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I. Introduction

Drugs and other pharmaceutical products are of such great importance, both to public health and to the national economy, that the issues surrounding their development, approval, use, and effects have spawned a considerable volume of litigation. Drug and pharmaceutical litigation can be broken down into three important categories based on distinct stages at which litigation is likely to arise. These include (1) suits for and against Food and Drug Administration (FDA) approval of new or reformulated drugs, which occur both before and after the drug is available on the market, (2) false advertising and patent infringement suits that develop as a result of the marketing of the drug, and (3) products liability suits that develop as a result of consumers' use of the drug.[1]

At each of these potential stages of litigation, parties are likely to encounter the concept of (or at least the use of the phrase) "clinical significance." This Note will demonstrate an absence of definition and an unevenness of understanding and application of that phrase in all of these drug-related contexts.[2]

It is not necessarily the case that the phrase itself is innately flawed (although "significance" is certainly a word that can present difficulties in interpretation).[3] When the words "clinical" and "significant" have specific

1. Another way in which it is possible to characterize these three types of cases is in terms of the typical party structure underlying them. FDA approval cases are typically Drug Company vs. United States Government. Patent infringement and false advertising cases are typically Drug Company vs. Competitor Drug Company. Products liability cases are typically Consumer vs. Drug Company. This varying structure is important in understanding the different roles that drug companies, in particular, must play in the different drug-related contexts.

2. *Infra* Part II.

3. *See infra* Part V.C (discussing problematic use of word "significance").

definitions, either alone or in concert, for a given context, the potential problems are minimized, if not obviated entirely.[4] Such definitions may come from statutes or from precedents in case law.[5] The definitions may be, and

4. Even when there is some consensus on a meaning of or a standard for the phrase "clinical significance," there still may be disputes on related issues; consensus on that element would not necessarily solve all of the problems. Even when an objective threshold exists for defining "clinically significant" evidence of a given disease, this does not settle the crucial question of causation. The causation analysis is related to the definitional problem, as there are cases that do associate the two concepts. For example, in a case of asbestos exposure, while there was no doubt that as a cumulative result of years of employment, a worker had contracted asbestosis, the question of clinical significance concerned the extent to which the last employer of a disabled worker should be liable for contribution to the disease acquired over a longer course of employment. *See* Mathis v. State Accident Ins. Fund, 499 P.2d 1331, 1333 (Or. Ct. App. 1972) (stating that principal issue on appeal is extent to which last employer of disabled workman caused or contributed to disability). The last employer conceded that there had been "some minimal degree of inhalation of asbestos fibers" during the final employment period, but it was deemed "not medically probable that *clinically significant* exposure to asbestos occurred during the four months at the last employer." *Id.* (emphasis added). This indicates that clinical significance is in some way related to causation, but fails to explain that association explicitly.

5. One example of this definition occurs in the context of Black Lung benefits cases, in which coal miners or their widows may claim workers' compensation benefits for the disease pneumoconiosis ("Black Lung disease"). To do so, the first thing that the claimant must prove is that he has the disease. 20 C.F.R. §§ 718.202, 718.205(a)(1) (2001). One of the ways in which he may do this is by means of radiographic (i.e. X-ray) evidence. *Id.* § 718.202(a)(1) (2). The relevant case law and statutes have established specific standards for finding this evidence "significant," such that a score of 1/0 or better on the X-ray reading indicates significant evidence of pneumoconiosis, while a score of 0/1 indicates no significance. Shuck v. Consolidation Coal Co., No. 99-2521, 2001 WL 120000, at *4 (4th Cir. Feb. 13, 2001). These standards cover the identification of the disease. The "significance" analyses in these cases and statutes are concerned with causation as well because to be eligible for benefits, the claimant must show that the pneumoconiosis arose at least in part out of coal mine employment. 20 C.F.R. § 718.203(a) (2001). Therefore, there are precise definitions for "significance" in that context as well. In the miners' cases, the standard for whether pneumoconiosis was significant in creating a total disability considers whether "the miner's pneumoconiosis arose at least in part out of coal mine employment." *Id.* § 718.203(a). In the widows' cases, the standard for significance is whether "pneumoconiosis was a substantially contributing cause or factor leading to the miner's death" (which the regulation glosses as "hastening the miner's death"). *Id.* § 718.205(c)(2), (5).

There still may be disagreement among experts in the reading of individual X-rays to decide whether the objective threshold (as to the existence of the disease) has been reached in a particular case. *See* Burchett v. Matthews, 575 F.2d 1189, 1190 (6th Cir. 1978) (citing conflicting reading and scoring of X-ray evidence). However, there is at least a recognized standard from which to work. *See* Colvert v. Ala. By-Prods. Corp., 115 F. Supp 493, 496-99 (N.D. Ala. 1953) (noting "unanimous agreement [among a group of specialists] that essential to the diagnosis of the clinically significant disease of pneumonoconiosis was roentgenographic identification of the disease in an X-ray of the chest," and noting that their agreement also is "currently accepted by an overwhelming majority of members of [the] medical profession who specialize in lung diseases," and rejecting other apparently less objective standards proposed by specialists in the minority).

indeed may have to be, only for very narrowly limited contexts.[6] When these definitions appear, there is clarity and uniformity sufficient to make the terms useful in their given context.

However, despite this apparent capacity for precision of meaning and relative uniformity of understanding when the terms are defined and used separately, confusion and ambiguity are much more typical where the phrase "clinical significance" is concerned. The contrast between the majority and the dissenting opinions in a Sixth Circuit case, *Glaser v. Thompson Medical Co.*,[7] exemplifies the confusion.[8] Although the majority in *Glaser* uses the phrase "clinical significance" several times throughout its opinion, nowhere does it provide any definition or explication. The best indication of the

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While these standards can be tied only to the word "significant," rather than to the entire phrase "clinical significance," the addition of "clinical" often appears in the Black Lung case law. Relevant medical definitions, for example, of chronic obstructive pulmonary disease (COPD), which are sometimes cited in the Black Lung cases, may incorporate the phrase. *See* Smith v. Dir., Office of Workers' Comp. Progs., Dep't of Labor, 999 F.2d 540 (6th Cir. 1993) (citing THE MERCK MANUAL 628 (14th 1982), which defines COPD as "clinically significant, irreversible, generalized airways obstruction associated with varying degrees of chronic bronchitis, abnormalities in small airways, and emphysema"). In this way, and even more directly, as shall appear in further discussions in this Note, the phrase has a way of creeping into the legal terminology in a somewhat misleading way, as even here there is no explicit definition for "clinical significance."

6. *See supra* note 5 (narrowing context to one means of finding one disease). It is perhaps realistic to acknowledge at the outset the possibility that one may be able to define the phrase only in a narrow context for a very precise issue, disease, or drug. As one author has pointed out, "importance" (the same, for the purposes of this Note, as "significance") is always necessarily context-specific. *See* WILLIAM A. SILVERMAN, HUMAN EXPERIMENTATION: A GUIDED STEP INTO THE UNKNOWN 121 (1985) (stating that "the definition of an 'important' difference requires some review from the point of view of the underlying theories about the pathologic process that is under study"). Because of the broad range of topics involved, it might be unrealistic to attempt to define clinical significance across the board for all drug cases. This is precisely why, after closer examination, it may appear to make little sense to use the phrase "clinical significance" in the ways in which it is currently used – that is, without more explicit, precise, and context-specific definitions.

