

The University of New Hampshire Law Review

Volume 22
Number 2 *Volume 22, Number 2 (2024)*

Article 13

6-1-2024

A Drug's Life: The Untapped Potential of Secondary Pharmacology Studies in Drug Development

Christina Scott

Follow this and additional works at: https://scholars.unh.edu/unh_lr



Part of the [Food and Drug Law Commons](#), and the [Pharmacology Commons](#)

Repository Citation

22 U.N.H. L. Rev. 483 (2024).

This Notes is brought to you for free and open access by the University of New Hampshire – Franklin Pierce School of Law at University of New Hampshire Scholars' Repository. It has been accepted for inclusion in The University of New Hampshire Law Review by an authorized editor of University of New Hampshire Scholars' Repository. For more information, please contact sue.zago@law.unh.edu.



Christina Scott

A Drug's Life: The Untapped Potential of Secondary Pharmacology Studies in Drug Development

22 U.N.H. L. Rev. 483 (2024)

ABSTRACT. The United States Food and Drug Administration has evolved over the past century to regulate new medicine and protect the public from harmful or ineffective drugs. Drug development and testing science have advanced rapidly alongside the FDA's increased regulation, enabling pharmaceutical companies to assess a drug's potential adverse reactions by studying its reactivity with various proteins called "off-target receptors." Off-target proteins are often screened and reported in the Investigational New Drug Application as a percentage indicating the drug's binding strength to each protein, which suggests the strength of a particular adverse drug effect. Adverse drug effects often lead to unfavorable side effects of a drug.

The *in vitro* testing of Investigational New Drugs, which is conducted during the preclinical phase of drug development, is not currently regulated. Large pharmaceutical companies are not required to provide secondary pharmacology screening information in preclinical reports if they decide not to test a particular protein or receptor. This lack of regulation can have serious consequences. Insufficient knowledge about a drug's interaction with certain body proteins during the clinical trials stage can lead to unexpected adverse effects or even abandonment of the drug. By requiring regulation for these investigations, the drug development process could be made more effective, economical, safe, and potentially more efficient. With more standardized and comprehensive preclinical testing, companies may have more confidence in their products by the time they are ready for human testing. Regulating these studies can also help to reduce the high rate of attrition in drug development, as potential issues can be identified earlier in the process. Ultimately, regulating *in vitro* testing can help ensure that approved drugs are as safe and effective as possible while also benefiting pharmaceutical companies by providing them with more reliable and comprehensive data to inform their decision-making.

AUTHOR. J.D. candidate for the class of 2024 at the University of New Hampshire Franklin Pierce School of Law. She is pursuing an Intellectual Property Law certificate upon completion of her law degree. Christina has always had a passion for science. She completed a B.S. in Chemistry at Wake Forest University (2020) and worked as a post-baccalaureate fellow at the U.S. Food & Drug Administration before attending law school. She would like to thank her wonderful supervisor and mentor Rebecca Racz, PharmD for teaching her about pharmacological research at the FDA. She would also like to thank her note mentor, Professor Roger Ford, for helping her proofread and edit this work. Christina would finally like to thank her loving family and friends for their support, and give a special shout-out to both Tanner and Hailey for checking every single footnote.

INTRODUCTION.....485

I. OVERVIEW AND HISTORY OF THE U.S. FOOD AND DRUG
ADMINISTRATION.....488

 A. *A Brief History of the U.S. Food and Drug Administration*488

 B. *The Current Drug Approval Framework and an Introduction to
 Preclinical Studies*490

II. SIGNIFICANCE OF IN VITRO SECONDARY PHARMACOLOGY STUDIES491

 A. *In Vitro Testing as a Tool for Efficient Drug Development*491

 B. *Enhancing Transparency: Reporting In Vitro Secondary
 Pharmacology Studies*493

III. STRUCTURING IN VITRO SECONDARY PHARMACOLOGY REGULATION
BY THE FDA498

 A. *Proposed Requirements*.....498

 B. *Potential Objections to Increasing Drug Regulations*499

 C. *The Benefits of Increasing Preclinical Drug Regulation*.....501

CONCLUSION503

INTRODUCTION

In 1947, the United States Food and Drug Administration approved a drug called DES, a synthetic estrogen, to prevent miscarriages.¹ For approximately the next two decades, during the 1950s and 1960s, DES was ingested by millions of pregnant women.² DES lost its status as a “new drug” by 1952, which meant drug manufacturers could distribute and sell without reporting data regarding the drug’s safety and effectiveness.³ In 1971, empirical evidence showed a connection between a rare form of cancer in daughters whose mothers had taken DES during their pregnancy.⁴ Soon after, the FDA issued a bulletin recommending against the sale of DES to pregnant women.⁵ The dangerous, lasting effects of DES continued to appear in both the daughters and the sons of mothers who ingested the drug during their pregnancies.⁶ Victims filed many lawsuits against pharmaceutical manufacturers, with varying results.⁷ The effects of DES continue to surface in third-generation family members of those who took the drug during the twenty-five years it was on the market.⁸ Evidence during the FDA recall revealed that manufacturers

¹ Apryl A. Ference, *Rushing to Judgment of Fen-Phen and Redux: Were the FDA, Drug Manufacturers, and Doctors Too Quick to Respond to American's Infatuation with a Cure-All Diet Pill for Weight Loss?*, 9 ALB. L.J. SCI. & TECH. 77, 89 (1998). DES was not originally sold as a miscarriage-prevention drug; it was approved by the FDA in 1941 for other uses before approving it as a miscarriage preventative. *Id.* at 88–89.

² See *Sindell v. Abbott Lab'ys*, 607 P.2d 924, 927 (Cal. 1980) (noting between 1.5 and 3 million women were estimated to have ingested DES).

³ See David M. Schultz, *Market Share Liability in DES Cases: The Unwarranted Erosion of Causation in Fact*, 40 DEPAUL L. REV. 771, 774–75 (1991) (stating that by the time the FDA banned DES, 300 manufacturers were estimated to have sold and distributed the drug).

⁴ See Ference, *supra* note 1, at 89 (“In 1971, however, the FDA recalled DES after a New England Journal of Medicine study confirmed a statistical association of adenocarcinoma, a rare form of vaginal cancer, with daughters who had been exposed to DES in the womb (DES daughters.”); see also Schultz, *supra* note 3, at 775 (“In 1971, two medical studies suggested that there was a statistically significant association between the outbreak of clear cell adenocarcinoma, a form of cancer, in young women and the maternal ingestion of DES during pregnancy.”)

⁵ U.S. FOOD AND DRUG ADMINISTRATION, DIETHYLSTILBESTROL CONTRAINDICATED IN PREGNANCY: DRUG'S USE LINKED TO ADENOCARCINOMA IN THE OFFSPRING (1971). The bulletin listed pregnancy as a “contraindication” to the use of DES. *Id.*

⁶ See *Rauscher v. Abbott Lab'ys*, 15 Phila. 251, 352 (Pa. 1987) (a mother who took DES during her pregnancy and suffered from cancer along with her son.); Ference, *supra* note 1, at 89 (listing the “serious ailments” those affected by DES suffered).

⁷ See, e.g., *Rauscher*, 15 Phila. at 251. “Some DES plaintiffs who could identify the manufacturer of the DES their mothers ingested have been able to proceed to trial.” Schultz, *supra* note 3, at 777 n.29 (“A number of juries have found the drug company defendants in DES cases not liable for the injuries suffered by DES daughters.”).

