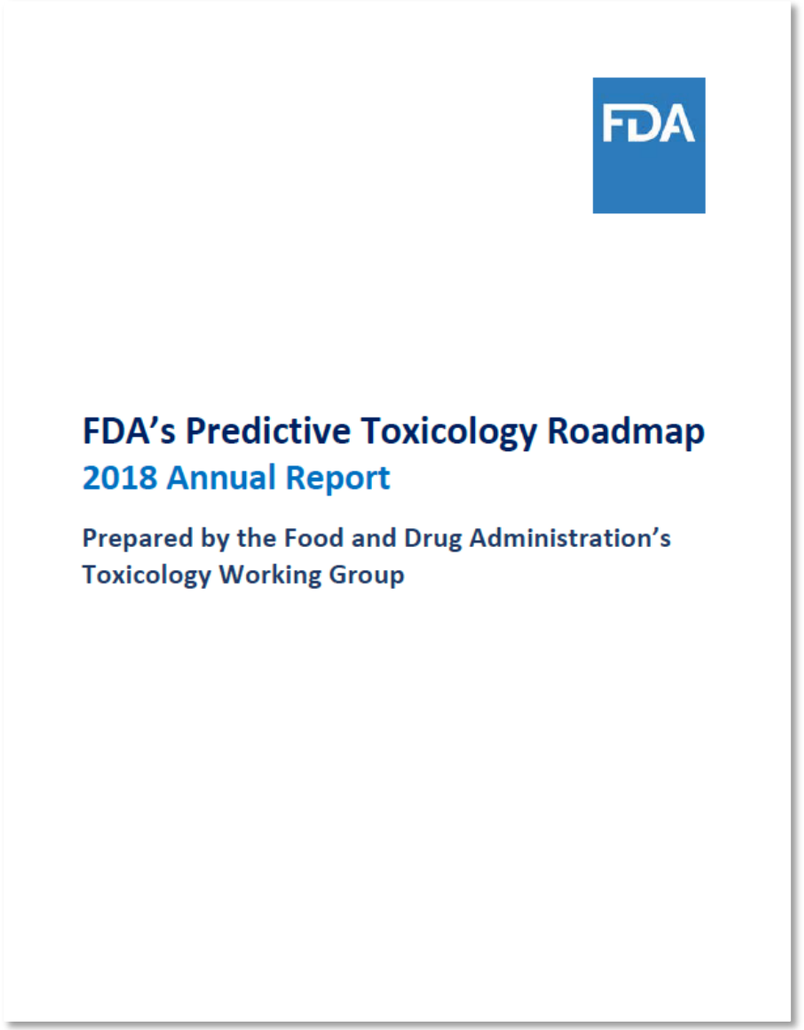
December 2003
NIH Publication No. 04-4509

National Toxicology Program (NTP) Interagency Center for the
Evaluation of Alternative Toxicological Methods (NICEATM)

Collate FDA research, policy and guidance related to 3Rs and alternative methods *and* Communicate



Collect FDA research, policy and guidance related to 3Rs and alternative methods *and* Communicate



Workshop:
Implementing FDA's Predictive Toxicology Roadmap: An Update of FDA Activities
September 18, 2019

2021

Collect FDA research, policy and guidance related to 3Rs and alternative methods *and* Communicate

