

## **Pharmaceutical Companies Acknowledge the Failure of Animal Models in their Drug Development Process, and Write about this Openly in the Scientific Literature**

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- \* The success rate for new drugs in all areas of development is dismal. Out of 5,000-10,000 chemicals that enter the drug development pipeline only one will enter the market. (European Commission 2008; [1] Hughes et al. 2011 [2]) Moreover, the major cost of drug development occurs during the clinical trials and the attrition rate during this stage is equally dreadful. (Unknown 2002 [3]; Shaffer 2012 [4]; Paul et al. 2010 [5]; Schachter 2007 [6])
- \* Drugs entering Phase I trials have approximately a 9% chance of coming to market. (FDA 2004 [7]; Sarkar 2009 [8]; Editorial 2007 [9]; Paul et al. 2010 [10])
- \* Of the drugs that advance to Phase III, less than 50% are marketed. (Arrowsmith 2011 [11])
- \* The failure rate for oncology drugs is even higher. (Editorial 2011 [12]; Caponigro & Sellers 2011 [13]; Arrowsmith 2011 [14]; Begley & Ellis 2012 [15])
- \* Only 5% of cancer drugs that have an Investigational New Drug Application (IND) eventually go to market. (Kummar et al. 2007[16])
- \* Lack of safety or efficacy accounts for approximately 90% of drug failures during clinical trials. (Kola & Landis 2004 [17]; Arrowsmith 2011 [18]).
- \* Both safety and efficacy determinations rely on animal models. To complicate matters further, the pipeline in Pharma is drying up and fewer drugs, especially new chemical entities (NCEs) are being marketed. (Editorial 2008 [19]; GBI Research 2011 [20]).
- \* Björquist and Sartipy state: "Furthermore, the compound attrition rate is negatively affected by the inability to predict toxicity and efficacy in humans. These shortcomings are in turn caused by the use of experimental pre-clinical model systems that have a limited human clinical relevance..." (Björquist & Sartipy 2007 [21])
- \* Then-U.S. Secretary of Health and Human Services Mike Leavitt stated in 2006: "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." (FDA 2006 [22])
- \* Johnson et al. found that out of 39 anticancer drugs tested on xenograft mice, only one mimicked the response in humans. (Johnson et al. 2001 [23])
- \* Oncology drugs fail more frequently in clinical trials than most other categories. (DiMasi & Grabowski 2007[24]; DiMasi et al. 2010 [25])

- \* There have been many attempts to reproduce human cancers in mice. The nude mouse lacked the FOX1 gene, the SCID mouse was created with a very deficient immune system, and there have been many more models. All have failed to predict human response and have misled researchers. Zielinska discusses mouse models of cancer stating they: "rarely predict how a human will respond to the same treatment." Zielinska then quotes Marks of the NCI, and who is also head of the Mouse Models of Human Cancers Consortium, as saying: "we had loads of models that were not predictive, that were [in fact] seriously misleading."(Zielinska 2010 [26])
- \* The NCI had previously tested mice with 12 anti-cancer drugs being successfully used to treat humans. The mice were growing 48 different kinds of human cancers. The study revealed that 30 out of 48 times (63%) the drugs that were effective against human cancers were ineffective in the mice that were growing the human cancers. The NCI believes efficacious treatments for human cancers have been lost because of animal testing. (Gura 1997 [27])
- \* The problem of animal models is well known to the drug development community. Cook et al state: "Over many years now there has been a poor correlation between preclinical therapeutic findings and the eventual efficacy of these [anti-cancer] compounds in clinical trials (Johnson et al. 2001; [28] Suggitt & Bibby 2005 [29]).
- \* The development of antineoplastics is a large investment by the private and public sectors, however, the limited availability of predictive preclinical systems obscures our ability to select the therapeutics that might succeed or fail during clinical investigation."(Cook, Jodrell, and Tuveson 2012 [30])
- \* Singh and Ferrara echo this, stating: "Over 90% of phase 3 clinical trials in oncology fail to meet their primary endpoints despite encouraging preclinical and even early-stage clinical data. This staggering and sobering figure underscores the limitations of existing animal models for the evaluation of potential anticancer agents. The paucity of models is especially apparent with the advent of drugs that target the tumor milieu, or microenvironment, such as anti-angiogenics . . . immunotherapies and compounds directed against tumor-associated fibroblasts."(Singh & Ferrara 2012 [31])
- \* Wittenburg and Gustafson agree, stating: "The current drug development pathway in oncology research has led to a large attrition rate for new drugs, in part due to a general lack of appropriate preclinical studies that are capable of accurately predicting efficacy and/or toxicity in the target population. . . . One of the most serious challenges currently facing pharmaceutical research of novel anti-cancer therapeutics is the lack of translation of efficacy and safety from preclinical models to human clinical trials, leading to a large attrition rate of investigational compounds. For new oncology drugs, only about 5% of investigational new drug applications submitted progress beyond the investigational phase due to a general lack of preclinical systems that can accurately predict efficacy and toxicity of new agents."(Wittenburg & Gustafson 2011 [32])
- \* Animal models fail to predict safety as well as efficacy. Reviewers of Phase I trials conducted by the National Cancer Institute (NCI) from 1991-2002 discovered that 15% of participants undergoing single agent chemotherapy agents suffered serious side effects. (Horstmann et al. 2005 [33])