⁸ Ference, *supra* note 1, at 89–90 (citing Tracey I. Batt, *DES Third-Generation Liability: A Proximate Cause*, 18 CARDOZO L. REV. 1217, 1222 (1996)).

neglected to thoroughly test the drug before receiving market approval.⁹ Furthermore, data produced ten years before FDA approval showed synthetic estrogen caused cancer and deformities in offspring when given to pregnant animals.¹⁰ If there had been existing regulations requiring manufacturers to show a drug's safety and efficacy before its approval, DES would have never made it to the shelves.

The U.S. Food and Drug Administration oversees drug development,¹¹ a procedure that has evolved through the years to include several stages of testing, ensuring consumer protection against unsafe or ineffective products.¹² A drug product in its nascent phase requires an Investigational New Drug (IND) Application submitted to the FDA for analysis and approval.¹³ After the IND phase, a pharmaceutical company can submit a New Drug Application (NDA), moving it to the clinical trials stage so human testing can begin.¹⁴ Before all of this, though, the FDA evaluates secondary pharmacology data that is submitted as part of the IND application.¹⁵

Secondary pharmacology screens indicate how a new drug affects off-target receptors.¹⁶ Off-target receptors are proteins that are not the drug's intended target, so this data could identify any adverse drug reactions that the drug could have on the body. Before a potential new drug enters Phase 1 clinical trials,¹⁷ secondary pharmacology studies are an efficient way for many pharmaceutical

⁹ See *Bichler v. Eli Lilly & Co.*, 436 N.E.2d 182, 185 (N.Y. 1982) (noting the jury's finding that manufacturers would have discovered DES caused cancer in offspring if they had tested the drug on pregnant mice); Ference, *supra* note 1, at 90 ("Many pharmaceutical companies simply relied on tests conducted by others rather than performing their own studies when applying for FDA approval.").

¹⁰ Tracey I. Batt, *DES Third-Generation Liability: A Proximate Cause*, 18 CARDOZO L. REV. 1217, 1220 n.17 (1996).

¹¹ AGATA DABROWSKA & SUSAN THAUL, CONG. RSCH. SERV., HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 3 (2013).

¹² See, e.g., Drug Amendments of 1962, Pub. L. 87-781, 76 Stat. 780 (describing Congress' act to "protect the public health by amending the Federal Food, Drug, and Cosmetic Act to assure the safety, effectiveness, and reliability of drugs, authorize standardization of drug names, and clarify and strengthen existing inspection authority; and for other purposes.").

¹³ U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND INVESTIGATORS: SAFETY REPORTING REQUIREMENTS FOR INDs AND BA/BE STUDIES (2012).

¹⁴ *Id.*

¹⁵ 21 C.F.R. § 312.23 (2024).

¹⁶ Thomas Papoian et al., *Secondary Pharmacology Data to Assess Potential Off-Target Activity of New Drugs: A Regulatory Perspective*, 14 NATURE REV. DRUG DISCOVERY, Mar. 20 2015, at 294.

¹⁷ See DABROWSKA & THAUL, *supra* note 11, at 5 (noting Phase 1 clinical trials are the first part of the human trials stage).

companies to assess the safety profile of the compound.¹⁸ This data aims to decrease the attrition rate of INDs and ensure the time-effective and cost-efficient development of new medicine.¹⁹ Secondary pharmacology plays a critical role in drug development in the United States.²⁰ As such, these studies should be regulated and standardized by the U.S. Food and Drug Administration. Currently, there is wide variation in the content of such preclinical screens; it is difficult to efficiently select which off-target receptors to test.²¹ The results are difficult to understand;²² there is a lack of uniformity in the content and distribution of such information.²³ The lack of uniformity impedes the efficient assessment of the drug regarding safety risks.²⁴ Consequently, the need for regulation of in vitro off-target testing is increasingly apparent.²⁵

This note proceeds in three parts. Part I introduces the FDA's role in drug development, the history of drug regulation in the US, and the current drug approval framework, including the IND process. Part II describes the significance of in vitro secondary pharmacology studies, primarily in the context of preclinical research. Part II seeks to describe how regulating in vitro secondary pharmacology studies would lead to more transparency in the pharmaceutical industry, ultimately streamlining the drug development process. Part III proposes a solution to the lack of oversight in regulating these studies and addresses criticisms of increased regulation, emphasizing the benefits of a new regulatory system that would create good incentives for pharmaceutical companies.

¹⁸ Gail A. Van Norman, *Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs*, 1 JACC. BASIC TO TRANSL. SCI. 170, 171 (2016). In the modern context of new drug evaluation, the term safety “determines the highest tolerable dose or optimal dose needed to achieve the desired clinical benefit and potential adverse effects in that exposure range.” *Id.*

¹⁹ Christina Scott et al., *Analysis of Secondary Pharmacology Assays Received by the US Food and Drug Administration*, 117 J. PHARM. TOXICOLOGICAL METHODS, 2022, at 1, 2.

²⁰ *Id.*

²¹ Joanne Bowes et al., *Reducing Safety-Related Drug Attrition: The Use of in Vitro Pharmacological Profiling*, 11 NATURE REV. DRUG DISCOVERY, Dec. 2012, at 909–22. See Stephen Jenkinson et al., *A Practical Guide to Secondary Pharmacology in Drug Discovery*, 105 J. PHARM. AND TOXICOLOGICAL METHODS, 2020, at (“Nevertheless, target composition, screening technologies, assay formats, interpretation and scheduling of panels can vary significantly between companies...”).

²² Scott et al., *supra* note 19, at 2.

²³ Andrew Dodson et al., *Aggregation and Analysis of Secondary Pharmacology Data From Investigational New Drug Submissions at the US Food and Drug Administration*, 111 J. PHARM. TOXICOLOGICAL METHODS, 2021, at 1, 6.

²⁴ *Id.* at 2.

²⁵ Jenkinson et al., *supra* note 21, at 1 (noting that “[r]egulators, drug makers and patients share a demand for deep characterization of secondary pharmacology effects of novel drugs and their metabolites”).

I. OVERVIEW AND HISTORY OF THE U.S. FOOD AND DRUG ADMINISTRATION

A. A Brief History of the U.S. Food and Drug Administration

In 1906, Congress passed the Food and Drug Act, making the sale of adulterated or misbranded drugs illegal.²⁶ This marked the creation of the United States Food and Drug Administration as a federal consumer protection agency. The national regulation of new drug approvals in the United States did not begin until 1938, however, with the Federal Food, Drug, and Cosmetic Act (FDCA).²⁷ The FDCA was the first time Congress required pre-market approval for all new drugs, requiring a manufacturer to prove to the FDA the drug's safety prior to sale or distribution.²⁸ The 1938 Act shifted the role of the FDA from being an enforcement body that policed adulterated drugs to a regulatory body responsible for overseeing the evaluation of new drugs before they enter the marketplace.²⁹ The FDCA of 1938 granted the FDA two important regulatory powers: the ability to prosecute non-complying drug companies and the power to require drug safety testing.³⁰ The law also created the New Drug Application (NDA), a procedure for the pre-marketing

²⁶ Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (repealed 1938); *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 185–86 (1971). See U.S. FOOD & DRUG ADMIN. PART I: THE 1906 FOOD AND DRUGS ACT AND ITS ENFORCEMENT, <https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-i-1906-food-and-drugs-act-and-its-enforcement> [<https://perma.cc/1B37-6CL2>] (this first regulatory law hinged on the “regulation of product labeling rather than pre-market approval.”).

