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September 13, 2016

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Sent via email to whiteld@niehs.nih.gov

**Re: Public Comments for the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) annual meeting**

Dear Dr. White:

The following comments are submitted on behalf of Center for Responsible Science (CRS). We appreciate the opportunity to submit these written comments and participate in the discussion regarding a strategy for implementing the vision for Toxicity Testing in the 21<sup>st</sup> Century. We applaud the efforts of all involved in developing this crucial strategy.

Our comments will address the four issues/questions posed in the SACATM Background Document: A Strategy for Implementing the Vision for Toxicity Testing in the 21st Century.

**Issue 1: Non-Scientific Considerations**

*“While advancements in science and technology are essential to the development of 21st century approaches, there a number of “non-scientific” considerations (e.g., political, institutional, international, social, ethical, trade, policy, education, training, and legal challenges) that could impede the adoption and implementation of such approaches. These issues must be delineated and addressed as part of a comprehensive*

*implementation plan. What are the most important “non-scientific” issues and how should they be prioritized?”<sup>1</sup>*

## **A. Regulation: Advancing Innovation and use of Human-Relevant Test Methods through ICCVAM Member Agency Regulation Updates**

“The regulation of drugs can either grease the wheels of progress or throw a wrench in the works” concludes former Food and Drug Administration (FDA) Commissioner, Dr. Margaret Hamburg and former National Institute of Health (NIH) Director Dr. Elias Zerhouni.”<sup>2</sup> Regulatory updates regarding preclinical test methods for new drugs and devices would advance the former.

As noted in the document developed for this meeting, *A Strategy for Implementing the Vision for Toxicity Testing in the 21<sup>st</sup> Century*:

“Over the ensuing decade, significant investments in technology development and biomedical research have resulted in many transformative scientific breakthroughs necessary for implementing the NRC vision. **However, these advances have yet to be met with a concomitant increase in our ability to more accurately predict the adverse human health effects caused by ubiquitous exposure to xenobiotic chemicals, whether alone or in mixtures. This limited translational impact is attributable, at least in part, to rapid scientific advancements outpacing the change in institutional standards required for their effective utilization.** Specifically, legacy test methods and classification systems developed using animal models cannot always evaluate the nuances of human pathophysiology and genetic variability important for modern safety and risk assessment. Ironically, however, the institutionalized use of animal-based methods is now preventing more human-predictive approaches from being developed and adopted by Federal agencies and industry. **Left unaddressed, this growing disparity between new scientific advancement and regulatory policy could soon impede our ability to capitalize on the remarkable knowledge and tools arising from projects such as ToxCast, Tox21, Human Tissue Chips, and the Precision Medicine Initiative.**”<sup>3</sup>

To illustrate the problem regarding rapid scientific advances outpacing change in regulatory policy, we simply have to look at FDA regulations. FDA’s Investigational New

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<sup>1</sup> SACATM Background Document: A Strategy for Implementing the Vision for Toxicity Testing in the 21st Century.

[http://ntp.niehs.nih.gov/ntp/about\\_ntp/sacatm/2016/september/vision20160927\\_508.pdf](http://ntp.niehs.nih.gov/ntp/about_ntp/sacatm/2016/september/vision20160927_508.pdf)

<sup>2</sup> *The need for global regulatory harmonization: A public health imperative*, E. Zerhouni and M. Hamburg, *Science Translational Medicine*, 11 May 2016:Vol. 8, Issue 338, pp. 338ed6

<http://stm.sciencemag.org/content/8/338/338ed6>

<sup>3</sup> SACATM Background Document, *supra*.

Drug (IND) and Investigational Device Exemption (IDE) regulations give FDA the flexibility to accept non-animal test methods (NATMs), such as in vitro studies or prior experience with the drug or biological product in humans, when appropriate.<sup>4</sup> **However, despite this stated willingness to accept NATMs when they are at least as valid as other methods, FDA has not modified the text of its regulations to reflect this willingness.** The current regulations facially require animal testing, which in turn discourages the use of non-animal tests which may be more predictive of human response.