- \* Richard Klausner, then-director of the NCI said: "The history of cancer research has been a history of curing cancer in the mouse. . . . We have cured mice of cancer for decades—and it simply didn't work in humans."(Cimons et al. 1998 [34])
- \* In an editorial to two articles, *Nature Medicine* stated: "The complexity of human metastatic cancer is difficult to mimic in mouse models. As a consequence, seemingly successful studies in murine models do not translate into success in late phases of clinical trials, pouring money, time and people's hope down the drain."(Ellis & Fidler 2010; [35] Van Dyke 2010 [36])
- \* Caponigro and Sellers of the Novartis Institutes For BioMedical Research, Oncology Research and Oncology Translational Medicine stated in 2011: "Despite an improved understanding of the biology of cancer, and an unprecedented volume of new molecules in clinical trials, the number of highly efficacious drugs approved by the regulatory authorities remains disappointingly low. The significant attrition rate of drugs entering clinical trials comes at a high price. This price is paid primarily by the underserved patient and secondarily by the pharmaceutical and biotechnology community, which invests enormous resources perfecting a molecule only to watch it fail in humans . . ." (Caponigro & Sellers 2011[37])
- \* Cancer researcher Robert Weinberg, of Massachusetts Institute of Technology, was quoted by *Leaf* in *Fortune* magazine as saying: "And it's been well known for more than a decade, maybe two decades, that many of these preclinical human cancer models have very little predictive power in terms of how actual human beings—actual human tumors inside patients—will respond . . . preclinical models of human cancer, in large part, stink . . . hundreds of millions of dollars are being wasted every year by drug companies using these [animal] models."(Leaf 2004 [38]) Leaf also quotes Homer Pearce, "who once ran cancer research and clinical investigation at Eli Lilly and is now research fellow at the drug company" as saying: ". . . that mouse models are 'woefully inadequate' for determining whether a drug will work in humans. 'If you look at the millions and millions and millions of mice that have been cured, and you compare that to the relative success, or lack thereof, that we've achieved in the treatment of metastatic disease clinically,' he says, 'you realize that there just has to be something wrong with those models.'"(Leaf 2004 [39])
- \* Others have also pointed out the inadequacy of animal models of cancer, including genetically modified animal models (Frese & Tuveson 2007; [40] Kerbel 2003; [41] Singh et al. 2010;[42] Talmadge et al. 2007; [43] Peterson & Houghton 2004;[44] Francia & Kerbel 2010; [45] Johnson et al. 2001; [46] Zielinska 2010; [47] Wade 2009 [48])
- \* Tamoxifen is a good example of the shortcomings of animal models in general. Tamoxifen was originally touted as a birth control pill based on rat studies and was only later found to be an anticancer chemical. Moreover, it was ineffective as an oral contraceptive as it actually increased a woman's likelihood of becoming pregnant. (Jordan & Robinson 1987 [49]) Tamoxifen acts by binding to the protein known as tubulin thus inhibiting cell division. After discovered to be effective against cancer, Tamoxifen was shown to causes liver tumors in some strains of rat, but not in mice or hamsters.(Powles 1992 [50]) If this had been discovered in preclinical trials, the drug