²⁷ Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. §§ 301–392 (1976)); Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL'Y 295, 302 (2000). See *Drug Efficacy and the 1962 Drug Amendments*, *supra* note 26, at 186–91 (The Food and Drug Act of 1906 did not, however, “regulate false claims of drug efficacy nor create any regulatory authority for pre-market review.”).

²⁸ Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. §§ 301–392 (1976). See *United States v. Dotterweich*, 320 U.S. 277, 283 (1943) (explaining that the purpose of the FDCA was its “distribution” and not “the proprietary relation to a misbranded or an adulterated drug.”). This Act was sparked by public outcry over the distribution of elixir sulfanilamide, an antibiotic that caused mass poisoning across the country. Greenberg, *supra* note 27, at 302; Paul M. Wax, *Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act*, 122 ANNALS INTERNAL MED., 456–57 (1995).

One hundred five patients died from [elixir sulfanilamide's] therapeutic use. Under the existing drug regulations, premarketing toxicity testing was not required. In reaction to this calamity, the U.S. Congress passed the 1938 Federal Food, Drug and Cosmetic Act, which required proof of safety before the release of a new drug.

²⁹ Wax, *supra* note 28, at 456.

³⁰ Sue McGrath, *Only A Matter of Time: Lessons Unlearned at the Food and Drug Administration Keep Americans at Risk*, 60 FOOD & DRUG L.J. 603, 604 (2005). Under the old legislation, violators could only be fined. *Id.*

assessment of drug safety.³¹

The 1938 FDCA, though a step toward comprehensive federal drug regulation in the United States, ultimately failed to police the effectiveness of drugs.³² The thalidomide crisis of the early 1960s involved the NDA of thalidomide in the United States, where a supposedly routine drug approval exposed serious shortcomings to the FDA's drug approval process.³³ Thalidomide had been approved in various European countries before it was discovered that the drug caused birth defects in pregnant women.³⁴ Luckily, thalidomide had not been approved for use in the United States.³⁵ The crisis nevertheless drove a hallmark congressional action.³⁶ In October 1962, Congress passed the Kefauver-Harris Drug Amendments to the FDCA.³⁷ The 1962 Amendments established that it was the FDA's responsibility to approve drugs before they reached the market.³⁸ Notably, the Amendments required that manufacturers prove a drug's effectiveness before market approval.³⁹

³¹ James R. Silkenat, *Laetrile: Statutory and Constitutional Limitations on the Regulation of Ineffective Drugs*, 127 U. PA. L. REV. 233, 238 (1978). Note that under the 1938 Act a new drug's effectiveness was not yet "a matter for agency concern." *Id.* at n.30.

³² *Id.* at 238. In the modern context of new drug evaluation, effectiveness "describes a drug's clinical benefits in a 'real world' situation, for example, where patients may have comorbid conditions or other medications that interact with the drug, and where drug administration may not follow strict study guidelines." Van Norman, *supra* note 18, at 174.

³³ Lisa A. Seidman & Noreen Warren, *Frances Kelsey & Thalidomide in the US: A Case Study Relating to Pharmaceutical Regulations*, 64 AM. BIOLOGY TCHR., Sept. 2002, at 495, 497. According to the law at the time, the pharmaceutical company seeking thalidomide's market approval would have been able to sell and distribute the drug if the FDA had not responded to their New Drug Application within 60 days. *Id.* One individual's pushback—Dr. Frances Kelsey—prevented thalidomide's approval. *Id.* Though she received significant pushback from the pharmaceutical industry, Dr. Kelsey held off the approval of thalidomide until it was found to have gruesome side effects in pregnant women. *Id.*

³⁴ Trent Stephens & Rock Brynner, *DARK REMEDY* 9, 22 (2001). The thalidomide crisis was a public health crisis that took place in the early 1960's. *Id.* at 22. Thalidomide was a drug manufactured in Europe and advertised as a sleeping pill. *Id.* It was prescribed to pregnant women to combat morning sickness and caused thousands of infants to be born with birth defects. *Id.* The drug was quickly removed from European markets. *Id.* at 28.

³⁵ Greenberg, *supra* note 27, at 303. See also Karen Geraghty, *Protecting the Public: Profile of Dr. Frances Oldham Kelsey*, *AMA J. ETHICS*, July 2001, at 253 (recognizing Dr. Kelsey's refusal to approve thalidomide despite enormous pressure from pharmaceutical manufacturers).

³⁶ See Silkenat, *supra* note 31, at 238 (noting the unanimous congressional action on drug reform legislation in 1962).

³⁷ Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, *FDA CONSUMER MAG.*, Jan.–Feb. 2006, at 3. The Amendments were made "[t]o protect the public health by amending the Federal Food, Drug, and Cosmetic Act to assure the safety, effectiveness, and reliability of drugs, authorize standardization of drug names, and clarify and strengthen existing inspection authority; and for other purposes." Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780.

³⁸ Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780.

³⁹ *Id.*

The FDA also gained the authority to continue monitoring any side effects while the drug was on the market.⁴⁰ This means the FDA could even pull a post-market drug from the shelves if it proved unsafe or ineffective.⁴¹ The previous 1938 FDCA operated such that absent agency disapproval, an NDA became effective after sixty days of its submission.⁴² The new 1962 Amendments, on the other hand, required affirmative approval before new drugs could be distributed commercially.⁴³ The FDA could now require that drugs exhibit sufficient data that they are safe and effective before they are approved to enter the market.⁴⁴ The standard for an applicant is that the drug be supported by “substantial evidence,” meaning “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness” of the drug candidate.⁴⁵ The sixty-day window for the FDA review process expanded to 180 days to allow for more thorough evaluations.⁴⁶

B. The Current Drug Approval Framework and an Introduction to Preclinical Studies

The passage of the 1962 Amendments initiated the multi-phase drug screening process familiar to today’s industry.⁴⁷ The first step in a new drug’s approval process is the submission of an IND application to the FDA.⁴⁸ The IND application contains extensive information on the company’s laboratory work and animal testing, as well

⁴⁰ *Id.*; Jeremy A. Greene & Scott H. Podolsky, *Reform, Regulation, and Pharmaceuticals – The Kefauver-Harris Amendments at 50*, 367 N. ENG. J. MED., Oct. 2012, at 1481–83 (noting that the FDA could require a drug’s proof of efficacy before it is approved and conduct retrospective reviews of drugs approved before the Amendments). The Amendments prompted the retrospective review of all drugs approved between 1938 and 1962, resulting in the removal of around 600 ineffective medicines from the market by the early 1970s. *Id.*

⁴¹ Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 355(e) (1976).

⁴² McGrath, *supra* note 30, at 607.

⁴³ Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780.

⁴⁴ Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 355(b) (1976). The Senate Committee set the canon, “[t]he only sound standard is that a drug must be safe and that there must be substantial evidence showing that the drug has produced the specific physiological effects claimed for it.” S. REP. NO. 87-1744, at 2922 (1962), *as reprinted in* U.S.C.C.A.N. 2892.

