

**Stop Monkeying Around with Human Health: Moving Human  
Drug Development into the 21<sup>st</sup> Century By Abandoning  
Animal Models, Validating Emerging Test Methods, Updating  
FDA Regulations, and Issuing FDA Guidance**

Elizabeth Baker  
California Western School of Law  
Juris Doctorate Candidate, May 2014

“A major problem in the pharmaceutical industry right now is that the drug development model is actually broken. It just does not work. It takes many, many years to get a drug to market, it’s incredibly expensive, innumerable animal lives are lost – and then the results from animals usually don’t predict what happens in humans.”<sup>1</sup>

---

<sup>1</sup> Don Ingber, *Building an Organ on a Chip*, MIT Technology Review, July/August 2012, <http://www.technologyreview.com/demo/427992/building-an-organ-on-a-chip/> (last visited May 3, 2013).

## **INTRODUCTION**

### **The Stark Statistics**

Ninety-two percent of all drugs found safe in animal tests fail during human clinical trials due to their toxicity and/or inefficacy.<sup>2</sup> Of the eight percent of drugs that do gain FDA approval, over half are later withdrawn or relabeled due to severe, unexpected side effects<sup>3</sup>. Moreover, adverse drug reactions to prescription drugs are the fourth leading cause of death in the United States.<sup>4</sup> Drug development is stuck in an innovation gap as research and development funds substantially increase without an increase in approved drugs.<sup>5</sup>

### **The Need for Change**

Despite rapidly developing technologies and emerging science, the drug development paradigm has changed little since its 1960s inception<sup>6</sup>. The combination of the complexities of assessing successful drug compounds, rising drug development costs and high clinical failure rates, have resulted in a need for re-evaluation of the current drug

---

<sup>2</sup> U.S. FOOD AND DRUG ADMIN., INNOVATION OR STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS 8 (2004).

<sup>3</sup> U.S. GENERAL ACCOUNTING OFFICE. *FDA DRUG REVIEW: POSTAPPROVAL RISKS 1976-1985* 3 (1990).

<sup>4</sup> Jason Lazarou, et al., *Incidence of Adverse Drug Reactions in Hospital Patients*, 279 JAMA 1200, 1200 (1998).

<sup>5</sup> H. Geerts, *Of Mice and Men: Bridging the Translational Disconnect of CNS in Drug Discovery*, 23 CNS Drugs 915, 916 (2009).

<sup>6</sup> Shivaani Kummar, et al., *Phase 0 Clinical Trials: Recommendations from the Task Force on Methodology for the Development of Innovative Cancer Therapies*, in 45 Eur J Cancer 741, 742 (2009).

development paradigm.<sup>7</sup> The Food and Drug Administration (FDA) acknowledged the drug development innovation gap in a 2004 report, and highlighted the urgent need for a better drug development toolkit.<sup>8</sup>

### **Animal Models are Deficient**

The current drug development paradigm relies on in vitro testing and in vivo animal models to screen which drugs should continue the development process and be tested in humans.<sup>9</sup> Data from animal models is a problematic screening tool for human drugs because it often cannot be transposed to human clinical testing,<sup>10</sup> and most animal-based testing methods have never been scientifically validated.

The premise that animal models are generally predictive of human outcomes is the basis for their widespread use in safety and efficacy testing during human drug development.<sup>11</sup> However, the FDA repeatedly acknowledges reliance on animal models is deficient and results in high clinical failure rates.<sup>12</sup> Further, the use of animal models arguably adds unnecessary expense and delay to the drug development process.

---

<sup>7</sup> *Id.*

<sup>8</sup> See U.S. Food and Drug Admin, *supra*, at 11.

<sup>9</sup> Paolo Preziosi, *Science, Pharmacoeconomics and Ethics in Drug R&D: A Sustainable Future Scenario?*, 3 *Nature Reviews Drug Discovery* 521, 522 (2004).

<sup>10</sup> Michael Spedding, et al., *A Pathophysiological Paradigm for the Therapy of Psychiatric Disease*, 4 *Nature Reviews Drug Discovery* 467, 468 (2005).

<sup>11</sup> Andrew Knight, *The Costs and Benefits of Animal Experiments* 41 (2011).

<sup>12</sup> “Currently, nine out of ten experimental drugs fail in clinical studies because we cannot accurately predict how they will behave in people based on laboratory and animal studies.” News Release, FDA, *FDA Issues Advice to Make Earliest Stages of Clinical Drug Development More Efficient* (Jan. 12, 2006) (on file with the FDA); “Consider just one stark statistic: Today, nine out of 10 compounds developed in the lab fail in human

## The Need to Accept and Implement 21<sup>st</sup> Century Science and Technology

The FDA recognizes creating scientific tools and processes necessary to bring drug development into the 21<sup>st</sup> Century is a monumental effort requiring collaboration of federal agencies, patient groups, academic researchers, industry, healthcare practitioners, and others.<sup>13</sup> As the federal agency that oversees and regulates drug development,<sup>14</sup> the FDA must take a spearheading role to initiate change.

Although the FDA has stated its concern with reliance on animal model data,<sup>15</sup> and a need for a better drug development toolkit,<sup>16</sup> FDA regulations still require animal data.<sup>17</sup> The FDA is involved in projects to move validation of emerging science

---

studies. They fail, in large part because they behave differently in people than they did in animal or laboratory tests.” Prepared Statement for FDA Teleconference: Steps to Advance the Earliest Phases of Clinical Research in the Development of Innovative Medical Treatments (January 12, 2006) (on file with FDA); “The main causes of failures before human testing or early in clinical trials dramatically escalates costs. For example, for a pharmaceutical, a 10-percent improvement in predicting failures before clinical trials could save \$100 million in development costs per drug.” U.S Food and Drug Admin., *supra*, at 8.