would not have come to market.(Editorial 2003 [51]) According to D. N. Richardson of the Imperial Chemistries Industries PLC: "No laboratory tests for anti-tumour activity were carried out for Nolvadex [tamoxifen] until after the activity in human patients had been confirmed."(Richardson 1988 [52]) The most common side effect of Tamoxifen is nausea and vomiting, which was not seen in dogs, which are touted as the best species to use when looking for that side effect.(Tucker et al. 1984 [53])

- \* Sadly, even the drugs that do come to market are too frequently not very effective against cancer. In the case of breast cancer, for instance, most women do not benefit from chemotherapy. As a general rule, one-third of women diagnosed with breast cancer would have improved without the chemotherapy and one-third would have died with or without it. Only one-third actually benefit from the treatment. Along the same lines, chemotherapies for cancer have decreased the size of the tumors but at the expense of an increase in frequency of secondary tumors and a very adversely affected lifestyle. Furthermore, most chemotherapy does not prolong life or result in a longer, high quality life. (Bear 2003; [54] Savage 2008; [55] Mittra 2007 [56])
- \* Enna and Williams, in 2009, state: Success in federally funded drug discovery initiatives has had a checkered history. As one example, while the 1971 National Cancer Act gave the National Cancer Institute a charter to cure cancer, the incidence of this disease in the United States remains the highest in the world, with a death rate that has remained unchanged for over 50 years (193.9 per 100,000 in 1950 vs. 193.4 per 100,000 in 2002). This lack of progress is both surprising and disappointing given the billions of dollars spent over the past 40 years on improving treatment options, reducing cancer-related behaviors, such as smoking, and increasing efforts in early detection (Aggarwal, Danda, Shan Gupta, & Gehlot, 2009). **Many are now coming to the realization that, as in other therapeutic areas, the greatest limitation for identifying new drugs for treating cancer are the deficiencies in the animal models used for testing NCEs** [new chemical entities, also referred to as new molecular entities or NMEs] (Aggarwal et al., 2009) . . .A major hurdle in the translational medicine undertaking is the fact that **most preclinical animal models of disease generally lack predictive value with respect to the human condition under study**. Indeed, the false positives that result from the present generation of animal assays are a major cause of NCE attrition in the clinic either because of lack of **efficacy** or the appearance of **unacceptable side effects** that were not detected preclinically [in animals]. While there are notable, albeit retrospective, exceptions (Zambrowicz & Sands, 2003), this weakness in the conventional drug discovery process has not been resolved with the use of transgenic animals which themselves contribute additional confounds that further complicate data interpretation. [57]
- \* Schreiber et al., in 2010, state: The ability of recombinant DNA to provide nearly unlimited access to human proteins resulted in a second approach that is also common today—target-based drug discovery. Here, therapeutic targets are selected using insights gained most often from biochemistry, cell biology and **model organisms**. Small molecules are identified that modulate the targets (often by small-molecule screening) followed by optimization and clinical testing. Although this is a robust process, **the common failure of candidate drugs in late-stage clinical testing, owing to unforeseen toxicity or lack of efficacy, reveals limits in our ability to select targets using surrogates of human physiology, such as in vitro assays and animal models**. [58]