⁴⁵ Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. § 355(d) (1976).

⁴⁶ Beth E. Myers, *The Food and Drug Administration’s Experimental Drug Approval System: Is It Good for Your Health?*, 28 Hous. L. REV. 309, 312 (1991) (citing Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified at 21 U.S.C. §§ 321-381 (1988))).

⁴⁷ Greenberg, *supra* note 27, at 304. *See* Greene & Podolsky, *supra* note 40, at 2 (“These market-making and -unmaking powers were also tied to a new structure of knowledge generation: the orderly sequence of Phase 1, Phase 2, and Phase 3 trials now seen as a natural part of any pharmaceutical life cycle.”).

⁴⁸ *See* McGrath, *supra* note 30, at 609 (noting that as a result of the 1962 Amendments, drug testing would be “conducted in phases, beginning after the company submitted an IND application to begin conducting tests on humans”).

as a clear plan for how the drug will be evaluated on human subjects.⁴⁹ Typically, the IND application includes preclinical data on the experimental drug's chemistry and toxicity.⁵⁰ If the FDA accepts the IND application proposal, then the drug can move to Phase I testing, which is the first of three stages of clinical trials.⁵¹ The three phases of clinical trials focus on human testing and, while necessary, are beyond the scope of this article.⁵² After human trials are concluded, the pharmaceutical company submits an NDA to the FDA, which is a compilation of all the data collected during human and animal trials.⁵³

II. SIGNIFICANCE OF IN VITRO SECONDARY PHARMACOLOGY STUDIES

A. *In Vitro* Testing as a Tool for Efficient Drug Development

Studies conducted during the IND phase involve both primary and secondary

⁴⁹ *Id.* (citing Philip J. Hilts, PROTECTING AMERICA'S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION 229 (Knopf pubs., 1st ed.) (2003)).

⁵⁰ See U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS (1995) (listing the required information for an IND Application). See also 21 C.F.R. 312.23(a) (2002) (codifying what is required in an IND Application). "Preclinical" studies and data are defined as "research using animals to find out if a drug, procedure, or treatment is likely to be useful. Preclinical studies take place before any testing on humans is done." *Preclinical*, NCI DICTIONARY OF CANCER TERMS. "Toxicity" is a word used to assess whether a substance can cause serious harm. *Toxicity*, NCI DICTIONARY OF CANCER TERMS.

⁵¹ Greenberg, *supra* note 27, at 304. In the greater drug development context, there are three phases. Greene & Podolsky, *supra* note 40, at 1482–83.

⁵² See 21 C.F.R. § 312.22(a) (2002).

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety . . . FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

⁵³ Melissa Marie Bean, *Fatal Flaws in the Food and Drug Administration's Drug-Approval Formula*, 2003 UTAH L. REV. 881, 884–85 (2003).

The NDA must include: (1) reports of the clinical trials and testing done to determine safety and effectiveness; (2) the complete ingredients or components of the drug; (3) the composition of the drug; (4) a complete description of the manufacturing, processing and packaging methods and controls; (5) samples of the drug and its components (if requested); and (6) samples of the proposed labeling.

Id. at 885 (citing Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48 RUTGERS L. REV. 883, 908 (1996)). See 21 C.F.R. § 314.50 (2001) (entitled "Content and format of an NDA").

pharmacology.⁵⁴ Primary pharmacology encompasses a drug's efficacy⁵⁵ at its desired therapeutic target or the intentional effects of the drug on an anticipated protein.⁵⁶ In contrast, secondary pharmacology involves a drug's effects on proteins that are not the desired therapeutic target.⁵⁷ Secondary pharmacology can be thought of as undesirable or unintended side effects of a drug at the molecular level.⁵⁸ A drug may activate, inhibit, or otherwise affect a protein in the body by binding to it, even though that protein is not intended to bind to the drug.⁵⁹ In scientific practice, secondary pharmacology studies are *in vitro* evaluations of how a new drug interacts with different proteins in the human body.⁶⁰

A drug sponsor's main objective in the early stages of preclinical drug development is to assess whether the product is generally safe for initial use in humans.⁶¹ Thus, secondary pharmacology studies can be an effective and

⁵⁴ U.S. FOOD & DRUG ADMIN., DA GUIDANCE FOR INDUSTRY: S7A SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS (2001). The term "pharmacology" means the scientific study of a drug's effects on living organisms, including how organisms handle drugs and the development of new drugs to prevent and cure diseases. *What is Pharmacology*, UNIV. ALBERTA DEP'T PHARMACOLOGY (2023), <https://www.ualberta.ca/pharmacology/about/what-is-pharmacology.html> [<https://perma.cc/8SKQ-9AMD>].

⁵⁵ Van Norman, *supra* note 18, at 174. In the modern context of new drug evaluation, efficacy "determines whether a drug has a positive clinical benefit over placebo or other intervention. Efficacy tests involve "ideal," that is, strictly controlled conditions." *Id.*

⁵⁶ U.S. FOOD & DRUG ADMIN., *supra* note 54 at n.2 (defining primary pharmacology as "[s]tudies on the mode of action and/or effects of a substance in relation to its desired therapeutic target are primary pharmacodynamic studies").

⁵⁷ *Id.* (defining secondary pharmacology as "[s]tudies on the mode of action and/or effects of a substance not related to its desired therapeutic target").

⁵⁸ INT'L CONF. ON HARMONISATION, ICH GUIDANCE FOR INDUSTRY S7A SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS at 10 (July 2000). The ICH defines secondary pharmacology as "studies on the mode of action and/or effects of a substance not related to its desired therapeutic target." *Id.* at n. 1–2 (noting, however, that there is no internationally recognized definition of the term secondary pharmacodynamics or safety pharmacology). *See, e.g.,* Scott et al., *supra* note 19, at 1 (defining secondary pharmacology studies as "*in vitro* assessments of a small molecule's reactivity with any target other than the primary receptor, known as off-target receptors."). Off-target receptors incorporate ion channels, receptors, enzymes, and transporters. *Id.*

⁵⁹ *See generally* Hongyi Zhou et al., *Comprehensive prediction of drug-protein interactions and side effects for the human proteome*, 5 SCI. REPORTS (2015).

⁶⁰ Scott et al., *supra* note 19, at 1. *In vitro* refers to studies "occurring outside of the body," contrasted to *in vivo*, meaning "occurring within the body." Jamil Ammar, *The "Medical Mile" Gearing Toward 3D-Bespoke Healthcare A Comparison of United States And European Union Patent Regimes*, 52 GONZ. L. REV. 279, 280 (2016). *In vivo* tests are executed in test tubes or with similar equipment. *In vitro* Diagnostics, WHO https://www.who.int/health-topics/in-vitro-diagnostics#tab=tab_1 [<https://perma.cc/TKK3-D2WL>] (last visited Mar. 25 2023). *In vivo* tests are executed inside the body. *Id.*

⁶¹ IND Application, FDA <https://www.fda.gov/drugs/types-applications/investigational-new->

economical way to estimate off-target drug effects and safety concerns that may arise later in a drug's clinical stage.⁶² Secondary pharmacology is employed in both the preclinical and clinical phases of drug development.⁶³ Pharmaceutical companies often conduct *in vitro* screening of drug candidates to evaluate their reactivity with proteins in the body, which is included in the drug's IND application.⁶⁴ When there is a chance a drug may have unintended effects on other parts of the body, scientists carefully study how much of a risk may pose if the drug were taken in real-life conditions.⁶⁵ Based on these analyses, they may recommend additional safety measures or additional research to better understand or minimize any potential risks before the drug is tested in clinical trials.⁶⁶

