July 31, 2015

VIA OVERNIGHT MAIL

Honorable Stephen Ostroff, M.D.
Acting Commissioner for Food and Drugs
C/o Division for Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Citizen Petition on Use of Modern Test Methods for Pre-Clinical Research

Dear Dr. Ostroff:

Pursuant to the requirements of 21 CFR §10.30, on behalf of the parties listed below, we submit and support this Citizen Petition for review and consideration by the Food and Drug Administration (FDA). We believe that updating existing regulations to permit FDA the discretion to allow the use of recognized existing modern pre-clinical test methods to support Investigational New Drug Applications (INDs) and Investigational Device Exemptions (IDEs) is consistent with advancing regulatory science. This objective reportedly remains a high priority of the Agency. Regulatory refinements will expedite drug and device development while maintaining, and potentially improving, the safety and efficacy of these investigational products. This request is based primarily on the availability of more modern preclinical testing methodologies in order to streamline and improve medical product development and applications, at FDA’s discretion, not to prevent the use of laboratory animals, which are still necessary in many circumstances.

We have incorporated citations to relevant legal and scientific literature, including internet references. All this information is available on-line and elsewhere, so we have not included copies with this Petition. Should the Agency require hard copies of any of this referenced information, please let us know and we will make this information available immediately for your reference.

Thank you for your prompt review and consideration of the issues presented in the attached Petition. Representatives of the organizations listed below are available to meet or for further discussion as you deem appropriate.
Sincerely,

Marc J. Scheineson
On Behalf of

Center for Responsible Science
Asterand Bioscience
AxoSim Technologies LLC
Empiriko
Friends of Cancer Research
HμREL® Corporation
In Vitro ADMET Laboratories
Invitro Cue
InVitro International
MatTek Corporation
National Organization for Rare Disorders
Safer Medicines Trust
United Spinal Association
3D Biomatrix, Inc.
July 31, 2015

VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Petitioners (listed in Exhibit A) submit this Citizen Petition under Sections 505, 515 and 701 of the Federal Food, Drug, and Cosmetic Act (“FDCA” or “the Act”) 21 U.S.C. §§ 355, 360, 360e, 371, and Section 351 of the Public Health Service Act (“PHS Act”) 42 U.S.C. § 262. This Citizen Petition requests that the Acting Commissioner of Food and Drug Administration (“FDA”) modify existing regulations in Title 21 of the Code of Federal Regulations (“CFR”) that govern requirements for investigational new drug (“IND”) applications, investigational device exemptions (“IDE”), and new drug applications (“NDAs”). In particular, Petitioner seeks changes allowing for the use of both animal test methods and non-animal test methods that are shown to be predictive of human response to satisfy the preclinical testing requirement. Unless FDA moves in Notice and Comment Rulemaking to modify some of its regulations to permit the use of modern test methods, the public health community and industry will not have the incentive necessary to validate and use these modern technologies.

I. Action Requested

Petitioner respectfully requests that the Acting Commissioner of the FDA amend certain regulations designated herein to establish and/or clarify that FDA will accept data from scientifically recognized modern and emerging test methods to support a drug or device investigational application. The requested amendments will broaden options in preclinical testing and will not require one type of testing over another. FDA and medical product
developers will retain discretion to choose or accept test methods. Per the requirements of 21 C.F.R. § 10.30(b)(3), Petitioner has provided the exact wording of the existing regulations subject to this request, as well the requested amendments to the existing regulatory text, in Exhibit B.

II. Statement of Grounds

A. Introduction

The FDA is the federal agency entrusted with reviewing submissions for new drug applications (“NDAs”) and for most medical devices through the submission of premarket applications (“PMAs”) or 510(k) clearances. The approval (or clearance) of these submissions is required prior to the legal marketing of new drugs or devices (collectively “medical products”). Prior to submitting a NDA, a drug sponsor must conduct preclinical testing and several phases of human clinical testing to establish its drug product’s safety and efficacy.