7. 32 F.3d 969 (6th Cir. 1994).

8. Glaser v. Thompson Med. Co., 32 F.3d 969 (6th Cir. 1994). In *Glaser*, a consumer brought a suit for negligence and breach of warranty against a pharmaceutical company on the grounds that ingestion of the drug Dexatrim caused hypertension, which in turn caused a stroke, which in turn caused the consumer to fall, hit his head, and suffer further severe injuries. *Id.* at 970-71. The district court granted summary judgment to the drug company, but the appeals court remanded the case due to unresolved issues of material fact as to questions of causation at each stage of the events alleged. *Id.* In analyzing causation, the court looked to studies performed on the drug, without being able to reach a conclusion on the question of whether it could cause hypertension. *Id.* at 975. Aside from the studies themselves, the court also emphasized the qualifications of the expert physician involved, in terms of his experience and expertise. *Id.* at 972, 975.

majority's understanding is its apparent reliance on one expert's statement that the averages necessarily involved in finding "statistical significance" actually hide the real variations that are "clinically significant" for individual patients.[9] This suggests a vague idea of clinical significance as something that can be determined by an individual physician by observation of an individual patient, in spite of statistics suggesting that the observation, and more importantly, the causal relationship posited, is untrustworthy. In his dissent in *Glaser*, Judge Boggs shows less confidence in the same expert's evidence.[10] He points to testimony from the expert's deposition that demonstrates the uncertainty of the expert's conclusions, as well as the flaws in the implications on which the court has relied.[11] He points to evidence of statistical significance without clinical significance and points out that "significant" in this context, when unmodified, really means "statistically significant."[12] It thus appears that even a single court cannot come to an agreement about the proper usage and meaning of the phrase "clinical significance."

This lack of clarity and uniformity presents a host of problems. It is not simply an academic problem of language and syntax, but also a practical problem that stands in the way of the clarity and predictability desirable for fair and efficient administration of the law.[13] The possible ramifications are serious.

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9. *Id.* at 975.

10. *Id.* at 979.

11. *See id.* at 981-82 (stressing expert's use of "opinion," "in my mind," "maybe," and "I believe" in expressing his testimony). Judge Boggs also noted: "A good bit of the disagreement that I have with the court's opinion is in its use, or acceptance of Dr. Zaloga's use, of words such as 'cause' and 'significantly.'" *Id.* at 988.

12. *Id.* at 983-984.

13. There are, of course, other important legal and non-legal ramifications here as well. One closely related example in the pharmaceutical context is the duty imposed upon pharmacists to recognize "clinically significant" drug interactions and to discuss them with the prescribing physician. *See, e.g.*, Paul G. Gussing, *A Comparison of Empirical Studies of Pharmacy Practice with Judicial Descriptions*, 44 DRAKE L. REV. 483, 495-497 (1996) (listing representative tasks of pharmacist including questioning prescribing physician about cases in which clinically significant drug interactions or contraindications exist); David W. Hepplewhite, *A Traditional Legal Analysis of the Roles and Duties of Pharmacists*, 44 DRAKE L. REV. 519, 566 (1996) (requiring that pharmacology candidates "be able to recognize clinically significant drug-drug or food-drug interactions, recognize the mechanism of interaction, and select alternative measures to minimize or reduce the interaction"); Kathy Laughter Laizure, Note, *The Pharmacist's Duty to Warn When Dispensing Prescription Drugs: Recent Tennessee Developments*, 22 MEMPHIS ST. U. L. REV. 517, 537-38 (1992) (discussing pharmacists' use of clinical significance). Laizure explains:

> Drug interactions, however, vary greatly in clinical significance, based on the probability that they will occur and the resulting effects of the interaction. This raises the question of when the pharmacist has the duty to intervene. Is the pharmacist required to intervene when the interaction is of moderate or minimal clinical

For example, if drug companies do not know what the definition of "clinical significance" is, or how it will be implemented, or what weight it will bear, they stand at a disadvantage in presenting their cases. Even if one jurisdiction resolves these issues, that resolution may have no basis at all in another jurisdiction. Without a uniform concept – even within a very particular context – large drug companies involved in litigation in multiple jurisdictions may have to bring or defend similar claims inconsistently.

From another angle, those researching new drugs, if they have no definition of clinical significance, will not be able to structure their studies from the outset to determine whatever the Food and Drug Administration (FDA), another drug company, or a consumer may later require them to show in the way of "clinical significance." Furthermore, if the government and the drug companies do not have a clear understanding of clinical significance, and if it is actually important, consumers run the risk of harm from improperly studied drugs or from over- or under-cautiousness in the use of the drugs due to a clash of statistical and clinical significance. Finally, consumers face the same difficulties as the drug companies in bringing claims in ignorance of the ways in which clinical significance may be used in their cases.

All of these potential problems hamper the sort of predictability that makes the justice system work smoothly, efficiently, and fairly. The Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*[14] developed gatekeeping standards for objective scientific determinations.[15] The intention of

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> significance? For example, certain antibiotics are known to reduce the effectiveness of oral contraceptives when given concomitantly. Is the pharmacist negligent if he or she fails to advise the patient to utilize alternative methods of birth control while taking this medication, even though this is classified a Level 2, or moderately clinically significant, interaction?

Id. (citations omitted).

Of course there are many other contexts in which the phrase "clinical significance" appears, none of which will be a part of the discussion in this Note. Some examples from among these are cases dealing with psychological conditions, living wills, disability and workers' compensation (although Black Lung cases will be used briefly for comparison), and FAA medical certification regulations.

14. 509 U.S. 579 (1993).

15. *See* Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 589 n.7 (1993) (noting that "Rule 702 confides to the judge some gatekeeping responsibility" and undertaking "to note the nature and source of the duty"). This case involved a suit against a pharmaceutical manufacturer for birth defects (limb reductions) allegedly caused by mothers' ingestion of the drug Bendectin. *Id.* at 579. The Supreme Court stated that "general acceptance" was not the proper criterion for admitting expert scientific testimony. *Id.* at 588-89. The Court held that it is the role of the trial judge to determine both reliability and relevance of scientific evidence. *Id.* at 589. The Court established the following four factors for determining reliability ofthis evidence: (1) whether the inference or assertion was derived by "scientific method," namely whether the theory can be tested and falsified; (2) subjection to peer review and publication; (3) existence of a known

the *Daubert* Court was to increase the reliability of expert scientific evidence.[16] Without a uniform objective definition for "clinical significance" in the drug context, the phrase easily may present an opportunity for litigants to frustrate the *Daubert* standards by doing an end run around them, offering subjective medical judgments unsupported by reliable data.[17] Should this problem remain unaddressed, it may become only more pervasive. Thus, it is important to determine what "clinical significance" means (if it means anything) and how it may or may not be appropriate for use in each of these types of litigation.

As Justice Benjamin Cardozo pointed out in the context of trying to define "ordinary and necessary," "[o]ne struggles in vain for any verbal formula that will supply a ready touchstone. The standard set up by the statute is not a rule of law; it is rather a way of life. Life in all its fullness must supply the answer to the riddle."[18] Perhaps this is also true of the search for the meaning of "clinical significance," but it is important at least to attempt to find the answer to the current riddle in case law as well as legislative and academic materials.