B. Enhancing Transparency: Reporting In Vitro Secondary Pharmacology Studies

There is untapped potential for collecting *in vitro* secondary pharmacology studies performed at the preclinical stage of drug development. As *in vitro* pharmacological profiling grows in popularity, drug developers can identify off-target activity before reaching clinical trials.⁶⁷ *In vitro* pharmacological profiling is increasingly being employed early in drug discovery to detect unfavorable off-target activity profiles that could impede, delay, or even result in market withdrawal if discovered after a drug is approved.⁶⁸ As discussed, secondary pharmacology studies are submitted to the FDA as part of an IND application⁶⁹ in a drug's preclinical stage of development.⁷⁰ This data provided to the FDA varies widely in

drug-ind-application [<https://perma.cc/JYE8-S28A>]. See Dodson et al., *supra* note 23, at 1 (investigational new drug molecules are “screened for activity at various secondary targets” to identify both target specificity and safety profile).

⁶² Jenkinson et al., *supra* note 21, at 2–3. Many pharmaceutical companies use *in vitro* testing to determine the safety profile of an investigational new drug before entering Phase 1 clinical trials. *Id.*

⁶³ Papoian et al., *supra* note 16, at 1 (noting that when *in vitro* information suggests that a drug might have unexpected effects, experts study how likely these effects are to occur in humans taking the drug under normal conditions. They then make recommendations to make sure the drug is safe for people to use. This may include asking for more studies to better understand or reduce the risk.).

⁶⁴ Dodson et al., *supra* note 23, at 2.

⁶⁵ Papoian et al., *supra* note 16, at 294.

⁶⁶ *Id.*

⁶⁷ Bowes et al., *supra* note 21, at 909.

⁶⁸ *Id.*

⁶⁹ INT'L COUNCIL OF HARMONISATION, S7A SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS (Aug. 2001).

⁷⁰ Chloe Weaver, *IND vs NDA: What is the Difference?*, IDEAGEN (Oct. 6, 2021), <https://www.ideagen.com/thought-leadership/blog/ind-and-nda-what-is-the->

trade secrets and confidential company information create obstacles to accessing data and information in which the public has a critical interest.⁷⁸ This may be especially true in the pharmaceutical industry, where many medicines are in high demand. The lack of regulation of in vitro secondary pharmacology studies impedes access to information required for speedy and efficient drug development; the alternative hinders scientific progress.⁷⁹

The public depends greatly on the comprehension of the safety and effectiveness of medicines currently available.⁸⁰ Regulators are frequently pressured to approve medicines swiftly; without access to extensive data on a drug's reactivity to various other proteins, it is difficult to attest a drug candidate's risks.⁸¹ More important to the scope of this note is that the inhibition of public access to drug development data may hinder successful new drugs.⁸² At present, pharmaceutical companies are not obligated to reveal the information obtained from preclinical and clinical trials that failed or were discontinued.⁸³ Such a system undercuts innovation and drives up drug development costs because previous unsuccessful drug candidates cannot be used as a learning experience for researchers in future development programs.⁸⁴

One of the most significant laws governing FDA duties identifies the Agency as the American people's guardian against the introduction of new drugs that are either harmful or ineffective.⁸⁵ To properly serve as a regulator, the FDA has taken on the role of a gatekeeper against dangerous products that the public is unable to evaluate on their own.⁸⁶ The FDA uses a highly technical regulatory system to make

⁷⁸ Allison Durkin et al., *Addressing the Risks That Trade Secret Protections Pose for Health and Rights*, 23 HEALTH HUM. RTS. 129, 130 (2021).

⁷⁹ *Id.*

⁸⁰ *Id.* at 132.

⁸¹ *Id.* at 133.

There are many examples where serious – sometimes deadly – side effects, or a lack of efficacy, were revealed only many years after a drug has been on the market because clinical trial data were kept secret from researchers. Prominent examples include rofecoxib (Vioxx), estrogen hormone therapy (Prempro), and extended-release oxycodone (OxyContin).

Id. (citing Alexander C. Egilman et al., *Confidentiality Orders and Public Interest in Drug and Medical Device Litigation*, 180 JAMA INT. MED. 292, 292 (2020)).

⁸² *Id.* at 133.

⁸³ *Id.*

⁸⁴ Joshua M. Sharfstein et al., *Blueprint for Transparency at the U.S. Food and Drug Administration: Recommendations to Advance the Development of Safe and Effective Medical Products*, 45 J. L., MED. & ETHICS 7, 14 (2017) (noting the multiple benefits to greater transparency regarding “FDA review, analysis, and decision-making.” Importantly, transparency allows researchers to learn what the FDA “thinks about products under review, including the real reasons why products were not approved.”).

⁸⁵ Greenberg, *supra* note 27, at 295.

⁸⁶ *See id.* at 295 n.4 (noting “two reasons why the public may be unequipped to evaluate the

decisions about the safety and effectiveness of new drugs. Though complex, the current regulatory scheme for drug development is more beneficial than it is burdensome.⁸⁷ The FDA has increased its regulation in the past because of public demand and following mass recalls after a drug was deemed unsafe or ineffective.⁸⁸ Now, the pharmaceutical industry has the scientific and technological capability to perform *in vitro* screens at various targets.⁸⁹ It follows that federal regulation should advance along with the technology used to test new drugs.

The FDA, as a drug regulator, has the authority to select proteins for screening and mandate their inclusion in the IND application.⁹⁰ FDA standards call for experimental data that support the approval of a new drug.⁹¹ Increasing regulation to incorporate scientific advancements is a fair course of action as technology develops and makes early detection of adverse drug reactions possible. Pharmaceutical companies should implore the use of technology to perform secondary pharmacology screens early in the drug development process if they possess the capability to do so. According to estimates, seventy-five percent of all adverse drug reactions (ADRs) are dose-dependent and predictable using the candidate compound's pharmacology profiles.⁹² It is, therefore, advantageous for pharmaceutical companies to test for adverse drug reactions early in the drug

dangers of new drugs: first, because of the technical complexities that are involved; and second, because the necessary information is only produced subject to the regulatory standards imposed by the FDA.”).

⁸⁷ *Contra* Michael D. Greenberg, *Information, Paternalism, and Rational Decision-Making: The Balance of FDA New Drug Approval*, 13 ALB. L.J. SCI. & TECH. 663, 664 (2003) (arguing the FDA's regulatory scheme is “quite burdensome to the development of new pharmaceuticals.”).

⁸⁸ U.S. FOOD & DRUG ADMIN., *Milestones in U.S. Food and Drug Law*, <https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law> [<https://perma.cc/HHQ9-TFZH>] (last updated Jan. 30, 2023).

⁸⁹ *See* Steven Whitebread et al., *Secondary Pharmacology: Screening and Interpretation of Off-Target Activities – Focus on Translation*, 21 DRUG DISCOVERY TODAY ISSUE 8 1232, 1233 (2016) (noting “[s]econdary pharmacology profiling panels have been further refined because several targets and pathways are now well established as contributors to clinical ADRs and mitigation strategies are introduced in early drug development by testing affinities of compounds at these targets.”).