Advancing Alternative Methods at FDA

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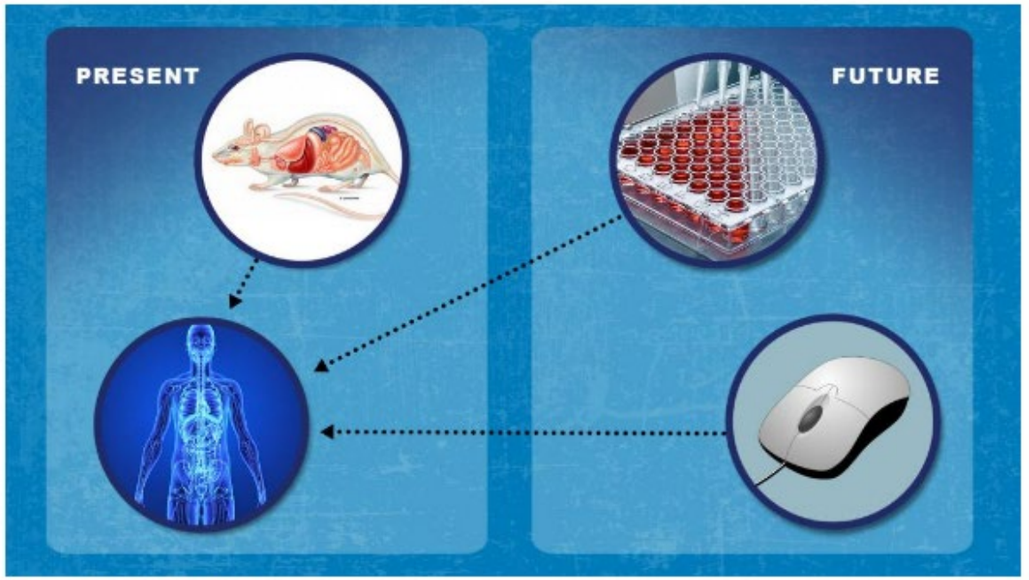
About Science & Research at FDA

- Emerging Sciences
- Public Access to Results of FDA-Funded Scientific Research
- Scientific Integrity at FDA
- FDA Sexual Harassment Policy Concerning Extramural Research
- Medical Product Development Tools at FDA
- Advancing Alternative Methods at FDA
- FDA's Predictive Toxicology Roadmap
- FDA Grand Rounds
- The FDA Science Forum



Advancing Alternative Methods at FDA

Content current as of:
01/05/2022

Topic(s)
Research

Read about the activities FDA scientists are undertaking to spur the development of new regulatory approaches that can help improve predictivity--and potentially replace, reduce and/or refine animal testing.

Advancing Alternative Methods at FDA

Website content

- FDA's Alternative Method Working Group
- FDA Webinar Series on Alternative Methods
- FDA Definitions – Microphysiological Systems, Organ-on-a-chip
- Publications, Presentations, Guidances
  - Publications Co-authored by FDA on Alternative Methods
  - Presentations by FDA Scientists on Alternative Methods
  - Guidances List: Alternative Methods
- Resources for You

Seminars Sponsored by the Alternative Methods Working Group

Date	Title	Attendance
9/15/21	Tissue model engineering	115
10/13/21	Development of an in vitro platform for evaluation of pharmacokinetic and toxicologic effects of drugs and chemicals	137
10/20/21	Using engineered 3D tissue models	146
11/8/21	Using new approaches in drug development	130
11/17/21	Synthetic embryology systems as potential models for reproductive testing	76
1/19/22	Alternative organ-on-a-chip	109
2/9/22	Increasing trust in non-animal methods	213
2/17/22	Organ-Chip Technology	141
3/16/22	Using brain organoids	118
4/13/22	Animal species organoids for use in veterinary medicine	67
4/20/22	A microphysiological system-based potency bioassay	46
5/18/22	Model of human physiology	61
6/8/22	Discussion of animal models	76
8/4/22	Characterization of rat and dog microphysiological system models	39
9/6/22	Automated, High-Throughput Experimentation on Complex Human Organ-on-Chip Models	108

FDA Tool Development Programs

Medical Device Development Tools (MDDT)

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Medical Device Development Tools (MDDT)