This Note examines the ambiguous and inconsistent meanings of "clinical significance" in four different modes of analysis.[19] Part II examines closely the vocabulary and syntax that courts have used in discussing clinical significance.[20] This section demonstrates the ambiguity, subjectivity, and inconsistency of the phrase as it is currently used. Part III examines and analyzes the use of the phrase "clinical significance" in the context of drug

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or potential error rate; and (4) general acceptance in the relevant scientific community. *Id.* at 589-95.

16. *See id.* at 590 n.9 (stressing importance of "evidentiary reliability" of scientific evidence). The *Daubert* standards require that an expert demonstrate that his conclusions are based in "a grounding in the methods and procedures of science" and that they constitute "more than subjective belief or unsupported speculation." *Id.* at 590.

17. *See infra* notes 78-84 and accompanying text (discussing *Linnen v. A.H. Robins Co.*, No. CIV.A.97-2307, 2000 WL 145758 (Mass. Super. Ct. Jan. 4, 2000)). *Linnen* illustrates how litigants can use a malleable formulation of "clinical significance" to frustrate *Daubert*.

18. Welch v. Helvering, 290 U.S. 111, 115 (1933).

19. The logical first step in approaching this problem is to look for an explicit definition in case law or statutes. This approach, however, has proven largely futile. While it is always difficult to prove a negative, there are enough instances in which a definition might be expected, and in which no definition appears, that one can have relative confidence in the general absence of a definition. An extensive search of print publications as well as websites and search engines related to the Code of Federal Regulations (CFR), the Federal Register, and the FDA (as well as its subsidiaries, the Center for Drug Evaluation and Research (CDER) and the Centers for Disease Control and Prevention (CDC)) has revealed nothing in the way of an explicit definition.

20. *Infra* Part II.

litigation.[21] This section attempts to uncover an indirect definition of the phrase by comparing and contrasting what clinical significance means and how it can be demonstrated in the three primary types of drug litigation. Part IV compares the concept of "clinical significance" with the more defined concept of "statistical significance."[22] Part V examines the use of the phrase in contexts outside of case law – first in regulatory and then in academic settings – both legal and medical in nature.[23] The Note concludes by evaluating several possible understandings of "clinical significance" and suggesting how, if at all, courts and litigants should understand and apply that concept.[24]

II. Looking at the Language of Ambiguity and Subjectivity

A. Vocabulary

The vocabulary surrounding the use of the phrase "clinical significance" demonstrates an uncertainty of meaning and a lack of standardization that calls into question its usefulness as an objective scientific standard. The verbs used to proclaim the presence or absence of clinical significance are particularly enlightening in this enquiry. Experts in the cases often "feel,"[25] "believe,"[26] or "opine,"[27] rather than stating outright that there is (or is not)

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21. *Infra* Part III.

22. *Infra* Part IV. This discussion also will incorporate the usage and meanings, for comparative purposes, of "medical significance" and "therapeutic significance." However, due to the clarity with which we can define statistical significance, that phrase will provide the focal point for all of these comparisons. *See infra* note 97 (defining statistical significance).

23. *Infra* Part V.

24. *Infra* Part VI.

25. *See* Cortez v. Brown, 408 So. 2d 464, 465 (Miss. 1991) (quoting physician's expert testimony: "*I felt that* this was not of clinical significance, since she had no symptoms referable to the right side.") (emphasis added).

26. *See, e.g.*, Taylor v. Shalala, No. CIV.A.92-7226, 1994 WL 111376, at *6 (E.D. Pa. Mar. 31, 1994) (citing opinion of examining physician who "agreed that [the plaintiff] had spinal stenosis, but *believed* that it was 'not functionally symptomatic or clinically significant'") (emphasis added); Riehm v. Sullivan, No. 89C20388, 1990 WL 304303, at *3 (N.D. Ill. Dec. 11, 1990) ("X[-]rays appeared normal with the exception of a tiny osteophyte on the anterior aspect of the Tibia. Dr. Treister *believed* this was not clinically significant.") (emphasis added); Volterano v. W.C.A.B. (Allied Corp. & Travelers Ins. Co.), 613 A.2d 61, 62 (Pa. Commw. Ct. 1992) (citing physician's conclusion that "[c]laimant was an 'emotional cripple' from asbestos exposure *'not as clinically significant as [claimant] believes'* . . . ") (emphasis added); Scott v. Porter, 530 S.E.2d 389, 391 (S.C. Ct. App. 2000) (stating, in wrongful death case, "[Dr.] Porter *did not believe* that Lance's low sodium levels were clinically significant") (emphasis added).

27. *See, e.g.*, Talley v. Sec'y of Dep't of Health & Human Servs., 945 F.2d 405, 405 (6th Cir. 1991) (noting that physician "*opined* that Talley had had 'clinically significant' arterial sclerosis since 1983" but stating that "[physician's] *opinion does not contain the specific findings that are necessary* to support a determination that Talley suffered from a listed impairment

clinical significance in a given situation. There is a tendency to use the passive voice to state that a symptom or condition, for example, "is not thought to be" clinically significant.[28] Similarly, the words "possible" and "unknown" often qualify the phrase.[29] One commentator remarks on the "difficulty of judging whether or not the [finding] is clinically significant."[30] This vocabulary not only underscores the lack of clarity associated with the phrase, but it also undermines any value a determination of "clinical significance" might lend to the questions of causation that so frequently lie at the heart of drug-related cases.

B. Usage and Syntax

There are interesting aspects of usage and syntax in a few cases that call into question the objective certainty of the meaning of the phrase, as well as the certainty with which courts demonstrate their understanding of the phrase. There are even instances showing a certain reluctance to use the phrase at all. One example of this is in the use of so-called "scare quotes." A court that is not actually quoting from another source may nevertheless set the phrase inside quotation marks.[31] The court seems in this way to indicate to the reader

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before February of 1985") (emphasis added); Edwards v. Sullivan, No. CIV.A.89-8882, 1990 WL 118750, at *2 (E.D. Pa. Aug. 14, 1990) ("Dr. Klinghoffer *opined* that the finding was *of questionable clinical significance*.") (emphasis added); Follmer Trucking v. Stump, 286 A.2d 1, 4 (Pa. Commw. Ct. 1972) (citing testimony of physician, describing plaintiff's condition: "which hemorrhage being described as slight and, in the *opinion* of the pathologist, *of little clinical significance*") (emphasis added); Boye v. Moore, No. 03A01-9812-CV-00424, 1999 WL 1068699, at *2 (Tenn. Ct. App. Nov. 24, 1999) ("The physician, who examined the scan at the hospital, *opined* that the abnormality was of '*doubtful clinical significance*' . . . ") (emphasis added).

28. *See* Kue v. Sec'y of Dep't of Health & Human Servs., 18 Cl. Ct. 777, 781 (1989) (remarking on "bacteria not thought to be of clinical significance" in regard to infant's death after receiving DPT vaccine).