To address the above, CRS and thirteen additional patient advocacy groups, technology developers and non-profit organizations<sup>5</sup> petitioned FDA<sup>6</sup> in July 2015 to update twenty-nine regulations to allow the use of the preclinical test method most predictive of human response. Under the proposed regulatory amendments, traditional testing would still be required in the absence of a scientifically recognized modern test method and would still be completely within the sponsors' discretion for use. Where a scientifically recognized modern test method exists for a particular purpose, sponsors would have the option to use the traditional method and/or the modern method. Petitioners merely seek an acknowledgment of regulatory acceptance of modern test methods in appropriate circumstances. Adoption of these conservative regulatory amendments would be an important first-step in moving forward. (See requested regulatory amendments attached).

The twenty-nine FDA regulations facially require traditional animal testing and promote the status quo, creating an unreceptive environment that fails to encourage innovation and development of more predictive test methods. Modification of regulatory language is needed to promote sponsor use of existing modern test methods and to signal further development to advance modernization of preclinical testing. The requested regulatory amendments would clear up any confusion, broaden testing options for sponsors, and spark innovation of more predictive methods.

As noted in the strategy document developed for this meeting, “non-scientific” limiting factors for implementing 21<sup>st</sup> century approaches to toxicity testing include policy and regulation. CRS’ proposal submitted to FDA over a year ago to make modest, non-controversial regulation amendments would be an important first step to overcome this limiting factor without protracted planning, discussion and resources. Clearly there is a need to overcome all of the additional roadblocks to adoption of human-relevant test

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<sup>4</sup> Letter from David H. Dorsey, Acting Deputy Commissioner for Policy, Planning and Budget, Food and Drugs to Katherine Meyer, Meyer Glitzenstein & Crystal 3-4 (May 20, 2010), available at <http://www.regulations.gov/#!documentDetail;D=FDA-2007-P-0109-0012>

<sup>5</sup> Asterand Bioscience, AxoSim Technologies LLC, Empiriko, Friends of Cancer Research, HuREL® Corporation, In Vitro ADMET Laboratories, Invitro Cue, InVitro International, MatTek Corporation, NORD (National Organization for Rare Disorders), Safer Medicines Trust, United Spinal Association, and 3D Biomatrix, Inc.

<sup>6</sup> Requests that the FDA modify existing regulations in CFR Title 21 that governs requirements for investigational new drug applications, investigational device exemptions, and new drug applications. <https://www.regulations.gov/#!docketDetail;D=FDA-2015-P-2820>

methods, and a concerted, coordinated effort is needed. However, in the context of FDA regulated drug and device development, minor amendments to outdated existing regulations would have great impact on the use and development of better tools for drug and device development.

Additionally, recent events underscore the need for more predictive preclinical tests and regulations that allow their use. Human participants in clinical trials are exposed to risks of adverse events, including death and disability.

- In July, a phase II clinical trial for a chimeric antigen receptor T-Cell (CAR-T) was put on hold due to the treatment related deaths of several participants due to severe neurotoxicity<sup>7</sup>.
- On March 15th, six clinical trials on a cancer drug (idelalisib) were halted because of serious adverse events, including several deaths<sup>8</sup>. This followed the FDA's termination of a phase III trial in February of a blood cancer drug (Pacritinib) after patients died from "intracranial hemorrhage, cardiac failure and cardiac arrest."<sup>9</sup>
- In January, a previously healthy man participating in a clinical trial in France died and five others were hospitalized due to severe adverse reactions, including brain damage.<sup>10</sup> The drug had undergone preclinical tests in four species of animals before first-in-human tests<sup>11</sup>. *Even with doses 400 times stronger than those given to the human volunteers, no adverse effects were noted in the animals.*<sup>12</sup> The trial was conducted in "full compliance with worldwide regulations,"<sup>13</sup> which further underscores the urgency for new regulations.
- In December 2015, a clinical trial participant died from bilateral pulmonary emboli, two months after FDA temporarily halted part of the clinical trial (Zafgen) due to the previous death of a 23 year-old clinical trial volunteer.<sup>14</sup>

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<sup>7</sup> FDA Lifts Clinical Hold on Phase II Trial of JCAR015 in ALL, OncLive, July 12, 2016 <http://www.onclive.com/web-exclusives/fda-lifts-clinical-hold-on-phase-ii-trial-of-jcar015-in-all>

<sup>8</sup> FDA Alerts Healthcare Professionals About Clinical Trials with Zydelig (idelalisib) in Combination with other Cancer Medicines, FDA website, March 15, 2016 [http://www.fda.gov/Drugs/DrugSafety/ucm490618.htm?source=govdelivery&utm\\_medium=email&utm\\_source=govdelivery](http://www.fda.gov/Drugs/DrugSafety/ucm490618.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery)