The FDA requires preclinical testing before a sponsor is permitted to test an investigational product in humans. This testing traditionally utilizes multiple species of laboratory animals in order to evaluate a candidate drug in a biological system through generating data on toxicity, mechanism of action, etc. Data from the preclinical testing are then used to support an IND (unless exempt) which must be approved by FDA in order to lawfully test a candidate drug in human clinical trials. The data generated from the human clinical trials are used to support a NDA. Similar processes apply to the review and approval of biological drugs and certain medical devices. A sponsor wishing to conduct a clinical trial with a medical device to support a PMA, or 510(k) clearance, must first obtain an investigational device exemption (“IDE”) if not otherwise exempted from the IDE requirement. As with INDs, IDE submissions contemplate the use of preclinical animal test data.

Former FDA Commissioner Margaret Hamburg and the Agency made it a high priority to “advance regulatory science at FDA” by focusing on “8 priority areas of regulatory science where new or enhanced engagement is essential to the continued success of FDA’s public health and regulatory mission.” The first priority area was to modernize toxicology to enhance product safety. A key component of that strategy was to develop better models of human adverse responses, recognizing that there is room for improvement. This includes, but is not limited to,

1 Biological products are approved under a biologics license application (“BLA”). 42 U.S.C. § 262(a).
2 See, e.g., 21 C.F.R. § 310.303.
3 See, e.g., 21 C.F.R. Part. 312.
4 21 C.F.R. § 312.1. An IND is also required for a biological product. 21 C.F.R. § 312.2(a).
5 See 21 C.F.R. § 314.50.
6 21 C.F.R. § 812.1.
7 See, e.g., 21 C.F.R. § 812.27(a).
8 See U.S. FOOD AND DRUG ADMIN., ADVANCING REGULATORY SCIENCE AT FDA, 7-8 (2011). http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm. (FDA seeks, in part, to evaluate and promote the use of cell and tissue-based assays that more accurately represent human susceptibility to adverse reactions.)
development of computer models of cells, organs and systems to better predict product safety and efficacy.\(^9\) FDA has stated that new models are required in order to move forward and improve prediction of toxicological risk. In its strategic plan for advancing regulatory science, FDA stated that “[m]odernizing toxicology and continually improving the ability of non-clinical tests, models, and measurements to predict product safety issues will increase the likelihood that toxicology risks will be identified earlier in product development, assuring patient safety, and mitigating the need to withdraw previously approved products.”\(^10\)

B. Current FDA Regulations and Policy on Preclinical Testing

A review of the FDA regulations governing INDs and IDEs demonstrates that traditional testing is a necessary prerequisite to generate the preclinical data required to pursue an IND or IDE. These regulations are facially written to mandate traditional test methods. FDA has made important statements suggesting that the Agency is amenable to scientifically recognized modern test methods in lieu of traditional testing:

FDA's IND regulation allows FDA the flexibility to accept NATMs\(^11\) such as in vitro studies or prior experience with the drug or biological product in humans, when appropriate. In the preamble to the IND regulation, FDA stated its intent to limit the scope and duration of toxicology and chemistry submissions [i.e., animal test data] to those necessary to support the scope and duration of the proposed human testing . . . . Similar to that for IND submissions, FDA’s IDE regulations allow flexibility to accept NATMs when they are appropriate to support proceeding with clinical investigation (21 CFR 812.20(b) and 812.27(a)).\(^12\)

Currently, FDA recommends and accepts NATMs when they are at least as valid as other methods.\(^13\)

Despite the foregoing, FDA has not modified the text of its regulations. Current regulations are read to require traditional test methods by FDA review divisions. Some examples are as follows:

(NDA Records and Reports) To acquire necessary data for determining the safety and effectiveness of long-term use of such

\(^9\) Id. at 9.
\(^10\) Id.
\(^11\) NATM is an acronym for non-animal test method
\(^13\) Information Advisory: FDA to Issue Response to Citizen Petition on Non-Animal Test Methods, May 18, 2010.
drugs, extensive animal and clinical tests are required as a condition of approval.\textsuperscript{14}

\textbf{(Early Consultation on IND)} Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. . . . The purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing.\textsuperscript{15}

\textbf{(Application Technical Sections)} 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.\textsuperscript{16}

On May 20, 2010, FDA, in a thoughtful 15-page response, denied a prior Citizen Petition submitted on November 14, 2007 by a coalition of animal rights groups regarding non-animal test methods (NATMs).\textsuperscript{17,18} In this current petition, Petitioner requests merely that designated regulations be modified slightly (as recommended in Exhibit B) to provide FDA reviewers and medical product developers with the option to use scientifically recognized modern test methods in lieu of traditional animal test methods \textit{completely within the Agency and medical product developer's discretion}. This clear signal will move product development forward by bringing written policy up to date with stated policy and science, and by paving the way for industry to develop and use emerging, superior technologies.