29. *See* Tobias v. Shalala, No. CIV.A.93-0188, 1993 WL 370637, at *2 (E.D. La. Sept. 15, 1993) (citing, in Social Security benefits case, physician's testimony: "Dr. James W. Keating, Jr. *opined* that plaintiff had [a condition] which was *possibly* clinically significant . . . .") (emphasis added); *see also* McNeil Pharm. v. Hawkins, 686 A.2d 567, 572 (D.C. 1996) (citing FDA-approved warning label statement: "Rarely, a patient may note discoloration of the urine resulting from a phenolic metabolite of chlorozoxazone. This finding is of *no known clinical significance*.") (emphasis added); Duffield v. Sec'y of Dep't of Health & Human Servs., No. 90-827V, 1991 WL 275005, at *5 n.19 (Cl. Ct. Dec. 2, 1991) (citing notation to study by cytogeneticist, who found that chromosomal anomaly had "*no known clinical significance*") (emphasis added).

30. Mendel E. Singer, *BRCA1: To Test or Not to Test, That is the Question*, 7 HEALTH MATRIX 163, 176 (1997).

31. *See* ZMI Corp. v. Physio-Control Corp., 887 F.2d 1094 (Table), 1989 WL 100888, at **1 (W.D. Wash. 1989) (summarizing one party's arguments and evidence, but selectively

that this is a phrase that they have used either because the parties involved have used it or because it is a phrase that is typically used in this type of case. In either case, this usage conveys a possible element of discomfort with the phrase. The extra punctuation may indicate that the court is not certain enough of the meaning of the phrase, for itself or for its readers, to use it without reservation. If, on the other hand, the phrase is placed in quotation marks because it alone is taken as a direct citation from another source, the phrase still stands out, as if to denote rather obviously, "this is not our own phrase, but we shall use it because someone else did" (or perhaps, more simply, "whatever that may mean").[32]

C. *Difference of Reasonable Minds and Credibility of Experts*

The fact that reasonable minds often differ over findings of clinical significance underscores the idea that "clinical significance" is not based on an objective standard, but a subjective impression. One court states that the decision before it regarding a battle of experts who differ as to the presence of clinical significance can be distilled to a simple credibility determination between the two.[33] Another court examined the testimony of two experts on the issue of whether there was a clinically significant difference between two competing drugs, only to decide that they found neither expert to be reliable, and preferred to consider the raw data independently.[34]

D. *Evaluation*

Examination of the language involved in the use of the phrase "clinical significance" in medically-related case law demonstrates a certain ambiguity not only of actual meaning, but also of understanding. It appears that not even all of the courts who use the phrase believe that they, or those arguing and testifying before them, have a clear understanding of what it means. Further-

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placing phrase "clinical significance" in quotation marks); *see also* Charles J. Walsh & Marc S. Klein, *From Dog Food to Prescription Drug Advertising: Litigating False Scientific Establishment Claims Under the Lanham Act*, 22 SETON HALL L. REV. 389, 436 (1991) (setting "clinical significance" in quotation marks and leaving "statistical significance" without them).

32. See *supra* note 31 for an example that may demonstrate this implication simply by the tenor of the usage.

33. *See* Bennett-Murray, Inc. v. Barnes, 473 S.E.2d 166, 167-68 (Ga. Ct. App. 1996). (citing, in workers' compensation context, absolute disagreement between two physicians as to clinical significance of patient's symptoms, noting that this simply leads to determination by court of superior credit and weight of one expert's opinion over another's).

34. *See* Am. Home Prods. Corp. v. Johnson & Johnson, 436 F. Supp. 785, 792-93 (S.D.N.Y. 1977) (stating court's dissatisfaction with both sides' expert opinions, finding experts' analyses unreliable, illogical, and unhelpful, and using raw data to draw direct conclusions).

more, the ambiguity appears to run in the direction of subjectivity, a direction that leads away from an objective or uniform standard. The purpose of this discussion is not to construct an iron man of objectivity out of the field of science, against which the straw man of legal language would stand no chance. It is instead to demonstrate that the standard, if any, that is used in the legal context is far less objective than the field of science might allow. This is not an attempt to set up a dichotomy, but only to uncover a lack of objectivity by means of a simple comparison.

III. Attempts at Discerning Definition Through Context

A. FDA Approval Cases

The FDA's approval and labeling procedures and requirements for new or reformulated drugs require an applicant to demonstrate the product's "effectiveness."[35] The requirement of effectiveness includes a showing not only of statistical, but also of clinical significance.[36] However, there is no apparent statutory or regulatory definition of "clinical significance."[37] Nevertheless, an examination of the use of the phrase "clinical significance" in the cases dealing with FDA approval may shed some light on the understandings of those who enforce the requirement, as well as those in the drug industry who must argue about it.[38]

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35. *See* 21 C.F.R. § 314.50 (d)(5)(iv) (2001) (including discussion of effectiveness in list of items required in application for approval of new drug). The definition of "effectiveness" used throughout the relevant portions of the CFR is as follows: "a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide *clinically significant* relief of the type claimed." *Id.* § 330.10 (emphasis added).

36. The Food, Drug, and Cosmetic Act does not itself provide explicitly for how the proponent must demonstrate effectiveness, other than to say "proof of effectiveness shall consist of controlled clinical investigations . . . ." *Id.* § 601.25. (The reference to "controlled clinical investigations" appears in the application requirements as well.) *Id.* § 314.50(d)(5)(iv). However, the FDA has the authority to construe a statute with whose administration it is charged and receives substantial deference when doing so. *See* Warner-Lambert Co. v. Heckler, 787 F.2d 147, 155 (3d Cir. 1986) (citing *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), for this proposition). The FDA has interpreted the language of the Act as requiring both statistical and clinical significance. *See Warner-Lambert*, 787 F.2d at 154-56 (approving FDA's interpretation).

37. *See infra* Part V.A (discussing usage without definition in CFR). Indeed, even an extensive examination of the websites of the FDA, the CDER, and the CDC affords no explanation or definition.

38. It is important to address not only how the FDA argues clinical significance and how judges rule on it, but also how the drug companies involved in litigation either against the FDA or against other drug companies may press for different understandings of the meanings and standards involved. The following example shows in greater depth the way in which this problem works in the approval cases.

1. What Does "Clinical Significance" Mean?

United States v. 225 Cartons, More or Less, of an Article of Drug (225 Cartons II)[39] comes as close as any of the drug approval cases to providing an actual definition of "clinical significance."[40] It sets off the word "clinically" with an appositive phrase, directly associating "clinically" with "therapeutically."[41] In *225 Cartons II*, as well as in *Serono Laboratories, Inc. v. Shalala*,[42] "significance" appears to require, as a threshold finding, some sort of observable effect.[43] Without some observable difference or change in status, there