<sup>9</sup> FDA Halts trial of Cancer drug by Seattle's CTI BioPharma after patient dies. February 11, 2016 <http://www.seattletimes.com/business/fda-halts-cti-biopharma-drug-trial-for-detrimental-effect-on-survival/>

<sup>10</sup> Nano News, *Nothing to justify stopping clinical trials, says French health minister*, January 25, 2016 <http://nanonews.org/nothing-to-justify-stopping-clinical-trials-says-french/>

<sup>11</sup> The Guardian, *Man who died in French drug trial had 'unprecedented' reaction, say experts*, May 7, 2016. <https://www.theguardian.com/science/2016/mar/07/french-drug-trial-man-dead-expert-report-unprecedented-reaction>

<sup>12</sup> *Id.*

<sup>13</sup> Nano News, *supra*.

<sup>14</sup> *Zafgen Says a Second Patient Died in Beloranib Study*, The Wall Street Journal, December 2, 2015.

- In August of 2012, Bristol-Myers Squibb discontinued development of a potential hepatitis C drug after nine participants in a phase II clinical trial of the therapy were hospitalized and one died<sup>15</sup>.

These tragedies echo an event in 2006 when six healthy men suffered multiple organ failure during testing of an arthritis and cancer drug candidate called TGN1412, even with a dose *500 times smaller than the dose found safe in preclinical animal studies*<sup>16</sup>.

**Further tests performed by officials showed that in vitro testing using human cells could have predicted the danger that TGN1412 posed to humans, which the animal tests failed to predict**<sup>17</sup>.

As *Archibald et al* point out: “On the question of human in vivo testing, it is widely held to be unethical to use humans as experimental subjects in the assessment of new medicine safety and efficacy. However, we must recognize that we are in fact doing exactly that. It is established that in excess of 90% of potential medicines that have successfully passed the preclinical testing process fail, on the basis of safety and/or efficacy, when evaluated in human subjects. It is clear that human subjects, be they healthy volunteers or patients, are currently the most powerful contributors to the identification of clinical suitability. The obvious failure of animal-based preclinical testing to ‘weed out’ the unsuitable leaves the eventual human recipient as the real arbiter on this issue. If we cannot do any better than this, then we must acknowledge the key role human subjects play in the process, and consider how best to minimize the possibility of harm to them.”<sup>18</sup>

Accordingly, the regulations must be updated to ensure that drug and device sponsors have the confidence to use the most predictive preclinical test available, whether animal or non-animal. These updates will legally establish the acceptability of scientifically recognized modern and emerging test methods to support a medical product submission.

With the recent documented failure of animal-based preclinical test methods to predict safety in humans, it is more urgent than ever that FDA update regulations to broaden drug sponsors’ options to use the most predictive tests available. While the high-level work described in the strategy document is essential, FDA’s adoption of conservative amendments to IND and IDE regulations can and should happen now.

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<sup>15</sup> *Hepatitis C Drug trial halted after patient death*, Nature.com News Blog August 24, 2012 <http://blogs.nature.com/news/2012/08/hepatitis-c-drug-trial-halted-after-patient-death.html>

<sup>16</sup> H. Attarwala, *TGN1412: From Discovery to Disaster*, J Young Pharm. 2010 Jul-Sep; 2(3): 332–336. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964774/>

<sup>17</sup> Expert Scientific Group on Phase I Clinical Trials, Final Report, 11/20/06, [http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/documents/digitalasset/dh\\_073165.pdf](http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf)

<sup>18</sup> K. Archibald, T. Drake, R. Coleman, *Barriers to the Uptake of Human-based Test Methods, and How to Overcome Them*, ATLA 43, 301–308 (2015).

## **B. Guidance: Agency Guidance on the Use of the Draize test for Skin and Eye Irritation in Pharmaceutical Development**

Since 2005, FDA has informally stated that Draize test data are not required for primary skin and eye irritation testing, but drug sponsors continue to provide Draize test data<sup>19</sup> - despite the prevalence of other primary skin and eye irritation methods that are more predictive.

In late 2015, FDA issued narrow guidance to industry, stating the Draize test was no longer recommended in some circumstances and that in vitro or ex vivo testing would satisfy regulatory requirements in those cases.<sup>20</sup> While this is an important step forward in communicating irritation testing requirements with sponsors, the guidance does not go far enough. It is limited in scope, and merely covers reformulated products and new routes of administration.