<sup>13</sup>FDA’s Critical Path Initiative, <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm> (last visited May 3, 2013).

<sup>14</sup> 21 U.S.C.A § 393 (West 2011).

<sup>15</sup> Donald Prater, U.S. Food and Drug Admin. Powerpoint Presentation, Development and use of Advancing Testing Approaches by the U.S. FDA, Presented at “Advancing Safety Science and Health Research Under Horizon 2020 with Innovative, Non-Animal Tools” (Oct. 10, 2012) (on file with FDA).

<sup>16</sup> U.S. Food and Drug Admin, *supra*, at 8.

<sup>17</sup> 21 C.F.R § 312.23(a)5(ii) (West 2012), 21 C.F.R § 312.23(a)5(iii) (West 2012), 21 C.F.R. 312.23(8)(a)(i) (West 2012), 21 C.F.R. § 312.23(8)(a)(ii) (West 2012), 21. C.F.R. § 312.23 (10)(i) (West 2012).

forward<sup>18</sup>, but until FDA regulations that govern drug development are changed, or clear FDA guidance documents that recommend use of non-animal testing methods are issued, sponsors will continue to use the outdated research methods the FDA wants to change.

Although the FDA accepts data from certain non-animal models which have passed the formal validation process<sup>19</sup>, animal models remain the regulated testing method of nonclinical safety assessment of pharmacology studies, general toxicity studies, toxicokinetic and pharmacokinetic studies, reproduction toxicity studies, nontoxicity studies and carcinogenicity studies, and this animal data must be provided regardless of whether the alternative method was validated.<sup>20</sup> These regulations may stifle development and use of emerging science because even when drug sponsors use emerging science to test drugs, they still use time and money to gather the required animal data, which may contradict the emerging science data.

## **Road Map**

This paper discusses reliance on the animal model as a problematic component of the current drug development paradigm, and the need for further FDA action to bring drug development into the 21<sup>st</sup> Century. Part one of this paper describes a brief history of animal models in drug development, outlines the current drug development paradigm, and then explains drug development problems stemming from the animal model. Part two summarizes current law and policy governing drug development. Part three identifies

---

<sup>18</sup> Summarized under Part III of this paper.

<sup>19</sup> David Dorsey, Response to Citizen Petition Docket No. FDA-2007-P-0109, at 2, (formerly Docket No. 2007P-0457) (May 20, 2012) (on file with Federal Registrar).

<sup>20</sup> Int'l Conference on Harmonization, Guidance for Industry: M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (1997).

emerging drug development test methods, summarizes FDA efforts to develop and validate more reliable test methods, and offers recommendations for further FDA action to allow drug development to transition into the 21<sup>st</sup> Century. This paper will not discuss ethical implications of using the animal model in human drug development.

## **PART 1**

### **HISTORY OF ANIMAL MODELS IN DRUG DEVELOPMENT**

The use of animal models for scientific research has been accepted as an appropriate research tool since the 2<sup>nd</sup> Century, when Galen became the father of animal testing.<sup>21</sup> The modern version of animal testing began in the 19<sup>th</sup> century with Claude Bernard who believed organs and tissues were interchangeable among animals, and differences could be accounted for by scaling.<sup>22</sup> However, animal testing was not a required part of drug development until the 20<sup>th</sup> century.<sup>23</sup>

In 1938, Congress enacted the United States Federal Food, Drug and Cosmetic Act (FDCA), marking the first attempt to regulate drug safety because the FDCA required passive FDA approval based on a showing the drug was safe for its intended purpose.<sup>24</sup> The FDCA was a reaction to mass poisoning and over 100 deaths related to use of a sulphanilamide elixir containing diethylene glycol<sup>25</sup>. Scientists administered the

---

<sup>21</sup> C. RAY GREEK & JEAN SWINGLE GREEK, SACRED COWS AND GOLDEN GEESE: THE HUMAN COST OF EXPERIMENTS ON ANIMALS 23 (2000).

<sup>22</sup> Ray Greek, *Animal Models in Drug Development*, in NEW INSIGHTS INTO TOXICITY AND DRUG TESTING 124, (Sivakumar Gowder ed., (2013).

<sup>23</sup> Rachel Hajar, *Animal Testing and Medicine*, 12 Heart Views 42 (2011).

<sup>24</sup> Preziosi, *supra*, at 521.

<sup>25</sup> *Id.*

elixir to animals, which also died.<sup>26</sup> This occasion of parity convinced the scientific community that animals should be used for testing all medications.<sup>27</sup>

Nearly two decades after passing the FDCA, doctors prescribed thalidomide to pregnant women for relief of morning sickness symptoms without knowledge that thalidomide caused birth defects.<sup>28</sup> Consequently, over 10,000 people from various countries were born missing limbs or deformed.<sup>29</sup> After three years of congressional hearings, Congress approved the 1962 Kefauver-Harris Amendments to the FDCA, which added an efficacy requirement.<sup>30</sup> The FDCA now required the FDA to review drug safety and efficacy data before granting drug approval.<sup>31</sup> Through FDA mandates, animal testing became the gold standard for testing drug safety and efficacy.<sup>32</sup>

#### **THE CURRENT DRUG DEVELOPMENT PARADIGM**

The Center for Drug Evaluation and Research (CDER) is the division of the U.S. Food and Drug Administration (FDA) charged with ensuring drugs are both safe and

---

<sup>26</sup> C. Ray Greek, *supra*, at 43.