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Warner-Lambert Co. v. Heckler, 787 F.2d 147 (3d Cir. 1986), demonstrates the lack of clarity in the meaning of clinical significance, as well as the tension between the use of clinical significance and statistical significance in approval cases. *Id.* at 154-56. In *Warner-Lambert*, drug manufacturers petitioned for review of an FDA decision to withdraw approval for oral proteolytic enzymes (OPEs). *Id.* at 148-49. OPEs are prescription drugs that manufacturers claim to be effective in alleviating swelling and inflammation. *Id.* at 149. The OPEs in this case previously had obtained approval under the pre-1962 "safe for human use" standard. *Id.* at 149. However, when the standard was changed in 1962 to require a showing of "substantial evidence" of "effectiveness," the old drugs had to meet the new guidelines. *Id.* at 151. The Third Circuit held that the FDA requirement of showing "effectiveness" was not satisfied by a showing of statistical significance alone, but required a showing of effectiveness in terms of "clinical significance." *Id.* at 156. While the regulations, as interpreted by the case law, require a finding of clinical as well as statistical significance for new drug approval, the Code of Federal Regulations provides no definition of clinical significance. *See infra* Part V.A. The *Warner-Lambert* court equated clinical significance with "therapeutic significance" and contrasted it with statistical significance, but did not provide any explicit definition of either term. *Warner-Lambert*, 787 F.2d at 154-156. Perhaps because there is a clearer general understanding of an objective standard for determining statistical significance, the drug company preferred simply to rely on that standard as a benchmark for comparison. *Id.* at 154. However, the court required that the further standard of clinical significance be met as well. *Id.* at 156, 163. If drug companies, in particular, lack an understanding of what that standard of clinical significance entails, and particularly if they lack that understanding during the development and clinical trial process, they are seriously handicapped in the approval process and in the litigation that process may spawn. A challenger to approval (other than the government) of course would meet with the same difficulty, but this Note focuses primarily on the position of the drug companies.

39. 871 F.2d 409 (3d Cir. 1989).

40. *See* United States v. 225 Cartons, More or Less, of an Article of Drug, 871 F.2d 409, 411, 420 (3d Cir. 1989) [hereinafter 225 Cartons II] (affirming district court in *United States v. 225 Cartons, More or Less, of an Article of Drug*, 687 F. Supp. 946 (D.N.J. 1988) [hereinafter *225 Cartons I*]). The court required that effectiveness be shown by means of clinical evidence. *Id.* at 417. The court reasoned that statements concerning the old formula are inadequate if the two are not bioequivalents and that adequate, well-controlled studies are legally necessary to show effectiveness. *Id.* at 417-19.

41. *Id.* at 416 (referring to previous decision, *Warner-Lambert*, 787 F.2d at 155, in which court "found persuasive the Commissioner's interpretation of the statutory requirement of effectiveness as requiring a showing that patients will receive a clinically, i.e., therapeutically, significant benefit from the drug").

42. 158 F.3d 1313 (D.C. Cir. 1998).

43. *See 225 Cartons II*, 871 F.2d at 416 (requiring "real clinical contribution"); *see also* Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (indicating that difference

can be no significance of *any* kind. "Significance," in *Serono Labs*, *could* simply denote *any* observable effect, but it appears that there may be more to the requirement because the argument in the case is, at one level, over the question of whether there can be a difference without significance.[44] The answer to this question is affirmative, so while a difference alone is not enough, there is no clear indication of what the further element might be.[45]

Relevant portions of the Code of Federal Regulations (CFR) define "effectiveness" as "a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug . . . will provide clinically significant relief of the type claimed."[46] It is possible to argue that the word "relief" indicates that a difference between two drugs should produce a difference of effect palpable to the consumer to reach the level of clinical significance.[47] This would suggest a highly subjective standard based on consumers' individual perceptions. On the other hand, a passage from *225 Cartons II* suggests that a finding may have clinical significance without even being necessary for the effect claimed for it, so the individual perception of the consumer may, therefore, be unnecessary to the determination.[48]

This leads to the question of causation. On the one hand, clinical significance may be a concept applicable to determinations of the *existence* of a disease or condition. On the other hand, it may be a concept applicable to *causation* determinations – that is, whether the drug was clinically significant in causing the condition. It is unclear whether the phrase as it is currently used is intended for both contexts or only one of the two and whether it has so broad a meaning as to apply in the same way to both analyses.

2. Where Does It Come From and How Can It Be Determined?

In contrast to the confusion surrounding *meaning*, the FDA approval cases demonstrate an impressive uniformity as to the types of research and

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alone is not enough). In *225 Cartons II*, a manufacturer sought an injunction preventing FDA approval of a new drug, which was granted, and appealed. *Id.* at 409-10. The court held that clinical equivalence is required between a pioneer and a generic drug. *Id.* at 410. The FDA said that if a variation is not clinically significant for the product's intended uses, it will not preclude a "sameness" finding for the clinical equivalence requirement. *Id.* at 411-412.

44. *See Serono Labs*, 158 F.3d at 1316-20 (examining questions of chemical equivalence, chemical identity, and limitations on inherent variations in discussion that, in effect, asks whether difference can exist between pioneer and generic drug without significance).

45. *See id.* (deferring to FDA's view that difference can exist without clinical significance).

46. 21 C.F.R. § 330.10 (2001).

47. *Id.* (referring to "clinically significant relief").

48. *See* 225 Cartons II, 871 F.2d 409, 419 (3d Cir. 1989) (requiring that each component of new drug formulation be proven to make "statistically significant clinical contribution to the effects claimed for the products").

evidence required to support a finding of "clinical significance." The cases are not identical in their specific requirements as to issues of formality of testing or research, size of test groups, re-analysis of previously gathered materials, or necessity of personal observation.[49] However, they are at least apparently unanimous in disallowing the idea of clinical significance found at the level of the individual subject – that is, in requiring some organized gathering of data from a larger group of subjects.[50] Each case shows a somewhat different understanding of what this research entails. In *Edison Pharmaceutical Co. v. FDA*,[51] the District of Columbia Circuit stated the following: "There are no well-controlled studies using blind and double-blind cross-over and randomization techniques or any other kind of control specified in 21 C.F.R. 130.12(a)(5)(ii), so that neither the clinical nor statistical significance of the reported results can be evaluated."[52] Similarly, in *225*

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49. On the factor of formality of studies, it will be helpful to describe and compare the standard types of epidemiological studies performed. "Case Control Studies" begin with a group that already has the disease (the test/case group). The researcher chooses a second group, matched except for the disease. The researcher then compares the two groups for past exposure to the study factor. Bruce R. Parker, *Understanding Epidemiology and its Use in Drug and Medical Device Litigation*, 65 DEF. COUNS. J. 35, 38 (1998). "Cohort Studies," on the other hand, examine the population exposed to a study factor and then compare that with an otherwise similar, but unexposed population. Thus, these studies compare the rate at which the disease develops in the two populations by comparing the risk ratios. *Id.* "Randomized Clinical Trials" compare the "efficacy and safety of two or more interventions or regimens." ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 185 (1986). These studies have four elements: (1) they are controlled; (2) significance is established statistically; (3) they are double-blind, when feasible; and (4) they are randomized (therapies are allocated by chance). *Id.* All three of these study methods are clearly at the other end of the spectrum of formality from the paradigm in which the individual physician observes an individual patient's condition and draws conclusions about the effects of a factor in the treatment.

Also worth noting is the apparent freedom with which the word "significant" is used in the context of clinical trials. Courts cite expert testimony regarding "significant clinical trials" without explaining by what standard (if any) the court, or the expert, determined the trial to be "significant." *See* Bickham v. Grant, No. 97-CA-01639-COA, 2001 WL 570018, at *18 (Miss. Ct. App. May 29, 2001) (referring to testimony concerning "significant clinical trial").

