

## QUESTIONS AND ANSWERS ABOUT U.S. ANIMAL TESTING OF PHARMACEUTICALS

### **What substances are considered to be pharmaceuticals?**

The term “pharmaceuticals” refers to medicinal products such as generic, over-the-counter, and prescription drugs.

### **Who regulates pharmaceuticals in the U.S. and under what laws?**

Responsibility for the regulation of human pharmaceuticals lies with the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA), while the FDA Center for Veterinary Medicine is charged with oversight of veterinary pharmaceuticals. FDA’s statutory authority is rooted in the Federal Food, Drug and Cosmetic Act.<sup>1</sup>

### **What animal tests are carried out on pharmaceuticals?**

“Preclinical” testing in animals is a longstanding requirement for all human and veterinary medicinal products. U.S. testing requirements for human<sup>2-3</sup> and veterinary pharmaceuticals<sup>4</sup> have largely been harmonized with those of other major markets (i.e., the Europe and Japan) under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the International Co-operation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH), respectively. Both entities publish guidelines specifying trilaterally agreed-upon methods for assessing safety, effectiveness and quality of pharmaceutical products. ICH guidelines call for a wide array of pre-clinical (animal) studies, followed by several phases of human clinical studies, before a new drug is deemed safe for marketing.<sup>5</sup> VICH guidelines likewise prescribe a significant battery of conventional toxicology studies, but also provide for evaluations of target animal and environmental safety, since a major use of veterinary drugs is in farm animals.<sup>6</sup>

Animal tests common to both ICH and VICH schemes include the following:<sup>7</sup>

- ▶▶ Absorption, distribution, metabolism and elimination studies in rodents and/or other species
- ▶▶ 3 month repeated-dose general toxicity studies in rodents, dogs, and sometimes primates
- ▶▶ 12-24 month repeated-dose general toxicity studies in rodents, dogs, and sometimes primates
- ▶▶ Lifetime (18-24 month) cancer studies in rats and mice (ICH allows for the substitution of the 18-month mouse study with a shorter test in transgenic mice)
- ▶▶ Genetic toxicity studies of at least 2 varieties

<sup>1</sup> <http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm>

<sup>2</sup> <http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200321>

<sup>3</sup> <http://www.fda.gov/cder/guidance/index.htm>

<sup>4</sup> <http://www.fda.gov/cvm/Guidance/published.htm>

<sup>5</sup> <http://www.ich.org/cache/html/250-272-1.html>

<sup>6</sup> <http://www.vichsec.org/en/guidelines2.htm>

<sup>7</sup> [http://www.hsus.org/animals\\_in\\_research/animal\\_testing/toxicity\\_testing\\_overview.html](http://www.hsus.org/animals_in_research/animal_testing/toxicity_testing_overview.html)

- ▶▶ Reproductive toxicity study in at least 2 generations of rodents (ICH allows for this to be broken into separate adult fertility and post-natal segments in the context of a 1-generation study design)
- ▶▶ Pre-natal developmental toxicity in rodents and rabbits
- ▶▶ Immunotoxicity in rodents

In addition to the “core battery” above, national regulators and quality-control bodies known as Pharmacopoeias impose additional testing requirements on a case-by-case basis. For example, medicated skin creams are often tested in the presence of UV light to be sure they do not foster sunlight-induced “photo”-toxicity, while drugs administered intravenously must be specially tested to ensure that they are not contaminated with fever-causing “pyrogens.”

### **How many animals may be used in pharmaceutical testing?**

Some of the tests above consume hundreds or thousands of animals per study, and such testing is typically required for both the active medicinal ingredient(s) as well as each formulated pharmaceutical product (and sometimes for each new batch of a product). Unfortunately, laboratory-bred rats and mice and non-mammalian species are not covered under the U.S. Animal Welfare Act standards for animals used in experiments, and as such, statistics concerning their use are not recorded or made publicly available.<sup>8</sup> However, according to European statistics for 2005, the “production and quality control of products for human medicine and dentistry and for veterinary medicine” consumed approximately 15.3% of all animals used for all experimental purposes that year.<sup>9</sup>