<sup>27</sup> *Id.*

<sup>28</sup> Hajar, *supra*, at 42.

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

<sup>30</sup> Federal Food, Drug, and Cosmetic Act Amendments, Pub. L. No. 87-781, 76 Stat. 1552 (1962).

<sup>31</sup> Preziosi, *supra*, at 541.

<sup>32</sup> C. Ray Greek, *supra*, at 48.

effective for their intended use.<sup>33</sup> CDER will only approve a drug after a sponsor has demonstrated the drug is safe and effective.<sup>34</sup> In order to meet these criteria, drug sponsors follow a step-by-step testing process, providing evidence to the FDA throughout the process.<sup>35</sup>

Drug development starts with the discovery phase where developers 1) determine a target disease, 2) determine each component of the disease including symptoms, 3) identify the target organ, and biochemical pathways, 4) search for the target drug, and 5) isolate the compound.<sup>36</sup> The challenge is to select and advance a small number of compounds that contain properties that will eventually predict safety and efficacy in humans.<sup>37</sup>

After a compound is selected during the discovery phase, researchers begin preclinical testing which includes testing compounds in vitro, then in vivo in laboratory animals.<sup>38</sup> During preclinical stages of drug development, scientists conduct multiple types of studies. Pharmacological studies vary in nature depending upon the type of drug

---

<sup>33</sup>About the Center for Drug Evaluation and Research, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm> (last visited May 5, 2013).

<sup>34</sup> The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm> (last visited May 2, 2013).

<sup>35</sup> *Id.*

<sup>36</sup> Drug Development Process: Stages of Drug Development, [http://www.pacificbiolabs.com/drug\\_stages.asp](http://www.pacificbiolabs.com/drug_stages.asp) (last visited May 2, 2013).

<sup>37</sup> J. Fred Pritchard, *Making Better Drugs: Decision Gates in Non-Clinical Drug Development*, 2 *Nature Reviews Drug Discovery* 542, 542 (2003).

<sup>38</sup> Michael Dickson, *Key Factors in the Rising Cost of New Discovery and Development*, 3 *Nature Reviews Drug Discovery* 417, 418 (2004).



being developed.<sup>39</sup> Researchers also conduct secondary pharmacological studies to assess drug safety by testing on major organs and organ systems.<sup>40</sup> Pharmacokinetic studies evaluate absorption, distribution, metabolism and excretion of the drug.<sup>41</sup> Finally, toxicological testing is conducted in an attempt to predict adverse effects in humans that might be triggered by the drug.<sup>42</sup>

If scientists decide the preclinical data indicates the drug is reasonably safe for initial use in humans, the developer submits an investigational new drug application (IND) to the FDA.<sup>43</sup> The IND includes a description of the compound's pharmacological profile, results of short-term toxicity testing in at least two animal species, manufacturing information, and proposed clinical protocols and investigator information.<sup>44</sup> If the FDA is satisfied that the drug is reasonably safe for human use, and a local institutional review board approves the clinical trial protocols, scientists begin human clinical testing.<sup>45</sup> When the compound enters human clinical trials, scientists conduct additional concurrent

---

<sup>39</sup> Preziosi, *supra*, at 521.

<sup>40</sup> Preziosi, *supra*, at 522.

<sup>41</sup> *Id.*

<sup>42</sup> *Id.*

<sup>43</sup>Investigational New Drug Application, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm> (last visited May 2, 2013).

<sup>44</sup> *Id.*

<sup>45</sup> The FDA's Drug Review Process : Ensuring Drugs are Safe and Effective, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> (last visited May 2, 2013).

toxicology studies on animals for the duration of clinical trials.<sup>46</sup> In addition, carcinogenicity studies continue for approximately two years, to examine whether the drug is carcinogenic if given for the lifetime of the animal.<sup>47</sup>

Human clinical trials are broken up into three phases.<sup>48</sup> Sponsors conduct Phase 1 clinical trials in twenty to eighty healthy volunteers<sup>49</sup> to determine safe dosing and toxicity.<sup>50</sup> If Phase 1 trials do not reveal unacceptable toxicity, the drug candidate moves to Phase 2 studies.<sup>51</sup> Sponsors conduct Phase 2 clinical trials in a few dozen to 300 patient volunteers who have the medical condition to determine whether the drug works in people who have the condition the drug is intended to treat.<sup>52</sup> The drug moves to Phase 3 trials if Phase 2 trials show evidence of efficacy.<sup>53</sup> Phase 3 clinical trials are conducted for safety and efficacy in groups of several hundred to 3000 patient volunteers.

After completing human clinical tests, the sponsor files a new drug application (NDA), seeking formal FDA approval of the drug for sale and marketing in the United

---

<sup>46</sup> Pritchard, *supra*, at 551.

<sup>47</sup> *Id.*

<sup>48</sup> The FDA's Drug Review Process : Ensuring Drugs are Safe and Effective, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> (last visited May 2, 2013).

<sup>49</sup> *Id.*

<sup>50</sup> Dickson, *supra*, at 418.

<sup>51</sup> The FDA's Drug Review Process : Ensuring Drugs are Safe and Effective, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> (last visited May 2, 2013).