50. *See infra* notes 52-56 and accompanying text (discussing *Edison Pharmaceutical Co. v. FDA*, 513 F.2d 1063, 1070 (D.C. Cir. 1975), *225 Cartons I*, 687 F. Supp. 946 (D.N.J. 1988), and *Warner-Lambert Co. v. Heckler*, 787 F.2d 147 (3d Cir. 1986)).

51. 513 F.2d 1063 (D.C. Cir. 1975).

52. Edison Pharm. Co. v. FDA, 513 F.2d 1063, 1070 (D.C. Cir. 1975). *Edison* involved a petition for review of a final FDA order that a new drug was not approvable because of a lack of substantial evidence showing its safety and effectiveness. *Id.* at 1065. The court held that factual questions as to the double-blind test requirement for new drug approval were material questions of fact requiring a new evidentiary hearing. *Id.* at 1070-72. The court reiterated the rule that the burden is on the sponsor to show the effectiveness of the new drug. *Id.* at 1065. The court discussed, in this context, the "substantial evidence" requirement and various testing methods. *Id.* at 1065-66.

Cartons I,[53] the District Court of New Jersey pointed to the importance of published, well-controlled clinical studies as a basis without which, it asserted, it could not make a reliable determination as to any clinically and statistically significant contribution to the drugs at issue.[54]

In *Warner-Lambert*, without an explicit statement of the court's understanding of the meaning of "clinical significance," the Third Circuit cited the FDA "effectiveness" requirements, suggesting that for approval cases, clinical significance cannot come simply from an individual physician's observation of effects on one or even a few subjects.[55] In discussing the FDA requirement of substantial evidence, the *Warner-Lambert* court implied that a finding of effectiveness, directly associated in the CFR language with the concept of clinical significance, would *have* to come from formal clinical trials.[56] *Serono Labs* also suggested (again without expressing explicit rules to this effect) that a finding of clinical significance comes from more formal research and evidence, such as clinical trials and published literature.[57] Furthermore, there are also strict requirements regarding the extrapolation of results from clinical trials, namely that "the results of tests on other products cannot be extrapolated without published dissolution, bioavailability or bioequivalence studies on the products compared."[58] Thus, the case law is clear on the proper method of determining clinical significance in this context.

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53. 687 F. Supp. 946 (D.N.J. 1988).

54. *See 225 Cartons I*, 687 F. Supp. at 961 (pointing to necessity of formal, published, controlled studies for determination of clinical and statistical significance). In *225 Cartons I*, the United States took action on behalf of the FDA to seize two prescription drug products. *Id.* at 948. The court held that the available clinical studies did not establish safety and effectiveness as required, that the clinical investigations relied upon were not well-controlled or published, and that data from old studies (of the old formula) cannot be extrapolated in reference to the new formula. *Id.* at 960. This case provides an excellent example of the way in which the word "significance" can be overused to the point at which it loses meaning and force. *See id.* at 952-55 (using "significance" so often and in so many contexts, without explanation, as to make word relatively meaningless).

225 Cartons II later reaffirmed the requirement, stating that significance *must* be proven by [formal] studies. 225 Cartons II, 871 F.2d 409, 416 (3d Cir. 1989). In *225 Cartons II*, defendant Sandoz wanted to show "general recognition" and extrapolate from previously gathered data. *Id.* However, the court accepted the FDA's position that "published clinical investigations" were necessary. *Id.* at 419.

55. *Warner-Lambert*, 787 F.2d at 156; *see also supra* note 38 (providing further commentary on this case).

56. *See Warner-Lambert*, 787 F.2d at 157 (implying necessity of formal clinical trials by reference to CFR definition of effectiveness).

57. *See* Serono Labs. Inc. v. Shalala, 158 F.3d 1313, 1320 (D.C. Cir. 1998) (following judgment of expert who relied on clinical trials and published literature to find differences between two drugs).

58. *225 Cartons II*, 871 F.2d at 419.

Although the FDA approval cases are clear about how to *determine* clinical significance, they remain unclear about what clinical significance *is*. From the examples of *225 Cartons II*, *Warner-Lambert*, *Serono Labs*, and others, it is apparent that in this context, clinical significance is something more than a simple difference. However, the further element or consideration required remains obscure. One potential suggestion might be that it involves the perception of the individual consumer, but this would be so unquantifiable and so unwieldy a standard as to make it an unlikely candidate for such a broad scientific standard. Furthermore, there is enough clarity on the issue of formality of clinical trials in this context to support determinations of "clinical significance," that the standard likely would not be the individual consumer's perception. Thus, any further element beyond a simple "difference" remains undefined.

B. Patent Infringement and False Advertising Cases

The cases dealing with issues of patent infringement and false advertising demonstrate a certain reliance on the concept of clinical significance without any explicit definition of what that means.[59] These cases are concerned primarily with showing differences (or lack thereof) between two drugs. The question of whether those differences are "significant" forms the crux of the lawsuit. Furthermore, those differences may or may not be significant specifically in statistical or in clinical terms. It is this crucial distinction between statistical and clinical significance that requires further definition.[60]

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59. A third, less common, but related type of case involves use of alleged false statements to promote increased use for off-label purposes. *See* United States v. Parke-Davis, 147 F. Supp. 2d 39, 48-49 (D. Mass. 2001) (citing allegation that "[m]edical liaisons were instructed to tell physicians that a great deal of data existed that supported the safe use of Neurotonin at levels that exceed 4800 mg per day. However, clinically significant safety data existed at only 1800 mg per day," without defining term "clinically significant.").

60. As in the previous subsection, it will be helpful here to give an in-depth illustrative example of how this problem manifests itself in this type of case. An example from the false advertising context demonstrates not only the lack of definition when clinical significance is required and relied upon, but also the tension between the use of clinical and statistical significance. In *McNeil-P.P.C., Inc. v. Bristol-Myers Squibb Co.*, 755 F. Supp. 1206 (S.D.N.Y. 1990), one manufacturer of an analgesic containing acetaminophen sued another manufacturer that advertised that its own product, containing acetaminophen and caffeine, provided superior relief. *Id.* at 1207-10. (The products involved in this case were AF Excedrin and ES Tylenol. *Id.* at 1207-08.) In order to establish that an advertisement claiming test-proven superiority is false or misleading in violation of § 43(a) of the Lanham Act, a party must show that the scientific study underlying the claim was flawed. *See id.* at 1210-11 (citing Procter & Gamble Co. v. Chesebrough-Pond's Inc., 747 F.2d 114, 119 (2d Cir. 1984) and Alpo Petfoods, Inc. v. Ralston Purina Co., 720 F. Supp. 194, 213 (D.D.C. 1989)). (The relevant portion of the Lanham Act appears at 15 U.S.C. § 1125(a).) The two manufacturers in this case argued extensively over the use of statistical and clinical significance. *McNeil*, 755 F.Supp. at 1212-

1. What Does "Clinical Significance" Mean?

In the context of patent infringement and false advertising cases, there is even less indication of a clear meaning of "clinical significance" than there is in the approval cases. For example, in a case dealing with the bleaching effects of a dental care product, there are vague references to a "significant amount" of the product causing "clinically significant" bleaching, but there is no attempt to define a standard for clinical significance.[61] "Clinically significant" in this context could mean anything from "noticeable" to "substantial," or it could refer to a more defined standard, but these are only guesses. In *Mead Johnson & Co. v. Abbott Laboratories*,[62] there is a suggestion that clinical significance might be synonymous with "medical significance," but because neither term is further defined, this reference adds little to an understanding of either phrase.[63] In discussing claims about effects made in lay