⁹⁰ *See* Federal Food, Drug, and Cosmetic Act 21 U.S.C. § 355(i) (current through Public Law 117-327, approved Dec. 27, 2022, with a gap of Public Law 117-263) (defining the requirements for an IND application, and the FDA's authority to approve or reject such applications.); *see also* IND Content and Format 21 C.F.R. § 312.23 (2024) (outlining the requirements for an Investigational New Drug (IND) application submitted to the FDA. Specifically, this section pertains to the content and format of the IND application, and it requires that the application contain certain information.).

⁹¹ 21 C.F.R. § 312.23(8) (2024).

⁹² Bowes et al., *supra* note 21, at 909 (citing William S. Redfern et al., *Safety Pharmacology - a Progressive Approach*. 16 FUNDAM. CLIN. PHARMACOLOGY. 161–73 (2002).); *see* Hamon et al., *supra* note 72, at 645 (noting one of the primary reasons a drug will fail in clinical development or post-market launch is “lacking or compromised safety margins at therapeutic doses.”).

discovery process.⁹³

The International Conference on Harmonisation (ICH) S7A Guidance for Industry provides “a definition, general principles, and recommendations for safety pharmacology studies.”⁹⁴ New drugs navigate preclinical safety pharmacology testing according to guidelines delivered in these documents.⁹⁵ As the name suggests, this is mostly a guidance for best practices for conducting safety pharmacology studies during drug development.⁹⁶ The FDA requires the submission of an IND application before a drug can move to its clinical study phase.⁹⁷ However, the required content for *in vitro* testing is relatively vague.⁹⁸ The FDA has the authority to promulgate regulations to govern the submission of *in vitro* testing and submission more adequately. This would remain in line with their current role as a drug regulator.⁹⁹ As history demonstrates, the FDA has matured into a strong governing body over pharmaceutical companies and the release of new drugs into the market.¹⁰⁰ The FDA safeguards consumers’ protection by requiring extensive safety testing before a new drug is approved for public use.¹⁰¹

Secondary pharmacology studies have indeed been proven useful.¹⁰² In

⁹³ Hamon et al., *supra* note 72, at 645.

⁹⁴ INT’L CONF. ON HARMONISATION, *supra* note 58, at 2.

⁹⁵ EUR. MED. AGENCY, CPMP/ICH/539/00, ICH TOPIC S7A: SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS (2001), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002831.pdf (2001) [<https://perma.cc/88Z3-CNHR>]; EUR. MED. AGENCY, CPMP/ICH/423/02, ICH TOPIC S7B: THE NONCLINICAL EVALUATION OF THE POTENTIAL FOR DELAYED VENTRICULAR REPOLARIZATION (QT INTERVAL PROLONGATION) BY HUMAN PHARMACEUTICALS (2005), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002841.pdf (2005) [<https://perma.cc/HAX2-NNXT>]; EUROPEAN MEDICINES AGENCY (EMA), EUR. MED. AGENCY, CPMP/ICH/286/1995, ICH TOPIC M3 (R2): NON-CLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS (2009), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002720.pdf [<https://perma.cc/6FDH-S36D>].

⁹⁶ *See generally* INT’L CONF. ON HARMONISATION, *supra* note 58.

⁹⁷ 21 C.F.R. § 312.23 (2024).

⁹⁸ 21 C.F.R. § 312.23(a)(8) (2024) (requiring “[a]dequate 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.”).

⁹⁹ Federal Food, Drug, & Cosmetic Act, 21 U.S.C. § 393 (2000).

¹⁰⁰ *See id.* (highlighting the FDA’s general powers and objectives). *See also* Greenberg, *supra* note 87, at 665 (noting that the FDA’s regulatory regime for new drug approvals essentially assumed its current form in 1962 after years of evolution.).

¹⁰¹ Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355.

¹⁰² *See* Whitebread et. al, *supra* note 89, at 1232 (noting that secondary pharmacology studies are an “essential component of drug discovery and is used extensively in the pharmaceutical

particular, employing in vitro activity screens during preclinical drug studies allows the identification of off-target interactions at an early stage before a significant amount of time and money is invested in a drug product.¹⁰³ In vitro screens can also aid in the detection of adverse drug reactions, revealing potential side effects of the drug in a cost-effective way.¹⁰⁴ Conducting secondary pharmacology studies can improve the efficiency of early drug development, resulting in time-saving benefits in later stages of drug development, such as the drug's clinical trials.¹⁰⁵

III. STRUCTURING IN VITRO SECONDARY PHARMACOLOGY REGULATION BY THE FDA

A. Proposed Requirements

Useful secondary pharmacology data include a list of proteins screened with a drug candidate,¹⁰⁶ a report on the correlation between in vitro findings and those observed in animals, and a discussion of potential drug-related effects that should be monitored in humans.¹⁰⁷ Secondary pharmacology study reports would improve in quality and regulatory utility by incorporating such data;¹⁰⁸ thus, it should be a required part of an IND application. Reporting such information reduces the risk of misinterpreting data during decision-making for drug approval.¹⁰⁹

The inclusion of secondary pharmacology data in the early stages of drug submission is standard practice for safety assessment.¹¹⁰ However, the timing, type, extent, and format of this data submitted to regulatory agencies can vary.¹¹¹ There is currently no agreement on the minimum set of targets that should be included in these profiling campaigns.¹¹² One key factor in selecting proteins for screening is assessing the cost-benefit ratio based on the probability of drug-protein binding and

industry for achieving optimal specificity of new drugs via early hazard identification and off-target mitigation.”).

¹⁰³ Bowes et al., *supra* note 21, at 911.

¹⁰⁴ *Id.*

¹⁰⁵ *See id.* (“Clinical side effects can be predicted that may be missed during in vivo safety pharmacology studies, toxicology studies or clinical trials”).

¹⁰⁶ *Id.* at 909 (referring to a selected list of proteins is called a “target panel.”).

¹⁰⁷ Papoian et al., *supra* note 16, at 1 (noting in Table 1 the aspects of secondary pharmacology that are deemed useful for regulatory review).

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ *Id.*

¹¹¹ *Id.*

¹¹² Bowes et al., *supra* note 21, at 909–10.

the resulting physiological response.¹¹³ A recent study found that creating an optimal target panel can improve preclinical screening efficiency.¹¹⁴ The researchers analyzed four major pharmaceutical companies and identified a list of targets, which included forty-four proteins associated with clinical adverse side effects.¹¹⁵ Despite the compilation of the most frequently tested proteins by AstraZeneca, GlaxoSmithKline, Novartis, and Pfizer in preclinical trials,¹¹⁶ no significant changes have been recorded since these recommendations were made.¹¹⁷

Note that such studies only analyze data submitted to the FDA in IND applications.¹¹⁸ It is highly possible that some abandoned drug candidates and their accompanying target profiles are omitted from the analysis.¹¹⁹ Another recent study explored the most commonly tested and most commonly affected proteins among a sample of 2701 IND applications.¹²⁰ This type of research could serve as a basis for creating a standardized list of proteins that must be tested and reported in an IND application.¹²¹

B. Potential Objections to Increasing Drug Regulations

One legitimate concern with increasing drug regulation is from the

¹¹³ *Id.* at 911 (highlighting that proteins that tend to bind to drugs more frequently that also have a high impact are typically included in *in vitro* secondary pharmacology profiling. *Id.* For example, the hERG protein, which is important for cardiovascular functioning, has a high probability of binding to a drug and thus causes an adverse side effect. *Id.* Thus, this protein is often tested at the preclinical stage. *Id.*).