<sup>52</sup> *Id.*

<sup>53</sup> *Id.*

States.<sup>54</sup> The NDA includes data gathered during animal and human testing, analyses of the data, information on how the drug behaves in the body from clinical studies, and manufacturing information.<sup>55</sup> Within sixty days, the FDA decides whether to file the NDA so it can be reviewed, or refuse to file the NDA.<sup>56</sup> If after NDA review, the FDA decides the known benefits of the drug outweigh the known risks, the FDA approves the drug and the drug can be marketed in the United States.<sup>57</sup>

### **DRUG DEVELOPMENT PROBLEMS RELATED TO ANIMAL MODELS**

Scientists test their ideas by comparing predictions based on theory to actual events in nature or the laboratory.<sup>58</sup> If a method gets the right answer often enough, it can be said to be predictive. In contrast, if a method does not get the right answer often enough, it cannot be said to be predictive.

The purpose of preclinical testing is to predict human outcomes.<sup>59</sup> Scientists gather animal data and extrapolate to form hypotheses regarding what is likely to occur

---

<sup>54</sup>New Drug Application, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm> (last visited May 2, 2013).

<sup>55</sup> The FDA's Drug Review Process : Ensuring Drugs are Safe and Effective, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> (last visited May 2, 2013).

<sup>56</sup> *Id.*

<sup>57</sup> *Id.*

<sup>58</sup> Daniel Sarewitz, et al., *Prediction in Science and Policy*, 21 TECHNOLOGY IN SOCIETY 121, 123 (1999).

<sup>59</sup> Ray Greek, *supra*, at 127.

when humans receive the drug<sup>60</sup> The rationale behind extrapolating results from animals to humans is based on homology and evolutionary similarity between morphological structures and physiological processes between animals and humans.<sup>61</sup> However, among other things, species differ in gene presence, gene mutation, number of alleles, gene expression, gene networks, and convergent evolution.<sup>62</sup>

Inter-species differences in pharmacodynamics and pharmacokinetics result in extrapolation issues.<sup>63</sup> According to the FDA, the inability to assess and predict product safety leads to failures during clinical development.<sup>64</sup> To further highlight the extrapolation disparity, the FDA uses the statistic that ninety-two percent of drugs that pass preclinical animal testing later fail during human clinical trials.<sup>65</sup> In studying adverse reactions, one study found only forty-six percent of visible human adverse reactions occurred in animals, making the predictive likelihood of adverse reactions akin to the results of a coin toss.<sup>66</sup>

---

<sup>60</sup> Niall Shanks, et al., *Are Animal Models Predictive for Humans?* 4 Philosophy, Ethics, and Humanities in Medicine (2009).

<sup>61</sup> Jann Hau, et al., *Animal Models*, 2 HANDBOOK OF LABORATORY ANIMAL SCIENCE 6 (Hau, et al. 2003).

<sup>62</sup> Ray Greek, *supra*, at 126.

<sup>63</sup> Knight, *supra*, at 92.

<sup>64</sup> U.S. Food and Drug Admin., *supra*, at 17.

<sup>65</sup> *Id.* at 8.

<sup>66</sup> C. Ray Greek, *supra*, at 48.

Furthermore, a 2012 study looked at whether post-marketing serious adverse reactions to small molecule drugs could have been detected from animal data.<sup>67</sup> Animal data identified only nineteen percent of human adverse reactions, leading researchers to conclude animal data is not relevant to predict serious adverse human reactions to new small molecule drugs.<sup>68</sup>

Extrapolating data misleads research because animal experiments may fail to predict lethal side effects and prevent or delay safe and effective medications from gaining FDA approval.<sup>69</sup> Animal testing that wrongly makes a candidate drug appear safe for humans is called a false negative.<sup>70</sup> As a result of false negatives, adverse drug reactions are the fourth leading cause of death in the United States, accounting for approximately 100,000 deaths per year.<sup>71</sup> There is a long list of drugs that were given to humans after the drug appeared safe in animal studies that resulted in severe adverse reactions and death in many people.<sup>72</sup> Scientists did not learn the drugs were dangerous to humans through animal testing; scientists learned the drugs were dangerous to humans through epidemiology, clinical observation, and autopsy.<sup>73</sup>

---

<sup>67</sup> Peter J.K. van Meer, *The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events is Limited*, 64 REGULATORY TOXICOLOGY AND PHARMACOLOGY 345, 346 (2012).

<sup>68</sup> *Id.*

<sup>69</sup> C. Ray Greek, *supra*, at 60.

<sup>70</sup> *Id.*

<sup>71</sup> *Id.*

<sup>72</sup> *Id.* at 61-66.

<sup>73</sup> *Id.* at 66.

In contrast, drugs that are safe and effective in humans, but cause severe adverse reactions in animals that keep the candidate drug from development are called false positives.<sup>74</sup> To say animal models keep good drugs from the market is difficult to prove because the compound is not generally developed after faring negatively in animals.<sup>75</sup> However, occasionally drugs are approved for use in other countries that are safe and effective in humans but are delayed in the United States because the FDA requires either abbreviated animal testing or the entire protocol.<sup>76</sup>

Scientists can judge the appropriateness of extrapolating data from models by their capacity to explain and predict the observed effects in the target species.<sup>77</sup> Systematic reviews of research data allow scientists to compare animal and human data to confirm or falsify the animal-based hypothesis.<sup>78</sup> A 2007 comprehensive survey of systematic reviews found that eighteen of twenty systematic reviews published in peer-reviewed scientific journals suggest animals are insufficiently predictive of human clinical or toxicological outcomes.<sup>79</sup> One explanation for the systematic review findings

---

<sup>74</sup> *Id.* at 60.