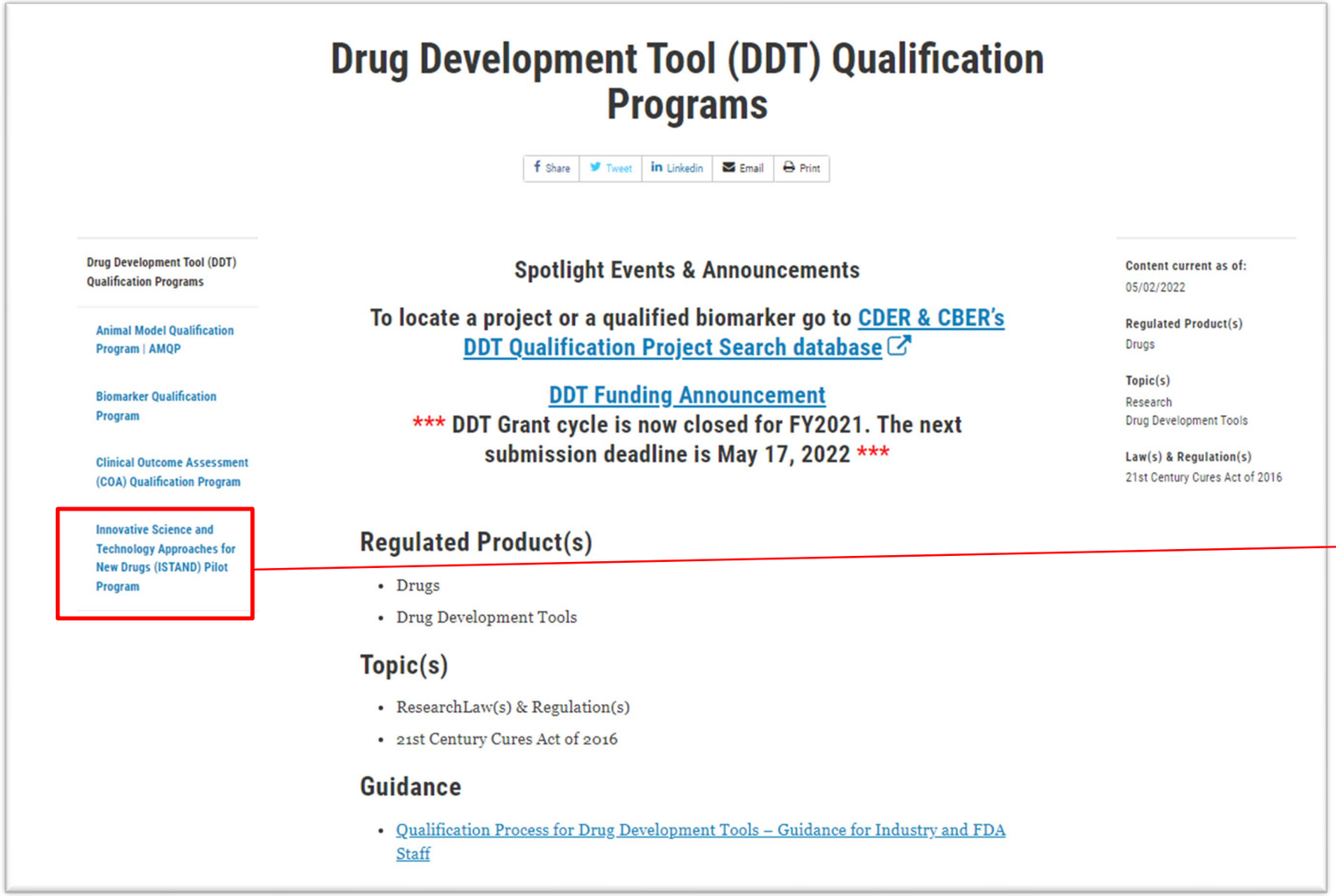
Content current as o
05/05/2022

Regulated Product(s
Medical Devices

On this page:

List of qualified tools includes “Nonclinical Assessment Models”

FDA Tool Development Programs



Drug Development Tool (DDT) Qualification Programs

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Drug Development Tool (DDT) Qualification Programs

- Animal Model Qualification Program | AMQP
- Biomarker Qualification Program
- Clinical Outcome Assessment (COA) Qualification Program
- Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program

Spotlight Events & Announcements

To locate a project or a qualified biomarker go to CDER & CBER's DDT Qualification Project Search database