A coalition<sup>21</sup> led by CRS has submitted a citizen petition urging FDA to issue broad guidance communicating clearly with drug and device sponsors that the Draize rabbit test for skin and eye irritation is no longer required and that human relevant in vitro tests will be accepted. To assist FDA with this request, CRS has submitted proposed draft guidance. It is our sincere hope that FDA will issue broad guidance regarding acceptable methods for skin and eye irritation for topically applied products.

## **C. FDA Reviewer Education and Training**

Agency submission reviewers must be educated and informed on available new technologies. Without reviewer education and uniform acceptance criteria, variability between reviewers' acceptance of new technologies will discourage their use and cause confusion for sponsors on their acceptability. Regular reviewer training and updated lists of available alternatives is crucial for early communication between regulators and sponsors on the acceptability of new test methods.

## **D. Technological Lock-In**

The phenomenon of 'technological lock-in' (where the superior long-term path is not necessarily the path chosen) applies strongly to the continued default use of animal testing, even where new technologies would be advantageous.<sup>22</sup> Animal testing is

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<sup>19</sup> *Id.*

<sup>20</sup> *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route, Guidance for Industry and Review Staff, Good Review Practice*, October 2015.  
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079245.pdf>

<sup>21</sup> Petitioners: Center for Responsible Science, Safer Medicines Trust, MatTek and Invitro International

<sup>22</sup> Archibald, *supra*.

subject to institutional, psychological and behavioral lock-in.<sup>23</sup> Therefore, intervention is necessary to ‘de-lock’ or change paths, in order to overcome the many factors contributing to entrenchment against change.<sup>24</sup> Stakeholder education and participation in the efforts to validate new methods is required to overcome this problem.

## Issue 2: Validation

*“Traditional approaches to validation often rely on comparing data obtained from a new method/strategy with results from an existing animal-based test. This becomes problematic for toxicity tests that have species-specific biases and also precludes any new test from performing “better” than the animal test, as any discordance will be assessed in favor of the existing method. In the absence of sufficient human data, how can new methods be validated as having equivalent (or better) performance than the animal-based test without a direct comparison to data from the animal test intended for replacement? Is there a place in our current paradigms to begin to apply a fundamental non-animal strategy that allows prospective validation without compromising near term human safety?”<sup>25</sup>*

The current validation process often serves to prevent instead of promote the introduction and adoption of new test methods.<sup>26</sup> The “gold standard” traditional tests have not been validated and comparison of new test methods to the traditional tests is problematic.

A possible solution to this problem is for validation to be relative rather than absolute.<sup>27</sup> If a new test or battery of tests can be shown to outperform the traditional animal test, that should be sufficient to ensure the continual and incremental replacement of underperforming tests with better ones.<sup>28</sup> Unless we can implement a system for gradual improvement, the “perfect” will remain the “enemy” of the good<sup>29</sup>.

Safer Medicines Trust (SMT), with input from many senior pharmaceutical, regulatory, and academic stakeholders, has developed a novel pragmatic approach to the validation of new tests for the safety testing of medicines. The approach consists of structurally and/or functionally paired drugs that have been marketed, one of which has caused adverse events in people (positive controls) while the other did not cause these events (negative controls). These drug pairs are to be subjected to a range of human-focused tests to see if any or all of them can identify the toxicities that led to each withdrawal. This approach is currently being tested in a proof-of-principle study as part

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<sup>23</sup> Frank, J. (2004). *Technological lock-in, positive institutional feedback, and research on laboratory animals*. *Structural Change Economic Dynamics* 16, 557–575

<sup>24</sup> Archibald, *supra*.

<sup>25</sup> SACATM Background Document, *supra*.

<sup>26</sup> Statement made at ICCVAM PUBLIC FORUM ON MAY 27, 2015

<sup>27</sup> Archibald, *supra*.

<sup>28</sup> *Id.*

<sup>29</sup> *Id.*

of the U.S. Environmental Protection Agency's ToxCast program, and is the basis of a larger Integrated Approach to Testing and Assessment proposed by a multi-partner international consortium brought together by SMT.

This pragmatic approach to validation of new tests for safety of medicines is a promising way to evaluate new test methods to bring a better understanding of which test method is better suited to predict human response. If a new test is shown to outperform the traditional test, the new test should be approved and accepted by FDA.