In its 2010 response to the prior Citizen Petition, FDA stated “FDA intends to issue a draft guidance to industry and to FDA staff regarding the use of NATMs.”\textsuperscript{19} Despite that commitment, FDA has not issued guidance to medical product sponsors on the acceptability of NATMs, or recommendations on NATM development and use in supporting a medical product submission. However, the usefulness of such guidance (even if it is actually being developed) may be limited given that federal courts have interpreted FDA regulations, as currently written, in a manner that may be interpreted to require traditional animal testing:

\begin{itemize}
  \item 21 C.F.R. § 312.23(a)(3)(iv) (emphasis added).
  \item 21 C.F.R. § 312.82(a) (emphasis added).
  \item 21 C.F.R. § 314.50(d)(5)(i) (emphasis added).
  \item See Dorsey letter at \url{http://www.regulations.gov/#!documentDetail;D=FDAC2007-P-0109-0012}.
\end{itemize}

\textsuperscript{17} Petitioner mentions the 2007 petition in order to distinguish the two petitions which both address NATMs. The 2007 petition was an animal welfare petition that sought to \textit{mandate use of NATMs} in lieu of animal test methods whenever such scientifically acceptable methods are available.

\textsuperscript{19} \textit{Supra}, note 19 at 2.
An IND is filed with the Food and Drug Administration after animal and laboratory studies have been completed.\textsuperscript{20}

The FDA's Pre-Market Approval application requires manufacturers to submit extensive animal and human data to establish their devices' safety and effectiveness.\textsuperscript{21}

FDA has determined, in limited cases, that scientifically recognized modern test methods can be used in place of traditional animal test methods. For example, FDA indicated that it will accept scientifically recognized modern test methods in lieu of rabbit pyrogen testing. FDA stated “a firm may substitute an endotoxins test or alternative cell-based test if the firm can demonstrate equivalent pyrogen detection.”\textsuperscript{22} Some NATMs for pyrogen testing include: human whole blood/interleukin-1B \textit{in vitro} pyrogen test, human whole blood/interleukin-6 \textit{in vitro} pyrogen test, monocytoid cell line Mono Mac 6/interleukin-6 \textit{in vitro} pyrogen test.\textsuperscript{23} FDA codified the acceptance of NATMs with respect to potency testing for biologic products. It stated that “[t]ests for potency shall consist of either in vitro or in vivo tests, or both.”\textsuperscript{24} There are two known modern test methods that have been developed for this biologic potency testing – the ELISA test and the ToBI test for human tetanus vaccine, which FDA accepts on a case-by-case basis.\textsuperscript{25} It should be noted that these two NATMs were developed to meet a regulation that explicitly permits use of modern test methods in 21 C.F.R. § 610.10 related to testing for potency in lot release. Needless to say, the regulatory text provided assurances that a modern test method could be acceptable for potency testing.

In the absence of new regulations that legally establish the acceptability of scientifically recognized modern and emerging test methods to support a medical product submission, the current regulations, if left unchanged, actually discourage innovation in developing modern technologies. It promotes the status quo requiring traditional testing during preclinical studies and creates an unreceptive environment that fails to encourage or support the development of modern and emerging test methods.

\subsection*{C. Inherent Costs and Risks of Medical Product Development Encourage Continued Animal Testing}

FDA is well aware that the financial costs and time commitment to develop a successful new medical product are enormous. With respect to drugs, it is estimated that for every 5,000