<sup>75</sup> *Id.* at 69.

<sup>76</sup> *Id.* at 71.

<sup>77</sup> Jann Hau, *supra*, at 8.

<sup>78</sup> Knight, *supra*, at 42.

<sup>79</sup> Knight, *supra*, at 183.

is animal models were never scientifically validated.<sup>80</sup> Therefore, animal models are not held to the validation standards emerging testing methods are held to.<sup>81</sup>

## **PART II**

### **CURRENT LAW AND POLICY GOVERNING DRUG DEVELOPMENT**

#### **Food and Drug Administration**

The FDA is partially tasked with ensuring human drugs are safe and effective<sup>82</sup>. By statute, the FDA has discretion whether to require animal data<sup>83</sup>. While the FDA says it will accept non-animal methods provided they are equal to or better than the animal model,<sup>84</sup> FDA regulations require preclinical animal data to examine: pharmacokinetics and biological disposition of the drug, pharmacological mechanisms including absorption, distribution, metabolism, and excretion, and a summary of toxicological effects<sup>85</sup>. Further, the FDA's website explanation of drug development states the sponsor must show the FDA results of preclinical testing in laboratory animals and what they propose to do for human testing.<sup>86</sup>

---

<sup>80</sup> Alison Abbott, *Animal Testing: More than a Cosmetic Change*, 438 NATURE 144, (2005).

<sup>81</sup> *Id.*

<sup>82</sup> 21 U.S.C.A § 393 (West 2001).

<sup>83</sup> 21 U.S.C.A § 355 (West 2010).

<sup>84</sup> Dorsey, *supra*, at 3.

<sup>85</sup> Investigational New Drug Application, 21 C.F.R. § 312.23 (2012).

<sup>86</sup> The FDA's Drug Review Process : Ensuring Drugs are Safe and Effective, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm> (last visited May 2, 2013).

In addition to promulgating regulations, the FDA issues guidance documents to communicate expectations to drug developers.<sup>87</sup> Although non-binding, FDA guidance documents often have a binding effect because failure to comply may result in disapproval of an application.<sup>88</sup> The FDA issues more guidance documents than regulations,<sup>89</sup> but has not issued any guidance that recommends the use of non-animal testing models.<sup>90</sup> In a 2010 citizen petition denial, the FDA expressed intention to issue a clear guidance to industry and FDA staff on use of adequate and validated non-animal testing methods.<sup>91</sup> This guidance has not been issued and is not included in the 2013 draft guidance agenda.<sup>92</sup>

### **Interagency Coordinating Committee on the Validation of Alternative Methods**

In 2000, Congress established the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).<sup>93</sup> Part of ICCVAM's purpose is to

---

<sup>87</sup> Jessica Mantel, *Procedural Safeguards for Agency Guidance: A Source of Legitimacy for the Administrative State*, 61 Admin. L. Rev. 343, 345 (2009).

<sup>88</sup> *Id.*

<sup>89</sup> *Id.*

<sup>90</sup> Guidances, <http://www.fda.gov/regulatoryinformation/guidances/> (last visited May 1, 2013).

<sup>91</sup> Dorsey, *supra*, at 2.

<sup>92</sup> Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2013, <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/webcontent/ucm314767.pdf> (last visited May 1, 2013).

<sup>93</sup> ICCVAM Authorization Act of 2000, Pub. L. No. 106-545, 114 Stat. 2721 (2000).



increase the efficiency and effectiveness of federal agency test method review.<sup>94</sup>

However, the ICCVAM process is recognized as an obstacle to test validation because the process is slow and expensive.<sup>95</sup> Although the FDA is an agency member of ICCVAM, the FDA retains final authority regarding whether to accept ICCVAM's recommendations.<sup>96</sup>

### **International Cooperation on Alternative Test Methods**

The International Cooperation on Alternative Test Methods (ICATM) is collaboration between the United States, Europe, Japan, and Canada.<sup>97</sup> ICATM represents an effort to promote international cooperation to accelerate regulatory acceptance of new testing methods.<sup>98</sup>

### **International Conference on Harmonization**

The International Conference on Harmonization (ICH) launched in 1990 to improve efficiency and harmonize research guidelines in the United States, Japan, and Europe.<sup>99</sup> The ICH issues guidelines on quality, safety, and efficacy.<sup>100</sup> Multiple ICH

---

<sup>94</sup> *Id.*

<sup>95</sup> Gilbert Gaul, *In U.S., Few Alternatives To Testing On Animals*, WA Post, April 12, 2008.

<sup>96</sup> 114 Stat. 2721 (2000).

<sup>97</sup> International Cooperation on Alternative Test Methods, <http://iccvam.niehs.nih.gov/about/icatm.htm> (last visited May 2, 2013).

<sup>98</sup> *Id.*

<sup>99</sup> ICH Harmonisation for Better Health, <http://www.ich.org/about/vision.html> (last visited May 2, 2013).

<sup>100</sup> ICH Guidelines, <http://www.ich.org/products/guidelines.html> (last visited May 2, 2013).

guidelines recommend testing a drug in animals to determine whether the drug is safe for human clinical trials.<sup>101</sup>

### **PART III**

#### **EMERGING DRUG DEVELOPMENT TESTING METHODS**

Although animal models are still regulated as a central part of the drug development process, the FDA has approved certain non-animal models for preclinical use. In addition, emerging science and technologies that aim to provide improved predictions of human drug safety with the objective of replacing the current preclinical paradigm are in progress.<sup>102</sup> Below are examples of emerging testing methods.