¹¹⁴ *Id.* at 910 (noting target panels designed by four major pharmaceutical companies, the panels aimed to cover a broad range of proteins by weighing the following concepts: “the expression and fundamental role of the target in physiology (including knockout mouse models and genetic evidence from humans); whether pharmacological modulation translates into a biological effect; and, more importantly, whether there is evidence from clinical (especially post-marketing) safety data that links an ADR to a specific target.”).

¹¹⁵ Dodson et al., *supra* note 23, at 6 (referencing the study performed in Bowes et al., *supra* note 21).

¹¹⁶ Bowes et al., *supra* note 21, at 909.

¹¹⁷ Dodson et al., *supra* note 23, at 6.

¹¹⁸ *Id.*

¹¹⁹ *Id.* For example, companies frequently test and record a response to the 5-HT_{2A} protein. *Id.* This protein has clinical implications in psychiatry, so it is possible that once a pharmaceutical company concludes a drug candidate binds to this protein, the company may likely choose not to continue developing the candidate. *Id.* This affects the dataset in studies like this. *Id.*

¹²⁰ Scott et al., *supra* note 19, at 2–3 (showing that of 2701 INDs that were analyzed, there were 747 distinct proteins tested in secondary pharmacology studies. The reports ranged in testing between one and 327 proteins).

¹²¹ See Papoian et al., *supra* note 16 (“We hope that such a discussion could be helpful for drug developers when considering the type and extent of secondary pharmacology data to submit to regulatory agencies in support of a drug application.”).

pharmaceutical companies' perspective. Concerns arise over the FDA exceeding its authority by arbitrarily limiting access to new medicine.¹²² In particular, the FDA's ability to strike a balance between the risks and benefits of approving new therapeutics is a subject of controversy.¹²³ The idea of a "drug lag" forming in the United States has gained traction, meaning the United States' drug approval process has become congested with supposedly arbitrary regulations compared with its Western European counterparts.¹²⁴ Both delays in development and production costs have steadily increased over time.¹²⁵ Pharmaceutical companies claim that FDA regulations raise research costs for new medications by hundreds of millions of dollars, thereby delaying their development.¹²⁶ The costliness of new drug development may potentially dissuade investigations on substances that may be riskier or more uncertain.¹²⁷ Outside the pharmaceutical industry, analysts predict the costs of drug development are so high they may discourage development for all but the most "commercially promising new medications."¹²⁸ Consumers are the ones thought to suffer for missing out on drugs that would have reached the market had FDA regulation been minimized or eliminated.¹²⁹

On the regulatory end, the FDA faces similar difficulties with regulating new drug development.¹³⁰ Is it a waste of resources to demand such rigorous testing of a new drug that may never make it to market? In the context of secondary pharmacology testing, *in vitro* screens are used to assess how a drug affects off-target receptors.¹³¹ The recorded response is non-binary, so it is difficult to predict, even with these screens, how strong of an effect a new drug has on a target.¹³² It is

¹²² See Greenberg, *supra* note 27, at 296 (citing *Revitalizing New Product Development from Clinical Trials Through FDA Review: Hearing on S. 1477 Before the Senate Comm. on Labor and Human Resources*, 104th Cong. 14–17 (1996) (statement of Sen. Judd Gregg)).

¹²³ *Id.* at 297.

¹²⁴ *Id.* at 306 (arguing that in 1970s Western Europe "new drugs were far more readily available and controls on development were much more limited and more market based.").

¹²⁵ *Id.* The average development time to FDA approval averaged eight years and "incurred costs in excess of fifty million dollars per drug" in the 1970s. *Id.* "By 1993, the average development time to FDA approval was about 12 years, at an estimated average cost of 350 million dollars per new drug." *Id.* at 343.

¹²⁶ *Id.* at 300.

¹²⁷ Greenberg, *supra* note 87, at 664.

¹²⁸ Greenberg, *supra* note 27, at 300 (citing Elizabeth C. Price, *Teaching the Elephant to Dance: Privatizing the FDA Review Process*, 51 *FOOD AND DRUG L.J.* 651, 656–57 (1996)).

¹²⁹ Greenberg, *supra* note 87, at 664.

¹³⁰ Greenberg, *supra* note 27, at 299.

¹³¹ Papoian et al., *supra* note 16, at 294.

¹³² Bowes et al., *supra* note 21, at 918. A response greater than or equal to fifty percent inhibition of control specific binding at a particular target is typically referred to as a "hit" when tested at a concentration of ten μ M. *Id.* It has been suggested, though, that a percent inhibition

also challenging to select which off-target receptors to test in preclinical studies without unreasonably driving up the costs of drug development.¹³³

C. *The Benefits of Increasing Preclinical Drug Regulation*

Secondary pharmacology is a vital part of drug discovery. It is used in the pharmaceutical industry to identify potential side effects of a new drug early on and ensure maximum specificity of the drug.¹³⁴ Therapeutic target specificity refers to a drug's chemical ability to selectively interact with a particular molecular target that is involved in a disease process.¹³⁵ In vitro secondary pharmacology studies can be used to predict the likelihood of various adverse drug reactions, making it possible to prioritize drug candidates based on their off-target activity.¹³⁶ This shows the potential for a drug to have adverse drug reactions, which are negative effects a drug may have on the body.¹³⁷ Understanding off-target activity facilitates a comprehensive understanding of the overall chemistry of a drug candidate for drug regulators.¹³⁸

The standardized use of in vitro secondary pharmacology studies has the potential to reduce development costs, increase the efficiency of bringing a drug to market, and increase confidence in the safety of new drugs.¹³⁹ Pharmaceutical companies presently use a wide variety of screens in preclinical development,¹⁴⁰ so new regulation may establish a minimum requirement for the most significant targets to be tested.¹⁴¹ Currently, there is one in vitro pharmacology assay that is required by regulatory authorities.¹⁴² A practical solution is to add a recommended

of control specific binding between thirty percent and fifty percent could still have significant biological effects. Jenkinson et al., *supra* note 21.

¹³³ Scott et al., *supra* note 19.

¹³⁴ Hamon et al., *supra* note 72, at 645–46.

¹³⁵ Simon K. Mencher & Long G. Wang, *Promiscuous Drugs Compared to Selective Drugs (Promiscuity Can Be a Virtue)*, 5 BMC CLIN. PHARMACOL. (2005).

¹³⁶ Scott et al., *supra* note 19, at 1; Whitebread et al., *supra* note 89, 1232–42 (2016).

¹³⁷ Adverse Drug Events, *Adverse Drug Reactions and Medication Errors Frequently Asked Questions*, VA CENTER FOR MEDICATION SAFETY AND VHA PHARMACY BENEFITS MANAGEMENT STRATEGIC HEALTHCARE GROUP AND THE MEDICAL ADVISORY PANEL (Nov. 2006).

¹³⁸ Whitebread et al., *supra* note 89, at 1232.