### **Are animal tests accurate predictors of pharmaceutical risks to people?**

Not necessarily, as catastrophic drug failure—such as the recent TGN 1412 incident in the United Kingdom—have revealed.<sup>10</sup> In fact, the World Health Organization reports that in some countries, adverse drug reactions are responsible for upwards of 10% of all hospital admissions.<sup>11</sup> And according to the US FDA, “a new medicinal compound entering Phase 1 testing [in humans], often representing the culmination of upwards of a decade of preclinical screening and evaluation, is estimated to have only an 8 percent chance of reaching the market” because animal studies so often “fail to predict the specific safety problem that ultimately halts development.”<sup>12</sup>

### **What are some practical alternatives to animal testing?**

A number of in vitro and other alternative methods germane to pharmaceutical safety and quality assessment have been endorsed as scientifically valid by the European Centre for the Validation of Alternative Methods (ECVAM) and its counterparts worldwide for endpoints including skin and eye irritation, sunlight-induced “photo”-toxicity, genetic toxicity, fever-inducing “pyrogenicity,” toxicity to the developing embryo, and toxicity to the blood.<sup>13</sup>

In addition, an expert group comprised of 15 international pharmaceutical companies and contract testing facilities, together with the UK National Centre for the 3Rs, has recently concluded that “the information obtained from conventional acute toxicity studies is of little or no value in the pharmaceutical development process,” and has recommended that single-dose acute systemic toxicity studies be dropped from ICH and related national guidelines for human pharmaceuticals.<sup>14</sup>

<sup>8</sup> <http://www.nal.usda.gov/awic/legislat/awa.htm>

<sup>9</sup> [http://ec.europa.eu/environment/chemicals/lab\\_animals/pdf/staff\\_work\\_doc\\_sec1455.pdf](http://ec.europa.eu/environment/chemicals/lab_animals/pdf/staff_work_doc_sec1455.pdf)

<sup>10</sup> [http://www.hsus.org/animals\\_in\\_research/animal\\_testing/limitations-of-animal-methods.html](http://www.hsus.org/animals_in_research/animal_testing/limitations-of-animal-methods.html)

<sup>11</sup> <http://www.who.int/mediacentre/factsheets/fs293/en/index.html>

<sup>12</sup> <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>

<sup>13</sup> [http://www.hsus.org/animals\\_in\\_research/animal\\_testing/alternatives.html](http://www.hsus.org/animals_in_research/animal_testing/alternatives.html)

<sup>14</sup> <http://www.nc3rs.org.uk/news.asp?id=512>

Another innovative technique with the potential to not only reduce animal use, but also to obtain much more relevant and meaningful scientific information, is called microdosing.<sup>15</sup> By administering a very small dose of a candidate drug to healthy human volunteers, important human-specific information can be obtained, without the uncertainties associated with extrapolating test results from one species to another.

### **What is the Humane Society doing to help animals used in pharmaceutical testing?**

The Humane Society of the United States and Humane Society Legislative Fund are actively working to end animal testing—permanently. We are working to promote greater reliance on available non-animal testing methods, and are actively supporting the vision of “twenty-first century toxicology” articulated by the U.S. National Research Council, which would see animal tests that are decades old, costly, slow and of dubious relevance to people replaced by ultra-modern, efficient and human-relevant non-animal methods.<sup>16</sup> We are calling for a “big biology” project to meet this challenge, akin to the Human Genome Project of the 1990s, and are forging an international, multi-stakeholder consortium to help make this landmark vision a reality as quickly as possible.



*The Humane Society of the United States is the nation’s largest animal protection organization—backed by more than 10.5 million Americans. For over 50 years, HSUS has worked to reduce suffering and to create meaningful change for animals in laboratories through public education, scientific outreach, legislative advocacy, and strategic partnerships.*

*Online at [HSUS.org/research](http://HSUS.org/research)*

*The Humane Society Legislative Fund is a social welfare organization incorporated as a separate lobbying affiliate of the HSUS. HSLF works to pass animal protection laws at the state and federal level, to educate the public about animal protection issues, and to support humane candidates for office.*

*Online at [HSLF.org](http://HSLF.org)*

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<sup>15</sup> <http://www.emea.europa.eu/pdfs/human/swp/259902en.pdf>

<sup>16</sup> [http://www.hsus.org/animals\\_in\\_research/animal\\_testing/hsus-projects/human\\_toxicology\\_initiative.html](http://www.hsus.org/animals_in_research/animal_testing/hsus-projects/human_toxicology_initiative.html)