##### **Human Organ-on-a-Chip System**

The Wyss Institute for Biologically Inspired Engineering at Harvard successfully created a lung-on-a-chip and gut-on-a-chip, which mimic the mechanical and biochemical behaviors of corresponding human organs.<sup>103</sup> In 2012, the Wyss Institute received funding to create ten human organs-on-a-chip, which will link together to mimic whole body human physiology.<sup>104</sup> The human-on-a-chip seeks to replace current

---

<sup>101</sup> Safety Guidelines, <http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html> (last visited May 2, 2013).

<sup>102</sup> C. Thomas Caskey, *The Drug Development Crisis: Efficiency and Safety*, 58 *Annu Rev Med.* 1, 5 (2007).

<sup>103</sup> Wyss Institute, <http://wyss.harvard.edu/viewpage/240/lungonachip> (last visited May 2, 2013).

<sup>104</sup> Wyss Institute, <http://wyss.harvard.edu/viewpressrelease/91/wyss-institute-to-receive-up-to-37-million-from-darpa-to-integrate-multiple-organonchip-systems-to-mimic-the-whole-human-body> (last visited May 2, 2013).

preclinical animal models by offering a system that rapidly assesses responses to new drug candidates, providing critical information on their safety and efficacy.<sup>105</sup>

### **Human Pluripotent Stem Cell**

Pluripotent stem cells give rise to almost all cell types of the body making them beneficial for drug development research.<sup>106</sup> Research using pluripotent stem cells may replace animal models for evaluating drug safety because candidate drugs may be tested on cells developed from human pluripotent stem cells.<sup>107</sup> Researchers at The Center for Regenerative Medicine at The Scripps Research Institute are building a bank of ethnically diverse induced pluripotent stem cells to screen for toxicity of drugs that is correlated with ethnic background.<sup>108</sup> The goal of this research is to allow drugs to be tested on groups of people who are least likely to have adverse side effects.<sup>109</sup>

Researchers at the Laboratory for Stem Cells and Tissue Engineering at Columbia University are working to develop a drug development model using pluripotent stem cells to make personalized models of organs on which to test new drugs.<sup>110</sup> These personalized

---

<sup>105</sup> Wyss Institute, <http://wyss.harvard.edu/viewpage/240/lungonachip> (last visited May 2, 2013).

<sup>106</sup> National Institutes of Health, <http://stemcells.nih.gov/news/newsArchives/pages/stemfactsheet.aspx> (last visited May 3, 2013).

<sup>107</sup> *Id.*

<sup>108</sup> The Center for Regenerative Medicine, <http://www.scripps.edu/loring/research.html> (last visited May 2, 2013).

<sup>109</sup> *Id.*

<sup>110</sup> Nina Tandon: Could Tissue Engineering Mean Personalized Medicine?, [http://www.ted.com/talks/nina\\_tandon\\_could\\_tissue\\_engineering\\_mean\\_personalized\\_medicine.html](http://www.ted.com/talks/nina_tandon_could_tissue_engineering_mean_personalized_medicine.html) (last visited May 2, 2013).

models seek to improve drug development by replacing traditional animal testing methods with those that mimic a particular person's response.

### **Phase 0/Exploratory IND**

Phase 0 trials are first-in-human clinical trials that involve limited human exposure, and have no therapeutic intent.<sup>111</sup> Phase 0 trials aim to increase the chance of success of the drug in development<sup>112</sup> by providing human pharmacokinetic and pharmacodynamics data early in the drug development process.<sup>113</sup> The goal is to select the most promising candidate from a set of analogues, and evaluate human bio distribution, binding, and target effects.<sup>114</sup> Phase 0 trials encourage rational drug development, as drugs unlikely to have a therapeutic effect can be de-prioritized early in the process allowing for development of more promising and potentially efficacious agents.<sup>115</sup> Only drugs showing sufficient promise in Phase 0 trials should progress to safety and tolerability evaluation in traditional Phase 1 trials.<sup>116</sup>

### **Microdosing**

Microdosing is a process where researchers administer small doses of a drug to human volunteers, then use positron emission tomography and accelerator mass

---

<sup>111</sup> Kummar, *supra*, at 288.

<sup>112</sup> *Id.*

<sup>113</sup> *Id.* at 289.

<sup>114</sup> *Id.*

<sup>115</sup> *Id.* at 288.

<sup>116</sup> *Id.*

spectrometry to assess pharmacokinetic data.<sup>117</sup> Current microdosing involves animal models to determine the starting dose.<sup>118</sup> Animal models can be eliminated from microdosing by starting the dosage at 1ng because the usual starting dose for drugs is between 100ng and 100µg, and 1 ng is lower than the most toxic substance currently known.<sup>119</sup> Although microdosing is currently used only to test pharmacokinetic data, microdosing could be used for evaluating other properties such as toxicity by increasing the dose incrementally.<sup>120</sup> This would allow researchers to determine toxicity early in the drug development process without distraction from animal data.<sup>121</sup>

### **FDA EFFORT TO VALIDATE MORE RELIABLE TESTING METHODS**

The FDA recognizes it should take an active role in developing new drug testing methods and validation of these methods.<sup>122</sup> The FDA is involved in the below projects which aim to develop more reliable test methods:

#### **Critical Path Initiative**

The FDA began its Critical Path Initiative (CPI) to drive innovation in the scientific processes through which medical products are developed, evaluated, and

---

<sup>117</sup> C. Ray Greek, *supra*, at 131.