- \* Markou, Chiamulera, Geyer, Tricklebank (of Eli Lilly), and Steckler (of Johnson and Johnson) state in 2009: Despite great advances in basic neuroscience knowledge, the improved understanding of brain functioning has not yet led to the introduction of truly novel pharmacological approaches to the treatment of central nervous system disorders. **This situation has been partly attributed to the difficulty of predicting efficacy in patients based on results from preclinical studies.** . . . Few would dispute the need to move away from the concept of modeling CNS diseases in their entirety using **animals**. However, the current emphasis on specific dimensions of psychopathology that can be objectively assessed in both clinical populations and animal models has not yet provided concrete examples of successful preclinical-clinical translation in CNS drug discovery. . . . Since the founding of the American College of Neuropsychopharmacology (ACNP) in December 1961, there have been tremendous advances in neuroscience knowledge that have greatly improved our understanding of brain functioning in normal and diseased individuals. Unfortunately, however, **these scientific advancements have not yet led to the introduction of truly novel pharmacological approaches to the treatment of central nervous system (CNS) disorders in general, and psychiatric disorders in particular** (Hyman and Fenton, 2003; Fenton et al., 2003; Pangalos et al., 2007). . . . [59]
- \* Neuzil et al., states in 2012: Animal testing is not ideal either, as **the predictive value of such tests is limited owing to metabolic differences between humans and animals**, and many ethical issues are raised by the testing.[60]
- \* Björquist et al., in *Drug Discovery World* 2007: Furthermore, the compound attrition rate is negatively affected by **the inability to predict toxicity and efficacy in humans**. These shortcomings are in turn caused by the use of experimental pre-clinical model systems that have a limited human clinical relevance . . . Animal models are today important tools to detect adverse effects of compounds but are costly and **their clinical relevance is widely debated. In fact, animal models are about 50% effective in predicting human toxicity to the liver, heart and during development.**[61]
- \* Sharp and Langer write in 2011: The next challenge for biomedical research will be to solve problems of highly complex and integrated biological systems within the human body. **Predictive models of these systems in either normal or disease states are beyond the capability of current knowledge and technology** [62].
- \* Zhang et al., state in 2010: [The publication of the report Toxicity Testing in the 21st Century: A Vision and a Strategy by the National Research Council of the National Academies of Science (NAS)] is a long-due response to the call by many for alternatives to the currently standard, **whole-animal-based methodologies, which are inefficient, costly, and have had only limited success in making informative connections to human health risk associated with environmental chemical exposures.** [63]
- \* Elias Zerhouni, former director of NIH and current head of R&D at Sanofi was quoted in the June 25, 2012 issue of *Forbes* as saying: "R&D in pharma has been isolating itself for 20 years, thinking that animal models would be enough and highly predictive, and I think I want to just bring back the discipline of outstanding translational science, which means understand the disease in humans before I even touch a patient."

- \* Raven wrote in 2012: " 'The mouse models really don't reflect the human condition,' says Shaw Warren, an infectious disease specialist at the Massachusetts General Hospital in Boston. 'Clearly, current animal models seem to be incapable of predicting results in human trials of new agents,' says Mitchell Fink, a surgeon at the University of California–Los Angeles." [64]
- \* Mullane and Williams [65] state in 2012: "The difficulties in predicting drug efficacy from preclinical models have been of concern for more than two decades . . . Thus, novel findings apparently related to the systems and targets involved in disease causality; the delineation of the **efficacy**, selectivity and **safety** of NCEs; and the **predictive relevance of biomarkers and animal model data to the human disease state, even when there is evidence for target engagement in humans, all frequently fail** to enhance the success rate for new drug applications (NDAs)." They continue stating that one reason for the problems Pharma is facing is: "(i) An over-reliance on animal models of diseases that are poorly validated in the manner they are applied."

Clearly, scientists, not just animal advocates, do link the failure rate of new drugs to animal models. This is mainly due to the inability of animal models to predict efficacy and safety—the very things they are supposed to predict. While there are many other problems with Pharma, reliance on the animal model is well recognized and discussed. Peruse just about issue of a drug development journal and you will find an article discussing the problems with animal models and why early human testing is the key to solving the pipeline problem as well as the efficacy and safety problems.

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