DDT Funding Announcement

*** DDT Grant cycle is now closed for FY2021. The next submission deadline is May 17, 2022 ***

Regulated Product(s)

- Drugs
- Drug Development Tools

Topic(s)

- ResearchLaw(s) & Regulation(s)
- 21st Century Cures Act of 2016

Guidance

- Qualification Process for Drug Development Tools – Guidance for Industry and FDA Staff

Content current as of:
05/02/2022

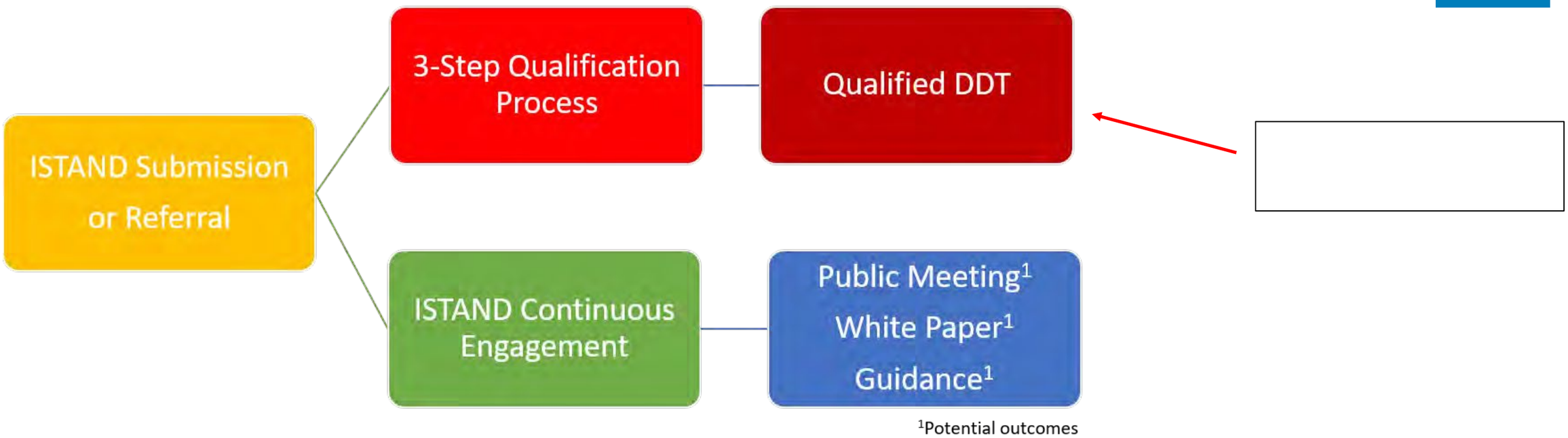
Regulated Product(s)
Drugs

Topic(s)
Research
Drug Development Tools

Law(s) & Regulation(s)
21st Century Cures Act of 2016

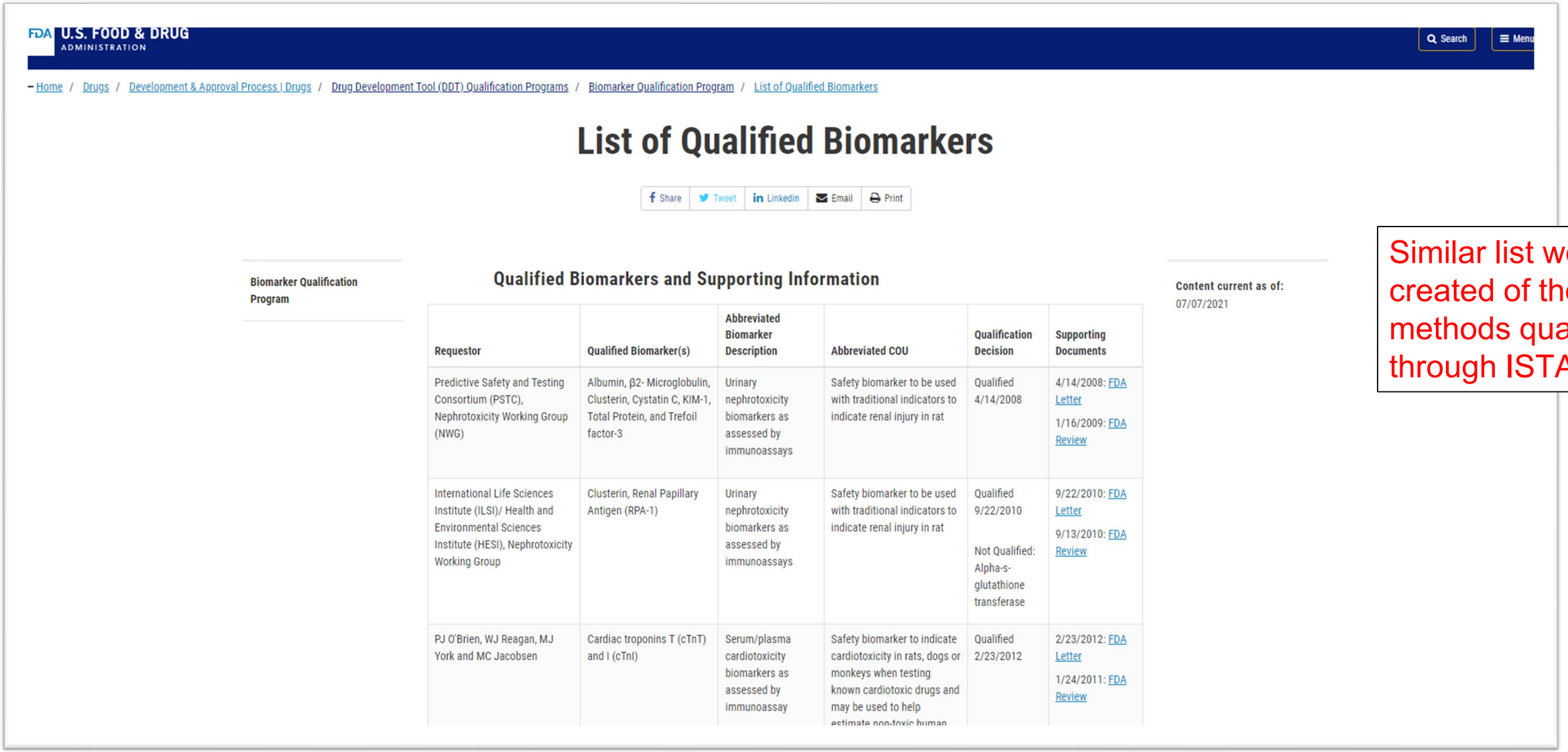
Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program

ISTAND Pilot Process



A transparent process – so all stakeholders are aware of tools in development, stage, and FDA determinations/recommendations

FDA Drug Development Tool Program – A Transparent Process



FDA U.S. FOOD & DRUG ADMINISTRATION

Search Menu

Home / Drugs / Development & Approval Process | Drugs / Drug Development Tool (DDT) Qualification Programs / Biomarker Qualification Program / List of Qualified Biomarkers

List of Qualified Biomarkers

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Biomarker Qualification Program

Qualified Biomarkers and Supporting Information