<sup>118</sup> *Id.*

<sup>119</sup> *Id.*

<sup>120</sup> *Id.* at 132.

<sup>121</sup> *Id.*

<sup>122</sup> Prater, *supra*, at slide 14.

manufactured.<sup>123</sup> CPI was launched in 2004 with a report that explained the need to reduce time and resources expended on candidate products that are unlikely to succeed, and the need to make new tools necessary to distinguish earlier in the process those candidates that hold promise from those that do not.<sup>124</sup> As part of the CPI, the FDA issued an exploratory IND guidance, which aimed to expedite the identification and development of promising candidate drugs.<sup>125</sup>

### **Advancing Regulatory Science**

Regulatory science is the application of science to the development and utilization of new tools, standards, and approaches for the assessment of product efficacy, safety, and quality.<sup>126</sup> In order to modernize testing and enhance product safety, the FDA recognizes the need to develop better models of human adverse response that are not based on animals.<sup>127</sup> In 2010, the FDA and NIH formed a joint leadership council that issues awards to advance regulatory science.<sup>128</sup>

---

<sup>123</sup>FDA's Critical Path Initiative, <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm> (last visited May 3, 2013).

<sup>124</sup>U.S. Food and Drug Admin., *supra*, at i.

<sup>125</sup> Kummar, *supra*, at 288.

<sup>126</sup> Prater, *supra*, at slide 3.

<sup>127</sup> Suzanne Fitzpatrick, U.S. Food and Drug Admin. Powerpoint Presentation, *FDA/NIH/DARPA Microphysiological Systems Program and Qualification of Drug Development Tools*, slide 5 (2012), [www.lorenzcenter.nl/lc/web/2012/510/.../Fitzpatrick.pptx](http://www.lorenzcenter.nl/lc/web/2012/510/.../Fitzpatrick.pptx).

<sup>128</sup>*Id.* at slide 6.

## **Microphysiological Systems Program**

The DARPA-FDA-NIH Microphysiological Systems Program formed in 2011 to support development of human microsystems, or organ chips, to screen for safe and effective drugs. Microphysiological systems are meant to replace the current preclinical paradigm.<sup>129</sup> This program awarded research contracts to The Wyss Institute at Harvard and Massachusetts Institute of Technology to develop microphysiological systems.<sup>130</sup>

Integrated Microphysiological Systems for Drug Efficacy and Toxicity Testing is another FDA program formed to advance microphysiological systems.<sup>131</sup> This program focuses on the development of physiologically and pathologically accurate human models of any organ system using tissue-engineering platforms that either already exist or are being developed simultaneously through the DARPA-FDA-NIH program.<sup>132</sup>

## **Stem/Progenitor Cell-Derived Human Micro-Organs and Micro-Tissues**

The focus of this program is development of in vitro multi-cellular models of human physiology that provide advancements over current human stem-cell and progenitor-derived cell type selectivity approaches through improvements in differentiation efficiencies, cell-type diversity, genetic complexity, and utilization of 3D culturing approaches to enhance cellular microenvironments.<sup>133</sup>

---

<sup>129</sup> *Id.* at slide 8.

<sup>130</sup> *Id.* at slide 7.

<sup>131</sup> Prater, *supra*, at slide 15.

<sup>132</sup> *Id.*

<sup>133</sup> *Id.* at slide 17.

## **Drug Development Tools Qualification Program (DDT)**

DDT is a FDA program that provides a mechanism for formal review by CDER to qualify new tools that would benefit drug development.<sup>134</sup> DDT is an example of a new validation strategy involving fit-for-purpose qualification, but is a complex process that requires significant time and resources.<sup>135</sup>

The qualification of a drug development tool begins with a meeting of CDER personnel and the biomarker sponsors who consult regarding the information needed to support the application.<sup>136</sup> Once the application is submitted, CDER and other FDA scientists complete a multi-disciplinary formal review of the submission.<sup>137</sup> If the tool is qualified, the decision is publicly communicated through a FDA guidance document and drug sponsors can submit data obtained by the validated DDT model.<sup>138</sup>

## **RECOMMENDATIONS FOR FURTHER FDA ACTION**

The FDA will play a fundamental role in making the goal of moving drug development into the 21<sup>st</sup> century a reality because the FDA regulates and oversees drug development. The need for updated FDA validation tools, clear regulations and guidance documents stems from the fact that scientific options exist today, and will continue to emerge, that did not exist when regulations that mandate animal testing were enacted.<sup>139</sup>

---

<sup>134</sup> Fitzpatrick, *supra*, at slide 18.

<sup>135</sup> Prater, *supra*, at slide 21.

<sup>136</sup> Fitzpatrick, *supra*, at slide 27.

<sup>137</sup> *Id.*

<sup>138</sup> *Id.*

<sup>139</sup>C. Ray Greek, *supra*, at 131.