¹³⁹ See Greenberg, *supra* note 27, at 306 (mentioning the United States is behind in the drug development context because the pharmaceutical industry is bogged down with so many regulations surrounding drug development). This may even reverse part of the “drug lag” critics claim to have resulted from increased FDA regulation. *Id.*

¹⁴⁰ See Dodson et al., *supra* note 23 (noting the “large range of variations in the nature and number of targets screened”).

¹⁴¹ Scott et al., *supra* note 19. There is no minimum number of receptors pharmaceutical companies are required to test. *Id.*

¹⁴² Bowes et al., *supra* note 21, at 909 (citing European Medicines Agency (EMA), *ICH Topic S7B*:

minimum panel of targets to the ICH guidance documents and also encourage pharmaceutical companies to test additional targets as needed. The Code of Federal Regulations already includes a section specifically for the IND Application,¹⁴³ so this is likely an appropriate provision to clearly add minimum in vitro screening¹⁴⁴ as a requirement for an IND application at the beginning of the drug development phase.

Of course, decreasing the high attrition rate in the drug discovery and drug development process is paramount in the pharmaceutical industry to ensure a successful and profitable road to market.¹⁴⁵ It is in the consumers' best interest that the FDA continues vigorous testing and safety requirements on these companies to ensure safe, effective products in the marketplace. In the 1990s, certain criticism was given to inadequacies in FDA and drug manufacturer communication regarding the design of clinical trial research.¹⁴⁶ Mass standardization of in vitro secondary pharmacology studies could further enhance the understanding of how secondary pharmacology predicts effective dosage levels, side effects, and safe alternative uses for drugs in the future.¹⁴⁷ Standardization of testing concentrations and target naming in a large dataset may increase greater understanding of in vitro studies, their outcomes, and their effects.¹⁴⁸

It is important to consider how crucial drug approval is from a consumer perspective.¹⁴⁹ The public is unable to perform such rigorous safety tests on each

The nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (2005)). The hERG protein, if blocked, can prompt potentially fatal cardiac arrhythmias. *Id.* The severity of this adverse drug reaction is one reason why this assay is a "mandatory regulatory requirement." *Id.*

¹⁴³ 21 C.F.R. § 312.23 (2024).

¹⁴⁴ Bowes et al., *supra* note 21, at 911. The Bowes study compared the lists of targets from each of the four major pharmaceutical companies and defined a minimum panel of targets that are tested in at least three out of the four companies. *Id.*

¹⁴⁵ *Id.* at 909.

¹⁴⁶ Greenberg, *supra* note 27, at 343 (citing *Drugs and Biologics: Hearings Before the Subcomm. on Oversight and Investigations of the House Comm. on Commerce*, 104th Cong. 13–15 (1995) (Statement of Christian W. Nolet, National Director, Life Sciences Industry Group) (noting costly delays to clinical research were linked to "confusing [FDA] communications" and "inadequate guidance.")).

¹⁴⁷ *See generally* Bowes et al., *supra* note 21.

¹⁴⁸ Dodson et al., *supra* note 23 (noting "we can determine the receptors that are tested most frequently and use the compiled data to link secondary pharmacology data to clinical safety outcomes. The analysis of such data can aid in the standardization of secondary pharmacology studies and therefore bolster uniformity across the pharmaceutical industry."). "As there is no standardized target naming system across the pharmaceutical industry, the results can be difficult to interpret and assess potential safety concerns. Previous studies conducted by Bowes et al. and Dodson et al. have addressed the variation in the content of secondary pharmacology reports." Scott et al., *supra* note 19.

¹⁴⁹ *See* Greenberg, *supra* note 27, at 665–66 (There are various consumer risks associated with the release of new drugs to market. These include harmful drugs, ineffective drugs that cause an

drug they take, particularly on an individual basis.¹⁵⁰ Ultimately, the consequences of untested drugs are borne by the consumers rather than the pharmaceutical stockholders. As such, the FDA strives to balance both the costs and the risks to consumers that accompany drug regulation.¹⁵¹ This is seemingly paradoxical,¹⁵² yet the alternative runs counter to the general policy of supporting federal regulation of new medicine entering the marketplace. Inadequately testing the safety and efficacy of new drugs can pose serious risks to public health.¹⁵³ Additionally, the premature introduction of new drugs can create problems such as uncertainty about the effectiveness of different treatments and a reduction in the number of individuals willing to participate in clinical trials.¹⁵⁴

CONCLUSION

The construction of a suitable legal framework for the creation of new drugs is one of the trickiest issues in science and technology policy.¹⁵⁵ Several legal issues pair with the drug development industry, including intellectual property protection, marketing approval, and liability sharing.¹⁵⁶ The FDA ensures public safety by enforcing rigorous standards that require manufacturers to demonstrate the safety and effectiveness of new medications.¹⁵⁷ To reduce the high rate of attrition in drug development, there is a trend towards focusing on drug safety earlier in the drug discovery process.¹⁵⁸ This primarily includes the routine use of high-capacity in vitro pharmacology panels.¹⁵⁹ It is clear that in the case of secondary pharmacology studies in IND applications, scientific development has surpassed regulation, leaving a gap in the oversight of preclinical drug safety assessments. The scientific utility of in vitro safety screens is clear, but the regulation and standardization of these

individual to forego alternative treatment, and a more “subtle form of consumer risk” involving the availability of prescription drugs that actually perform the treatments for which they are prescribed.)

¹⁵⁰ *Id.* at 665 n.4 (noting that the public is unable to assess the potential dangers of a new drug considering how complex the drug evaluation process is and how important clinical information is only produced subject to FDA regulatory standards.).

¹⁵¹ Greenberg, *supra* note 27, at 296–97. The costs to regulation involve fewer drugs reaching the market, while the risks to regulation include safety and inefficacy concerns. *Id.*

¹⁵² Van Norman, *supra* note 18, at 171 (noting, “the drug/device development environment in the United States involves a constant balance between accelerating pressures to expedite effective therapies to the public, and the mission to minimize major adverse events.”).

¹⁵³ Greenberg, *supra* note 27, at 297.

¹⁵⁴ *Id.*

¹⁵⁵ Bohrer & Prince, *supra* note 75, at 366.

¹⁵⁶ *Id.*; see also Food and Drug Administration Modernization Act of 1997, 21 U.S.C. § 301 (1997).

¹⁵⁷ See Greenberg, *supra* note 27, at 298.

¹⁵⁸ Bowes et al., *supra* note 21, at 919.

¹⁵⁹ *Id.*

studies have not been updated. The regulation of in vitro secondary pharmacology studies would standardize in vitro pharmacological safety profiling, making the potential liability for off-target effects, dose selection, and clinical trial design more readily apparent.¹⁶⁰ The increase in standardization may aid in understanding the link between preclinical and clinical drug studies¹⁶¹ and streamline the identification of safety liabilities early on for a drug candidate.¹⁶²

¹⁶⁰ See Papoian et al., *supra* note 16 at 294 (“Information on the potency of a drug for a given biological target can be used to determine structure–activity relationships, assess potential liability for off-target effects, and influence early clinical trial design, dose selection and patient monitoring.”).

¹⁶¹ Dodson et al., *supra* note 23, at 1.

¹⁶² Scott et al., *supra* note 19, at 1 (encouraging “FDA-industry collaborative working groups” to develop best practices for regulatory submission of secondary pharmacology data and facilitate the creation of a standard target panel.).