Requestor	Qualified Biomarker(s)	Abbreviated Biomarker Description	Abbreviated COU	Qualification Decision	Supporting Documents
Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Albumin, β2- Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil factor-3	Urinary nephrotoxicity biomarkers as assessed by immunoassays	Safety biomarker to be used with traditional indicators to indicate renal injury in rat	Qualified 4/14/2008	4/14/2008: FDA Letter 1/16/2009: FDA Review
International Life Sciences Institute (ILSI)/ Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group	Clusterin, Renal Papillary Antigen (RPA-1)	Urinary nephrotoxicity biomarkers as assessed by immunoassays	Safety biomarker to be used with traditional indicators to indicate renal injury in rat	Qualified 9/22/2010 Not Qualified: Alpha-s-glutathione transferase	9/22/2010: FDA Letter 9/13/2010: FDA Review
PJ O'Brien, WJ Reagan, MJ York and MC Jacobsen	Cardiac troponins T (cTnT) and I (cTnI)	Serum/plasma cardiotoxicity biomarkers as assessed by immunoassay	Safety biomarker to indicate cardiotoxicity in rats, dogs or monkeys when testing known cardiotoxic drugs and may be used to help estimate non-toxic human	Qualified 2/23/2012	2/23/2012: FDA Letter 1/24/2011: FDA Review