## Validation of New Methods

Despite efforts to develop better testing methods, most of the tools used for toxicology and human safety testing are decades old.<sup>140</sup> This is a problem because researchers are using last century's tools to evaluate this century's scientific advances.<sup>141</sup> Further, animal models for testing drug safety and efficacy are presumed valid, while non-animal methods must be validated.<sup>142</sup> Consequently, most animal model test methods have never been validated; while current formal approaches to validation of non-animal methods involve lengthy processes that require validating the non-animal data against the animal data.<sup>143</sup>

The FDA acknowledges a clear need to determine the relevance of new testing methods to what occurs in humans, rather than what occurs in test animals.<sup>144</sup> This justifies abandoning animal models as the gold standard for new preclinical method to be measured against.<sup>145</sup> Applying the animal model one-size fits all approach to validation is not conducive to incorporating emerging science into regulatory decision-making

---

<sup>140</sup> U.S Food and Drug Admin., *supra*, at 16.

<sup>141</sup> Janet Woodcock & Raymond Woosley, *The FDA Critical Path Initiative and Its Influence on New Drug Development*, 59 Annual Review of Medicine 1, 1 (2008).

<sup>142</sup> Prater, *supra*, at slide 20.

<sup>143</sup> Prater, *supra*, at slide 20.

<sup>144</sup> Fitzpatrick, *supra*, at slide 17.

<sup>145</sup> *Id.*

framework because the purpose of each test in the regulatory paradigm must be taken into consideration.<sup>146</sup>

### **FDA Regulation**

FDA regulations require animal testing as part of the current drug development paradigm.<sup>147</sup> The FDA stated the IND regulation allows flexibility to accept non-animal models when appropriate.<sup>148</sup> Further, the FDA claims information from models validated through DDT is sufficient without other data.<sup>149</sup> However, FDA regulations mandate animal data, making this alleged flexibility seem non-existent.

Researchers who use validated non-animal methods still complete the traditional animal testing in order to comply with FDA regulations and fear of disapproval of their NDA.<sup>150</sup> This suggests current FDA regulations stall the drug development process by dis-incentivizing researchers from using newer validated methods because the animal data is required and accepted.<sup>151</sup> Current regulations that mandate animal data perpetuate the notion that animal models are reliable for use in human drug development, despite FDA efforts to move away from animal models. To correct the regulation language, the

---

<sup>146</sup> Prater, *supra*, at 4.

<sup>147</sup> 21 C.F.R. § 312.23(a)(5)(ii) (West 2012), 21 C.F.R. § 312.23(a)(5)(iii) (West 2012), 21 C.F.R. 312.23(8)(a)(i) (West 2012), 21 C.F.R. § 312.23(8)(a)(ii) (West 2012), 21. C.F.R. § 312.23 (10)(i) (West 2012).

<sup>148</sup> Dorsey, *supra*, at 2.

<sup>149</sup> Fitzpatrick, *supra*, at slide 28.

<sup>150</sup> Celia Henry Arnaud, In the Search for New Drugs, Diverging Roads For Microdosing, 91 CHEMICAL AND ENGINEERING NEWS 9 (2013).

<sup>151</sup> *Id.*

FDA would simply need to replace the language calling for animal testing with language calling for data obtained from a scientifically validated testing method.

### **Guidance**

The FDA has issued twenty-eight guidance documents regarding animal testing. In contrast to FDA efforts to develop human-based methods, none of the guidance documents recommend the use of non-animal methods. The issued guidance documents, including those accepted through DDT, either state a specific non-animal model can be used, or seek to improve upon existing animal models. As part of the ICH, the FDA tends to accept ICH guidelines. Contrary to the alleged flexibility of the FDA IND regulation, the ICH has issued fifteen guidance documents for animal testing and none recommending non-animal models.

The FDA outlined the importance of issuing a clear guidance to industry and FDA staff that recommends researchers use non-animal models when validated, adequate, and feasible.<sup>152</sup> To date, this guidance has not been issued and is not on the 2013 guidance agenda, suggesting it is not in the pipeline. If the FDA sincerely wants to move from animal testing as the gold standard for preclinical studies, the FDA should issue a general guidance recommending the use of non-animal testing methods where the method is scientifically validated, adequate and feasible. This would further communicate the FDA's commitment to propel research forward because the recommendation is likely to keep researchers from interpreting the animal data as necessary.

The FDA should continue to issue specific guidance documents for each new validated method that becomes available. However, the guidance document should

---

<sup>152</sup> Dorsey, *supra*, at 2.

recommend the use of the validated method over the animal model, not simply communicate the approval of the new method, given that the animal model was not validated.

## **Conclusion**

Human drug development costs consistently increase while drug development success rates remain low, and many uncertainties exist, including failures in predicting toxicity, safety, and efficacy despite extensive animal testing.<sup>153</sup> While collaboration of all interested parties is important, change must start with the FDA because the FDA is the ultimate decision-maker in the drug development process. The FDA acknowledges the need to move away from animal models, but 21<sup>st</sup> Century emerging methods are tested against animal models, FDA regulations require animal data, and guidance recommending new models over animal data is non-existent.

The FDA and industry are working to develop safer and more effective models, but acceptance of these models is slow, and the solution to replacing animal models is likely a combination of in vitro, in silico, and microdosing. Once regulations and guidance documents are updated, interested parties may be more inclined to invest research and development funds into developing testing methods that are human-based, resulting in safer and more effective drugs. Further, drug sponsors may be more confident in their decision to use emerging methods because expectations will be clearer.

All emerging testing methods share a similar goal – to replace traditional animal testing methods that are not sufficiently predictive of human response, with safer and more effective human-based testing methods. With action and collaboration among all

---

<sup>153</sup> Fitzpatrick, *supra*, at slide 2.

interested parties, drug development will move into the 21<sup>st</sup> Century and drug testing will produce safer and more effective drugs.