19. Bristol-Myers argued that there was a statistically significant difference between the two products in favor of Excedrin, while McNeil denied the existence of any statistical difference. *Id.* at 1214. McNeil argued further that even if a statistical difference did exist, Bristol-Myers' claim was nonetheless false because no *clinically* significant difference existed. *Id.* at 1219 n.12. The court stated categorically, without further explanation, that a lack of clinical significance necessarily follows from a lack of statistical significance. *Id.* The court found that the statistical analyses were sufficient to meet the burden of proof. *Id.* at 1219. Statistical significance is defined clearly in the case as a ninety-five percent certainty that given results are not due to chance. *Id.* The court found that the statistical analyses were sufficient to meet the burden of proof. *Id.* at 1219. However, the court did not attempt to define clinical significance or to explain why it cannot exist in the absence of statistical significance. *Id.* at 1219 (providing no definition of clinical significance when one obviously would be helpful). Thus, in this type of litigation, as at the approval stage, the drug companies are faced with continuing uncertainty both as to the meaning of, or the standard for, this important term, "clinical significance," and as to the relationship of clinical significance to statistical significance.

61. *See* Ultradent Prods., Inc. v. Life-Like Cosmetics, Inc., 924 F. Supp. 1101, 1113 (D. Utah 1996) (providing only the following gloss on "clinically significant bleaching": "This means that a significant amount of the matrix material must remain in the tray at the end of two hours and that the bleaching agent dispersed in the matrix material must remain active so as to provide more than an insubstantial level of bleaching."). The most a reader can take from this gloss is that clinically significant means "significant" and not "insignificant." Because neither is defined, the gloss adds no meaning to the reader's understanding of clinical significance. There is also no indication how, if at all, this finding relates either to the identification of condition or to a causation analysis.

62. 41 F. Supp. 2d 879 (S.D. Ind. 1999).

63. *See* Mead Johnson & Co. v. Abbott Labs., 41 F. Supp. 2d 879, 883 (S.D. Ind. 1999) (aligning phrases "clinical significance" and "medical significance" without defining either), *rev'd on other grounds*, 201 F.3d 883 (7th Cir. 2000). In *Mead Johnson*, a manufacturer of one infant formula, Isomil, sued a competitor, the maker of Similac, for misleading advertising under the Lanham Act. *Id.* at 880-81. Abbott advertised Similac as "1st Choice of Doctors." *Id.* The court examined the substance of the claims of the advertisers and considered whether there was a basis for the claim of superiority. The court looked for evidence of a clinically significant difference between the products. *Id.* at 883. Having determined that no scientific

advertising, another court deciding a Lanham Act case stated that "[a] claim concerning a drug's effect made in lay advertising to consumers must be understood as representing that the effect will be experienced in humans and thus that it has some significance in a clinical context."[64] This raises again the possibility that clinical significance (if that is the meaning of "significance in a clinical context") could be a determination related to an individual consumer's perception of a drug's effects. Similarly, another case looked to demonstrations of differences in "symptomatic relief" provided by two different drugs.[65] In that case, however, there were objective methods of measuring the difference in relief achieved.[66] These cases leave us again with the vague idea that clinical significance denotes something that can be observed, but without any idea of the level at which it must be observable, or the level to which it must rise.

One case involving television commercials for non-prescription heartburn medications demonstrates the way in which definition of the term "clinical significance" may involve a battle of experts over characterization.[67] The parties directed the court's attention to six clinical studies, of which two showed statistically significant differences between the two products involved in the commercials, two showed no statistically significant differences, and two showed borderline statistical significance.[68] A battle of experts ensued over the borderline cases, with a disagreement as to whether

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evidence showed such a difference, the court allowed the testimony of a physician with "great expertise" in the area, whose evaluation it credited. *Id.* The court held that although there were some differences, there was no clinically significant difference between the two products. *Id.* The court granted Mead Johnson's motion for a preliminary injunction against Abbott. *Id.* at 908. On appeal, the Seventh Circuit reversed, holding that the phrase meant that more physicians favored the brand in question than favored other brands, not that the majority of physicians favored that brand. Mead Johnson & Co. v. Abbott Labs., 201 F.3d 883, 887 (7th Cir. 2000).

64. Am. Home Prods. Corp. v. Johnson & Johnson, 436 F. Supp. 785, 799 n.9 (S.D.N.Y. 1977). This case examined the question of whether Anacin, at over-the-counter dosages, reduces inflammation to a clinically significant extent in conditions listed in advertisements. *Id. passim.* The court held that the state of medical knowledge was not such as to allow a definitive conclusion as to the falsity of the claim. *Id.* at 801-03.

65. *See* Johnson & Johnson-Merck Consumer Pharms. Co. v. Rhone-Poulenc Rorer Pharms. Co., CIV.A.No. 91-7099, 1993 WL 21239, at *3-*4 (E.D. Pa. 1993) (discussing results of in vivo studies of antacids Mylanta II and ESMP).

66. *See id.* at *3 (discussing determinations of significant differences in effects of two antacids by measuring esophageal pH levels).

67. *See* SmithKline Beecham Consumer Healthcare, L.P. v. Johnson & Johnson-Merck Consumer Pharms. Co., No. 01CIV.2775(DAB), 2001 WL 588846, at *13 (S.D.N.Y. June 1, 2001) (denying SmithKline's request for preliminary injunction against Merck's commercial for Pepcid Complete).

68. *Id.* at *3.

a 7% difference[69] constituted a "modest" difference or a "clinically significant" difference between the products.[70] The court noted that the clinical differences, when reduced to absolute numbers, were indeed "modest."[71] There was no dispute concerning the methodology in the studies, nor the validity of their results, only concerning the characterization of the resulting figures.[72] However, nowhere did the court further elaborate on what it considered to be the meanings of the terms "modest" and "clinically significant," nor did the court explain how those terms related to the 7% figure. Having raised the question of clinical significance, the court moved on to another question without resolving the characterization dispute.[73]

Perhaps the best indication in the existing case law of the current status or understanding of "clinical significance" appears in the following excerpt from a case concerning advertising for lotions:

> These studies have shown that there is no clinically significant difference between any of the products in their ability to relieve dry skin. Of course, whether differences are "significant" depends upon how fine a line is being drawn. Thus, in the final analysis, this case becomes little more than a dispute over testing methods, with neither side able to show fraud, deception, or bad faith on the part of its competitor.[74]

This provides an excellent practical assessment of the current state of the phrase. Because no one agrees about what is "clinically significant," each party simply will develop the meaning that best supports its argument.

2. Where Does It Come From and How Can It Be Determined?

According to the court in *Mead Johnson*, clinical significance should be shown by "scientific evidence."[75] The court did not elaborate on what might constitute this evidence or how it might be found.[76] However, when the court

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69. The court accepted the 7% average figure, although Merck's expert challenged the validity of averaging figures and urged a figure of 11%. *Id.* at *3.

70. *Id.* at *3-*4.

71. *Id.* at *4.