Content current as of:
07/07/2021

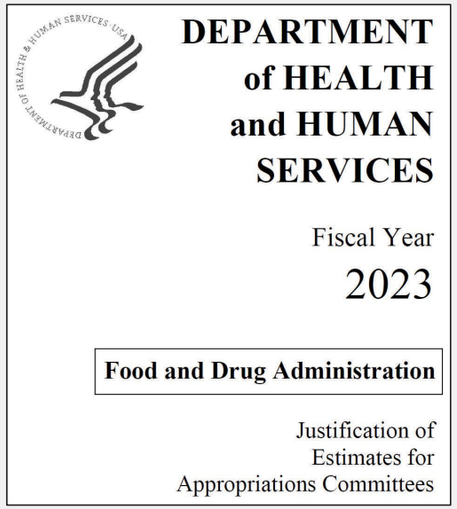
Similar list would be created of those methods qualified through ISTAND

Future FDA efforts to implement alternative methods and communicate those efforts

FDA's Proposed New Alternative Methods Program

The FY2023 President's Budget proposes new funding to implement a cross-agency New Alternative Methods Program to:

- **Spur the adoption of new alternative methods for regulatory use that can replace, reduce and refine animal testing and improve predictivity of nonclinical testing to**:
  - Streamline development of FDA-regulated products
  - Bring products to US public and patients more rapidly and more efficiently
  - Ensure products are safe, effective, and that patients can depend on them



Link

FDA's Proposed New Alternative Methods Program

- **Centrally coordinated through FDA's Office of the Chief Scientist with FDA Centers implementing Agency-wide programmatic objectives**

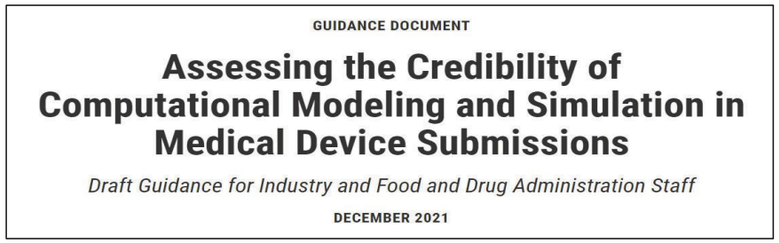
- **If this initiative is funded, FDA hopes to**
  - Expand processes to qualify alternative methods for regulatory use
  - Provide guidance to external stakeholders developing alternative methods
  - Fill information gaps with applied research to advance new policy and guidance development

- **Collaborations with external stakeholders are vital**
  - Federal partners, public-private partnerships, international regulators

What are Potential Guidances to Stakeholders Developing Alternative Methods?

- Guidance on qualification process
- Topical guidance on specific safety or development areas
- Guidances on assessing credibility of specific types of alternative methods or what to include in regulatory submissions – examples:

Policy & Guidance to Streamline Qualification & Implementation


GUIDANCE DOCUMENT

Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

Draft Guidance for Industry and Food and Drug Administration Staff

DECEMBER 2021

Link


GUIDANCE DOCUMENT

Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry

SEPTEMBER 2018

Link

Role for microphysiological systems-related general considerations guidance?

Future communication efforts

Improve Advancing Alternative Methods at FDA website

- make more user-friendly
- add interpretative language to explain significance of some publications
- add information about collaborations with external groups
- provide additional links to resources for the regulated industry (e.g., to tool qualification programs)

Write more publications specifically related to alternatives