Additionally, sponsor use of rat/dog/primate on-a-chip could be used as a stepping-stone to human chips and could serve to encourage use by those only familiar with animal data.

### **Issue 3: Obstacles to collection of and access to human data**

*“The utilization of human data will be an essential component of future validation efforts needed to establish confidence in new approaches for screening, prioritization and testing. Therefore, mechanisms for the ethical collection and sharing of data derived from human subjects exposed to xenobiotics need to be addressed. What obstacles currently prevent the collection and use of human toxicological data and what are some potential solutions to facilitate the use of human data in the future?”<sup>30</sup>*

With regard to drug development, data generated during preclinical and clinical testing are proprietary. Scenarios which impact on sharing the toxicity data produced are: a) a drug is toxic and testing is stopped during preclinical trials; this information may never be published and is kept in the archives of a sponsor; b) a drug undergoes clinical testing which reveals unexpected side-effects in humans and thus it is not put on the market; the preclinical and clinical data are kept in the files of the sponsor and, in the files of regulatory authorities (FDA); information on compounds which fail to reach the market because of late stage adverse effects is rarely published and is therefore not generally available; and c) successful drugs pass preclinical and clinical testing; the data on these are in the files of both regulatory authorities and the drug sponsor, and this information may be published. In addition to the data held within regulatory agencies, the sponsor may have other relevant data which could contribute to the development and validation of alternative methods. Data on compounds that have been taken out of testing early on are particularly important with respect to the development of predictive in vitro tests and structure activity models.<sup>31</sup>

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<sup>30</sup> SACATM Background Document, *supra*.

<sup>31</sup> *Issues Relating to the Release of Proprietary Information and Data for Use in the Validation of Alternative Methods*, The Report and Recommendations of ECVAM Workshop 27, ATLA 26, 13-20, 1998. <https://eurl-ecvam.jrc.ec.europa.eu/about-ecvam/archive-publications/publication/WorkshopReport27.pdf>

A joint effort amongst pharmaceutical sponsors to share data is essential. There are collaborations now between sponsors,<sup>32</sup> however, broader collaboration is needed for the data to be useful. Cooperation and data sharing between sponsors and those developing new methods is required if these methods are to be validated and used by sponsors. Currently, the new technology developers are burdened with attempting to convince sponsors, on an individual basis, to participate in the effort. This is a major roadblock to the validation and adoption of these human-relevant methods.

FDA Commissioner, Robert Califf, has also suggested a database for preclinical research, “something like a clinicaltrials.gov for preclinical work.” Currently there is no such database for preclinical research, but it would be useful to help solve two interconnected problems: lack of transparency and the inability to reproduce research results<sup>33</sup>.

#### **Issue 4: Increase communication and coordination of activities amongst and between government agencies and stakeholders**

*“Increased strategic coordination amongst and between Federal agencies and stakeholders (including international partners) would improve scientific and fiscal efficiency, providing greater return on investments while expediting the development and utilization of new technologies. What strategies and mechanisms could be employed to increase communication and coordination of activities amongst and between the federal government and key stakeholders?”<sup>34</sup>*

It is essential to coordinate efforts of all involved in the development, validation and regulation of new technologies. Enormous effort is being made to develop new technologies that are more predictive, but coordination between government and stakeholders has to happen if we are to advance the development and adoption of new methods. To achieve both scientific and fiscal efficiency, there must be a critical mass of core capabilities and a sharing of resources to facilitate the integration and industrialization of new technologies. Official working groups or committees must be formed with strong leadership. These committees should include all stakeholders. Participation of those developing new technologies and non-profits that focus on public

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<sup>32</sup> TransCelerate Biopharma, Inc., a non-profit organization whose mission is to collaborate across the global biopharmaceutical R&D community to identify, prioritize, design and facilitate implementation of solutions designed to drive the efficient, effective and high quality delivery of new medicines. TransCelerate has a Clinical Data Transparency Initiative. BioCelerate, a subsidiary of TransCelerate, is focused on enabling access to a broader set of toxicology data and is motivated in part by FDA’s 2011 Strategic Plan for Regulatory Science, which includes objectives to modernize toxicology to enhance product safety. The information gathered through this initiative should help with translation of preclinical findings to the clinic.

<sup>33</sup> Califf’s big idea: Build a database for research done before clinical trials, STAT News, June 10, 2016 <https://www.statnews.com/2016/06/10/califf-database-preclinical-trials/>

<sup>34</sup> SACATM Background Document, *supra*.

health issues, including, but not limited to patient advocacy groups should be involved in the process.