\begin{thebibliography}{99}
\bibitem{21} Reeves v. Acromed Corp., 44 F.3d 300, 303 (5th Cir. 1995) (emphasis added).
\bibitem{23} NATIONAL TOXICOLOGY PROGRAM, Regulatory Acceptance of Alternative Methods, \url{NTP.NIEHS.NIH.GOV}, \url{http://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/acceptance-of-alternative-methods/index.html}.
\bibitem{24} 21 C.F.R. § 610.10.
\bibitem{25} NATIONAL TOXICOLOGY PROGRAM, \textit{supra} note 28.
\end{thebibliography}
candidate compounds discovered, only one will eventually reach the marketplace.\textsuperscript{26} In addition, less than one-third of marketed drugs receive profits sufficient to recoup their research and development expenditures.\textsuperscript{27} Given these long odds, and the delays inherent in product reviews, sponsors are highly incentivized to proceed in a conservative risk-adverse manner and conduct tests that have been accepted by FDA in the past. As noted above, current FDA regulations are reasonably read to require traditional test methods. Notwithstanding certain FDA statements that FDA may accept modern test methods, the current regulatory text and lack of formal guidance create a situation where the clearest, safest path for sponsor drug and device development is to conduct traditional testing in lieu of any modern test method that might be appropriate to the product development.

There are potential financial incentives for sponsors to use modern test methods if the data are provided in lieu of data from traditional test methods. Modern methods such as computer modeling or reconstructed human tissue are potentially less costly than traditional models such as traditional rodent bioassay to determine carcinogenicity that can cost up to $4 million dollars.\textsuperscript{28} However, despite the potential cost savings, a sponsor is unlikely to advance the use of a modern method when it appears that traditional testing is legally required under FDA regulations. In pursuing the use of modern methods, a sponsor, and perhaps the FDA reviewer, would face uncertainty concerning whether traditional non-animal test data could be utilized at all in support of a medical product submission. This risk is compounded by the potential for delay in approval of the IND or IDE (through several rounds of follow-up questions or information requests) as FDA evaluates and responds to a proposed modern method. Needless to say, without clearly establishing (and signaling industry) that scientifically recognized modern methods can be used, substantial barriers and inertia exist that hinder advancement of regulatory science at FDA.

D. Modifications to IND, IDE, and NDA Regulations Needed to Encourage Development and Usage of Modern Test Methods

Petitioner acknowledges that FDA has made statements that it will entertain modern test methods. Petitioner’s proposal to modify relevant FDA regulations to allow drug sponsors to use scientifically recognized modern test methods in appropriate circumstances will eliminate uncertainty regarding the use of modern methods in preclinical testing. Petitioner is unaware of any information that is unfavorable to the Petitioner’s positions and/or proposed regulation modifications. The regulation modification proposals do not disallow the use of traditional preclinical test methods, but broaden options to allow drug sponsors to use both animal testing and non-animal testing that is shown to be predictive of human response. The suggested modifications (included in Exhibit B) would help effectuate FDA’s stated goal in its objective to advance regulatory science by removing barriers to use of modern test methods while maintaining the existing regulatory

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\textsuperscript{26} Herman Saftlas & Wendy Diller, \textit{Healthcare: Pharmaceuticals}, Standard & Poor’s Industry Surveys 27 (2011).

\textsuperscript{27} Id.

\textsuperscript{28} Russell S. Thomas et al., \textit{Application of Genomic Biomarkers to Predict Increased Lung Tumor Incidence in 2-Year Rodent Cancer Bioassays}, 97 Toxicological Sci. 55, 55 (2007), available at http://toxsci.oxfordjournals.org/content/97/1/55.full.pdf
structure, thus ensuring adequate review to establish safety and effectiveness for drugs and devices.

E. Conclusion

For the reasons set forth above, Petitioners request FDA to initiate notice and comment rulemaking to modify existing regulations to broaden sponsors’ testing options by establishing clearly that both animal testing and non-animal testing that is shown to be predictive of human response may be accepted as preclinical test methods. These modifications will not adversely impact the integrity of FDA’s drug or device review processes. In addition, these changes will have the positive impact of removing uncertainty regarding the acceptability of scientifically recognized modern and emerging test methods. This action would reinvigorate exploration of safety testing models and demonstrate FDA’s commitment to advancing regulatory science.

III. Environmental Impact

Petitioners claim a categorical exclusion from the environmental assessment requirement under 21 C.F.R. § 25.31.

IV. Economic Impact

Petitioner will submit an assessment of the economic impact of the actions it requests herein should the Acting Commissioner determine that such assessment is necessary in evaluating this petition.