It is also essential for stakeholders to have access to regulators knowledgeable about this process. Designated agency liaisons who are dedicated to the process of validation and acceptance of new test methods must be available to communicate with all stakeholders.

### **Conclusion**

As *Archibald et al* point out: “In order to realize the potential of a human-based approach, we must continue to research and refine human based tests, improve and accelerate validation, educate researchers, regulators and insurers about the limitations of extrapolating between species and the advantages of a human-focused approach, clarify, pro-actively communicate and enforce official guidelines, and, most importantly, set timelines for action.”<sup>35</sup>

As stated earlier, an important first step would be adoption of conservative regulation changes regarding drug and device development. In addition, development of a comprehensive strategy that brings all stakeholders to the table with consistent communication is required to overcome obstacles to the development, validation, and regulatory acceptance of new test methods.

We appreciate the opportunity to submit these comments. We look forward to continued progress and collaboration.

CRS advocates for advances in regulatory science including the use of modern, effective preclinical test methods to streamline development and bring safer, more effective products to market more quickly at less cost.

Sincerely,

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<sup>35</sup> Archibald, *supra*.

## CITIZEN PETITION – Exhibit B: Regulation Updates

Petitioner requests the following regulatory text be issued and placed under the definition sections of 21 C.F.R. §§ 310.3, 312.3, 314.3, 315.2, 601.31, 812.3, 860.3:

*Preclinical tests, testing, or studies means (1) animal testing or (2) non-animal testing that has been shown to be predictive of human response.*

In addition, Petitioner requests the following changes to these existing regulations:

1. 21 C.F.R. § 310.303 (Continuation Studies for FDA Approved Drugs)

**Current wording:** *(a) A new drug may not be approved for marketing unless it has been shown to be safe and effective for its intended use(s). . . . To acquire necessary data for determining the safety and effectiveness of long-term use of such drugs, extensive animal and clinical tests are required as a condition of approval.*

**Proposed wording:** *(a) A new drug may not be approved for marketing unless it has been shown to be safe and effective for its intended use(s). . . . To acquire necessary data for determining the safety and effectiveness of long-term use of such drugs, extensive preclinical and clinical tests are required as a condition of approval.*

2. 21 C.F.R. § 312.22(c) (General Principles for IND Submissions)

**Current wording:** *The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. . . .*

**Proposed wording:** *The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of preclinical toxicology studies or other human studies as appropriate. . . .*

3. 21 C.F.R. § 312.23(a)(3)(iv) ((IND Content and Format)

**Current wording:** *A brief description of the overall plan for investigating the drug product for the following year. The plan should include . . . . (f) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.*

**Proposed wording:** *A brief description of the overall plan for investigating the drug product for the following year. The plan should include . . . . (f) any risks of particular severity*

*or seriousness anticipated on the basis of the toxicological data from preclinical studies or prior studies in humans with the drug or related drugs.*

4. 21 C.F.R. § 312.23(a)(5)(ii) (IND Investigator's Brochure)

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

**Proposed wording:** *A summary of the pharmacological and toxicological effects of the drug in preclinical tests and, to the extent known, in humans.*

5. 21 C.F.R. § 312.23(a)(5)(iii) (Investigator's Brochure)

**Current wording:** *A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.*

**Proposed wording:** *A summary of the pharmacokinetics and biological disposition of the drug in preclinical tests and, if known, in humans.*

6. 21 C.F.R. § 312.23(a)(8) (IND Pharmacology and Toxicology Information)

**Current wording:** *Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. . . .*

**Proposed wording:** *Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving preclinical tests, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of preclinical tests required varies with the duration and nature of the proposed clinical investigations. . . .*

7. 21 C.F.R. § 312.23(a)(8)(i) (Pharmacology and Drug Disposition)

**Current wording:** *Pharmacology and drug disposition. A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.*

**Proposed wording:** *Pharmacology and drug disposition. A section describing the pharmacological effects and mechanism(s) of action of the drug in preclinical tests, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.*

8. 21 C.F.R. § 312.23(a)(8)(ii) (Toxicology)

**Current wording:** *Toxicology. (a) An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; preclinical tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.*

**Proposed wording:** *Toxicology. (a) An integrated summary of the toxicological effects of the drug in preclinical tests. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any other studies intended to evaluate drug toxicity.*