V. Certification

Petitioners certify to the best of petitioners’ knowledge and belief: (a) this petition contains all information and views upon which the petition relies; (b) this petition contains representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) petitioners have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed. Petitioners further certify that the information upon which petitioners have based the action requested herein first became known to the party on whose behalf this petition is submitted on July XX, 2015. Petitioners neither received nor expect to receive payments, including cash and other forms of consideration, to file this information or its contents (other than by virtue of petitioners retention by petitioners client). Petitioners verify under the penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.
July 31, 2015

Respectfully submitted,

Marc Scheineson, Attorney at Law

Alston & Bird on behalf of Petitioners
Center for Responsible Science

Center for Responsible Science (CRS) is a non-profit comprised of scientific, medical, regulatory, business, and legal professionals who promote advances in regulatory science. Such advances include the use of modern, predictive preclinical test methods in an effort to streamline drug and device development and bring safer, more effective products to patients more quickly at less cost.

Through collaboration with scientific, educational, legal, health care, patient advocacy and biotech communities, CRS pushes for better results for patients.

Asterand Bioscience

Asterand Bioscience (Asterand Bio) is a leading global provider of high quality, well-characterized human tissue and human tissue-based research solutions to drug discovery scientists. Based in Detroit, Michigan and Royston, U.K., Asterand Bio’s mission is to provide human-based solutions to accelerate the identification and validation of drug targets and enhance the selection of drug candidates with an increased likelihood of clinical success.

Asterand Bio has a well-established human tissue heritage, having been formed in 2006 through the merger of Asterand (founded 2000), a human tissue biorepository, and Pharmagene (founded 1996), a human tissue-based drug discovery company. Asterand Bio is uniquely positioned to provide a comprehensive approach to meet the research needs of pharmaceutical, biotechnology and diagnostic companies, as well as academia.

AxoSim Technologies LLC

AxoSim Technologies LLC (AxoSim) is a Louisiana based contract research organization dedicated to improving preclinical pharmaceutical development. AxoSim facilitates the prediction of neurological safety and efficacy early in the drug development pipeline using its patent pending “nerve-on-a-chip” technology. Employing micro-engineering techniques and novel biomaterials, AxoSim has developed a 3D cell-based in vitro model which mimics living tissue in both form and function. By providing an advanced alternative to animal testing, pharmaceutical companies will have access to high content data faster and earlier than currently possible.
Empiriko

Empiriko is a biotechnology company based in Newton, MA that designs game-changing solutions for drug discovery, development and patient treatment. Empiriko’s unique biomimetic platform – Biomimiks™ – closely mimics the oxidative function of the liver by incorporating chemical catalysts, biological processes and computational modeling. The power of these “chemosynthetic livers” is that they quickly and precisely predict the liver’s metabolic reactions to drugs – accelerating drug development, uncovering safety issues, decreasing time and cost, and reducing animal testing.

Friends of Cancer Research

Friends of Cancer Research (Friends) is a leading voice in advocating for policies and solutions that will get treatments to patients in the safest and quickest way possible. Friends develops groundbreaking partnerships and creates a more open dialogue among both public and private sectors and tears down the barriers that stand in the way of conquering cancer. By collaborating with premier academic research centers, professional societies, and other advocacy organizations, Friends is able to accelerate innovation.

Friends works closely with government agencies (FDA, NCI, NIH, HHS) and congressional leadership to create educational, policy, and scientific approaches to improve health outcomes and cancer care.

HµREL® Corporation

HµREL® Corporation is a privately held bioanalytic tools company with laboratories situated in North Brunswick, New Jersey and executive offices in Beverly Hills, California. HµREL® researches, develops, and commercializes products and services based on its patent-pending, co-cultured cell-based tissue constructs comprised of primary (i.e., actual) cells drawn from the human or other species; as well as on its patented HµRELflow™ microfluidic devices, which further enhance the already high functionality and range of application of its cell-based models. At the present time HµREL® offers primary cell-based hepatic models of the human, canine, cynomolgus monkey, rat, and Goettingen minipig species. The Company's products are utilized in pharmaceutical safety and drug metabolism and pharmacokinetics studies, and in the toxicological testing of environmental and industrial chemicals and consumer products. HµREL®’s initial technology development was sponsored and enabled substantially through R&D collaborations with major pharmaceutical firms, most notably with the Schering-
Plough Research Institute (“SPRI,” now Merck & Co.).