9. 21 C.F.R. § 312.23(a)(10)(i) (Drug Dependence and Abuse Potential)

**Current wording:** *Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.*

**Proposed wording:** *Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in preclinical tests.*

10. 21 C.F.R. § 312.23(a)(10)(ii) (Radioactive Drugs)

**Current wording:** *Radioactive drugs. If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. . . .*

**Proposed wording:** *Radioactive drugs. If the drug is a radioactive drug, sufficient data from preclinical or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. . . .*

11. 21 C.F.R. § 312.33(a)(6) (Content of Annual Reports)

**Current wording:** *A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.*

**Proposed wording:** *A list of the preclinical studies, completed or in progress during the past year, and a summary of the major preclinical findings.*

12. 21 C.F.R. § 312.82(a) (Early Consultation)

**Current wording:** *Pre-investigational new drug (IND) meetings. Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. . . .*

**Proposed wording:** *Pre-investigational new drug (IND) meetings. Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of preclinical studies needed to initiate human testing. . . .*

13. 21 C.F.R. § 312.88 (Safeguards for Patient Safety)

**Current wording:** *All of the safeguards incorporated within Parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. . . . These safeguards further include the review of animal studies prior to initial human testing (☐ 312.23) . . . .*

**Proposed wording:** *All of the safeguards incorporated within Parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. . . . These safeguards further include the review of preclinical studies prior to initial human testing (☐ 312.23) . . . .*

14. 21 C.F.R. § 312.160 (Drugs for Investigational Use in Laboratory Research  
Animals on In Vitro Tests)

**Current wording:** *Drugs for investigational use in laboratory research animals or in vitro tests. . . . A person may ship a drug intended solely for tests in vitro or in animals used only for laboratory research purposes if it is labeled as follows:*

*CAUTION: Contains a new drug for investigational use only in laboratory research animals or for tests in vitro. Not for use in humans. . . . (2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for tests in vitro or in animals used only for laboratory research.*

**Proposed wording:** *Drugs for investigational use in preclinical tests. . . . A person may ship a drug intended solely for preclinical tests if it is labeled as follows:*

*CAUTION: Contains a new drug for investigational use only in preclinical tests. Not for use in humans. . . . (2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for only for preclinical testing.*

15. 21 C.F.R. § 314.50(d)(2) (NDA Technical Sections)

**Current wording:** *Nonclinical pharmacology and toxicology section. A section describing, with the aid of graphs and tables, animal and in vitro studies with drug . . . .*

**Proposed wording:** *Nonclinical pharmacology and toxicology section. A section describing, with the aid of graphs and tables, preclinical studies with drug . . . .*

16. 21 C.F.R. § 314.50(d)(2)(iv) (NDA Non-Clinical Sections)

**Current wording:** *Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.*

**Proposed wording:** *Any preclinical studies of the absorption, distribution, metabolism, and excretion of the drug.*

17. 21 C.F.R. § 314.50(d)(5)(i) (Clinical Data Section)

**Current wording:** *A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the animal pharmacology and toxicology data.*

**Proposed wording:** *A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the preclinical pharmacology and toxicology data.*

18. 21 C.F.R. § 314.50(d)(5)(vi)(a) (Clinical Data Section)

**Current wording:** *(a) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations . . . .*

**Proposed wording:** *(a) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent preclinical data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations . . . .*

19. 21 C.F.R. § 314.50(d)(5)(vi)(b) (Clinical Data Section)

**Current wording:** *(b) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug . . . . These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format . . . .*

**Proposed wording:** *(b) The applicant shall, under section 505(i) of the act, update periodically its pending application with new safety information learned about the drug . . . . These "safety update reports" are required to include the same kinds of information (from clinical studies, preclinical studies, and other sources) and are required to be submitted in the same format . . . .*

20. 21 C.F.R. § 314.93(e)(2) (ANDA Petition to Request Change from Listed Drug)

**Current wording:** *For purposes of this paragraph, "investigations must be conducted" means that information derived from animal or clinical studies is necessary to show that the drug product is safe or effective. Such information may be contained in published or unpublished reports.*

**Proposed wording:** *For purposes of this paragraph, "investigations must be conducted" means that information derived from preclinical or clinical studies is necessary to show that the drug product is safe or effective. Such information may be contained in published or unpublished reports.*

21. 21 C.F.R. § 315.6(d) (Evaluation of Safety)

**Current wording:** *Radiation safety assessment. The radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. The maximum tolerated dose need not be established.*

**Proposed wording:** *Radiation safety assessment. The radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate preclinical models. The maximum tolerated dose need not be established.*

22. 21 C.F.R. § 330.10 (a)(2) (Procedure for Establishing OTC Drug Monographs)

**Current wording:** *Request for data and views. The Commissioner will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel . . . . All submissions must be in the following format:*

*OTC DRUG REVIEW INFORMATION*

- I. Label(s) and all labeling (preferably mounted and filed with the other data -- facsimile labeling is acceptable in lieu of actual container labeling).*
- II. A statement setting forth the quantities of active ingredients of the drug.*
- III. Animal safety data . . . .*

**Proposed wording:** *Request for data and views. The Commissioner will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel . . . All submissions must be in the following format:*

*OTC DRUG REVIEW INFORMATION*

- I. Label(s) and all labeling (preferably mounted and filed with the other data -- facsimile labeling is acceptable in lieu of actual container labeling).*
- II. A statement setting forth the quantities of active ingredients of the drug.*
- III. Preclinical safety data. . . .*

23. 21 C.F.R. § 601.35(d) (Diagnostic Radiopharmaceuticals)

**Current wording:** *Radiation safety assessment. The radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate animal models. The maximum tolerated dose need not be established.*

**Proposed wording:** *Radiation safety assessment. The radiation safety assessment must establish the radiation dose of a diagnostic radiopharmaceutical by radiation dosimetry evaluations in humans and appropriate preclinical models. The maximum tolerated dose need not be established.*

24. 21 C.F.R. § 812.2(c) (IDE Exempted Investigations)

**Current wording:** *Exempted investigations. This part, with the exception of § 812.119, does not apply to investigations of the following categories of devices . . . (6) A device shipped solely for research on or with laboratory animals and labeled in accordance with § 812.5(c).*

**Proposed wording:** *Exempted investigations. This part, with the exception of § 812.119, does not apply to investigations of the following categories of devices . . . (6) A device shipped solely for preclinical research and labeled in accordance with § 812.5(c).*

25. 21 C.F.R. § 812.5(c) (Labeling of Investigational Devices)

**Current wording:** *Animal research. An investigational device shipped solely for research on or with laboratory animals shall bear on its label the following statement: "CAUTION--Device for investigational use in laboratory animals or other tests that do not involve human subjects."*

**Proposed wording:** *Preclinical research. An investigational device shipped solely for preclinical research shall bear on its label the following statement: "CAUTION--Device for investigational use in preclinical or other tests that do not involve human subjects."*

26. 21 C.F.R. § 812.27(a) (IDE Report on Prior Investigations)

**Current wording:** *General. The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation.*

**Proposed wording:** *General. The report of prior investigations shall include reports of all prior clinical and preclinical testing of the device and shall be comprehensive and adequate to justify the proposed investigation.*

27. 21 C.F.R. § 812.35(a)(3)(iii) (Supplemental Applications)

**Current wording:** *Definition of credible information. (A) Credible information to support developmental changes in the device (including manufacturing changes) includes data generated under the design control procedures of § 820.30, preclinical/animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing.*

**Proposed wording:** *Definition of credible information. (A) Credible information to support developmental changes in the device (including manufacturing changes) includes data generated under the design control procedures of § 820.30, preclinical testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing.*

28. 21 C.F.R. § 860.5(f) (Medical Device Classification Procedures)

**Current wording:** *For purposes of this section, safety and effectiveness data include data and results derived from all studies and tests of a device on animals and humans and from all studies and tests of the device itself intended to establish or determine its safety and effectiveness.*

**Proposed wording:** *For purposes of this section, safety and effectiveness data include data and results derived from all preclinical studies and tests of a device, studies and tests of a device on humans, and from all studies and tests of the device itself intended to establish or determine its safety and effectiveness.*

29. 21 C.F.R. § 860.7(d)(2) (Determination of Safety and Effectiveness)

**Current wording:** *Among the types of evidence that may be required, when appropriate, to determine that there is reasonable assurance that a device is safe are investigations using laboratory animals, investigations involving human subjects, and nonclinical investigations including in vitro studies.*

**Proposed wording:** *Among the types of evidence that may be required, when appropriate, to determine that there is reasonable assurance that a device is safe are investigations using preclinical studies and investigations involving human subjects.*