**In Vitro ADMET Laboratories**

Based in Columbia, Maryland, In Vitro ADMET Laboratories (IVAL) seeks to enhance drug development efficiency through state-of-the-art contract research services. IVAL’s dedicated group of professionals have worked and collaborated with various government agencies and for small to big pharma both domestic and international. IVAL aims to expedite the drug development process by providing innovative research techniques to get data to decision-makers fast. By partnering with clients, IVAL serves as an extension of their research arm to get tomorrow’s solutions here today. IVAL offers products and contract services that represent their past three decades of expertise in the application of in vitro experimental systems to evaluate drug absorption, metabolism, drug-drug interactions and drug toxicity.

**InvitroCue**

InvitroCue provides innovative products and services in the fields of *in vitro* DMPK, *in vitro* toxicology and digital pathology utilizing cell-based models and image analytics. InvitroCue’s technologies have been developed and validated together with leading pharmaceutical companies and scientific collaborators, such as the Agency for Science, Technology and Research (A*STAR), National University of Singapore, Massachusetts Institute of Technology and renowned pathologists. The company uses these technologies and assays to support better decision-making in preclinical studies, clinical trials and diagnostics. InvitroCue’s solutions can be applied in the realms of drug testing as well as the research and development of cosmeceuticals and medical devices. InvitroCue was established in 2012 as a spin-off from A*STAR and is based in Singapore.

**InVitro International**

InVitro International (IVRO), headquartered in Placentia, CA was established in September 1985 and is a customer and technology driven provider of non-animal testing methods. IVRO develops and commercializes globally both test kits, and laboratory services.

IVRO’s testing technologies are designed to produce data re: corrosivity, or ocular/dermal irritation, which correlate with animal and human test results.
Corrositex, IVRO's dermal corrosion testing assay, is accepted or approved by a large number of regulatory agencies including DOT, EPA, EU/OECD, European Centre for the Validation of Alternative Methods (ECVAM), OSHA, FDA, Consumer Product Safety Commission, Transport Canada, and IATA as a replacement for Draize testing.

**MatTek Corporation**

MatTek Corporation (MatTek) was founded in 1985 by two chemical engineering professors from MIT. MatTek is at the forefront of tissue engineering and is a world leader in the production of innovative 3D reconstructed human tissue models. Their skin, ocular, and respiratory tissue models are used in regulatory toxicology (OECD, EU guidelines) and address toxicology and efficacy concerns throughout the cosmetics, chemical, pharmaceutical and household product industries.

MatTek's human cell-derived tissue models are used throughout the United States and Canada, Europe, Japan, and Eastern Asia.

**National Organization for Rare Disorders**

The National Organization for Rare Disorders (NORD), a 501(c)(3) organization, is a patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 230 patient organization members, is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

**Safer Medicines Trust**

Safer Medicines Trust (Safer) is an independent patient safety charity with a mission to change the way medicines are tested, so they are safer for patients: moving from a system based mainly on tests on animals to one focused firmly on human biology. Safer comprises scientists and doctors with extensive expertise in drug development, who have hosted conferences at the UK Royal Society and House of Lords, and are working with the US EPA and FDA to test a method for qualifying innovative human biology-based safety tests.
United Spinal Association

United Spinal Association is the largest disability-led national non-profit organization founded by paralyzed veterans in 1946 and has since provided service programs and advocacy to improve the quality of life of those across the life span living with spinal cord injuries and disorders (SCI/D) such as multiple sclerosis, amyotrophic lateral sclerosis (ALS), post-polio syndrome and spina bifida. United Spinal represents over one million individuals with spinal cord injuries and disorders, 47 chapters, 105 rehabilitation hospital members and close to 200 support groups nationwide. Throughout its history, United Spinal Association has devoted its energies, talents and programs to improving the quality of life for these Americans and for advancing their independence. United Spinal Association is also a VA-recognized veterans service organization (VSO) serving veterans with disabilities of all kinds.

3D Biomatrix, Inc.

3D Biomatrix, Inc. designs and manufactures patented three-dimensional Hanging Drop Plates in 96 & 384-well formats for cell culture researchers who grow and test spheroids and micro-tissues for drug discovery. 3D Biomatrix Inc. was founded in 2010 and is based in Ann Arbor, Michigan.
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, updated 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."


**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.
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.

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.

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.