72. *Id.*

73. The court moved on to the question of "the extent to which re-dosing is the experience of the average Tums user and the alleged burden upon J&J Merck to disclose in its advertising that for whatever reason, re-dosing is the experience of only a small number of consumers." *Id.* at *4.

74. Procter & Gamble Co. v. Chesebrough-Pond's Inc., 588 F. Supp. 1082, 1092 (S.D.N.Y. 1984).

75. Mead Johnson & Co. v. Abbott Labs., 41 F. Supp. 2d 879, 883 (S.D. Ind. 1999), *rev'd on other grounds*, 201 F.3d 883 (7th Cir. 2000).

76. *Id.*

states that in the absence of "scientific evidence," it will instead accept the opinion testimony of a credible expert in the field, it suggests that the court was referring to more formal clinical trials or investigations.[77] Thus, it is apparently possible, although less preferable (perhaps because less reliable), in this area to determine clinical significance through the expertise and experience of an individual expert. Thus, in the false advertising cases, no clear standard emerges, either as to meaning or as to method of determination.

C. Products Liability Cases

The products liability cases deal with evidence and statistical concepts from epidemiological studies to a greater extent than the other types of cases. This is almost certainly due to a greater emphasis on causation. In these cases the question of what "clinical significance" means is intertwined more closely with that of how it may be determined. A diet drug case, *Linnen v. A.H. Robins Co.*,[78] demonstrates the ways in which, as well as the reasons for which, these concepts of significance can be particularly problematic in a products liability context.[79] In a *Daubert* hearing to determine whether an expert witness for the plaintiff would be allowed to testify, the defendant drug company relied upon the typical requirement in these cases of deference to epidemiological studies (when available) to determine causation by statistical

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77. *Id.*

78. No. CIV.A.97-2307, 2000 WL 145758 (Mass. Super. Ct. Jan. 4, 2000).

79. *See* Linnen v. A.H. Robins Co., No. CIV.A.97-2307, 2000 WL 145758, *passim* (Mass. Super. Ct. Jan. 4, 2000) (discussing use of statistical and clinical significance in determining admissibility of expert testimony). The case in which this hearing occurred was based on the death of a thirty-year-old woman from Primary Pulmonary Hypertension (PPH), alleged to have been caused by her short-term ingestion of the diet drug Phen/Fen. *Id.* at *1. This is an order on a motion by the defendant drug manufacturer to exclude the testimony of plaintiff's expert witness. *Id.* Linnen was exposed to the drug for less than one month. *Id.* at *3. The epidemiological study offered by the plaintiff did not cover exposure periods under three months in length, so no odds ratio was calculated for a relevant length of exposure. *Id.* at *1 n.4. Furthermore, the data from the three-month-exposure period is arguably inapplicable because the cutoff time distinguishing "possible users" from "definite users" (drawn at one full month of use) lies between the three-month-use period and Linnen's exposure for approximately three weeks. *Id.* at *3-*4. The primary argument in this hearing concerned which, if any, of the available statistics were applicable to Linnen's case. *Id.* at *2-*4. While relevant epidemiological studies showing statistical significance with an odds ratio of at least 2.0 are typically required, and despite the fact that Linnen's use did not fit the parameters of the study offered, the court held that the expert's basis for using the statistics for three months was reliable and denied the motion to exclude. *Id.* at *5. *But cf.* Barrow v. Bristol-Myers Squibb, No. 96-689-CIV-ORL-19B, 1998 WL 812318, at *23 (M.D. Fla. Oct. 29, 1998) ("None of these studies have resulted in a relative risk factor of 2.0 or more, meaning the results of these studies are not statistically significant sufficient to denote that silicone gel breast implants are the cause of these problems.").

significance standards.[80] The plaintiff's expert, however, testified that while the odds ratio in the case, which was less that 2.0, did not meet the requisite level of statistical significance, it was nevertheless "clinically and diagnostically significant" and could, therefore, demonstrate causation.[81] Without addressing the meaning of "clinical significance" and without providing any explanation for its decision to depart from the standard probability and statistics analysis previously accepted in this field, the court simply accepted

80. *Linnen*, 2000 WL 145758, at *3. One court requiring epidemiological evidence cited the following statement from an affidavit: "The most important evidence relied upon by scientists to determine whether an agent (such as breast implants) cause disease is controlled epidemiologic studies. Epidemiology can be viewed as the study of the causes of diseases in humans." *In re* Breast Implant Litig., 11 F. Supp. 2d 1217, 1224 (D. Colo. 1998) (citation omitted). The court then concluded the following:

> Therefore, epidemiological studies are necessary to determine the cause and effect between breast implants and allegedly associated diseases. A valid epidemiologic study requires that study subjects, cases, and controls are chosen by an unbiased sampling method from a definable population. Epidemiology is the best evidence of causation in the mass torts context.

Id.; *see also* Smith v. Ortho Pharm. Corp., 770 F. Supp. 1561, 1573 (N.D. Ga. 1991) (stating that type of rigorous examination of expert's testimony was so important to toxic tort contexts in particular, "[t]he court will examine whether the expert's conclusions lack a sufficient basis in the use of epidemiological and genetic data"). *But see* Vassallo v. Baxter Healthcare Corp., 696 N.E.2d 909, 917-18 (Mass. 1998) (allowing experts to opine on causation in silicone breast implant case in absence of epidemiological studies, when experts showed adequate knowledge, skill, experience, and methodology).

81. *Linnen*, 2000 WL 145758, at *4.

Some background on the basics of terminology in the epidemiological studies may be helpful at this point. An "odds ratio" is a measurement that compares the rate or level of exposure to the study factor in the case population and the control population. Bruce R. Parker, *Understanding Epidemiology and its Use in Drug and Medical Device Litigation*, 65 DEF. COUNS. J. 35, 48 (1998). Odds ratios are distinguishable from "relative risk," which is the measure of the degree to which it is more likely that an exposed population will develop the disease than those who are not exposed. *Id.* at 46-47. For both relative risk and odds ratios, a finding of 1 indicates no association, less than 1 indicates a negative association, and greater than 1 indicates a positive association. *Id.* at 47. Neither relative risk nor odds ratios are measures of causation, although, as one court has pointed out, for proof of "more likely than not" causation, one would need to prove an association of *at least* 2.0. *See* Marder v. G.D. Searle & Co., 630 F. Supp. 1087, 1092 (D. Md. 1986) ("In epidemiological terms, a two-fold increased risk is an important showing for plaintiffs to make because it is the equivalent of the required legal burden of proof – a showing of causation by the preponderance of the evidence or, in other words, a probability of greater than 50%."). The "confidence interval" associated with both of these statistical measurements consists of a percentage (typically, though arbitrarily, set in advance of a study at 95%) and a range of values including the high and low ends of the scale of the relative risk or the odds ratio. Parker, *supra*, at 50-51; Neil Cohen, *Confidence in Probability: Burdens of Persuasion in a World of Imperfect Knowledge*, 60 N.Y.U. L. REV. 385, 399-401 (1985). On all these matters, see generally D.H. Kaye, *Is Proof of Statistical Significance Relevant?*, 61 WASH. L. REV. 1333 (1986); DAVID KLEINBAUM ET AL., EPIDEMIOLOGICAL RESEARCH: PRINCIPLES AND QUANTITATIVE METHODS (1982).

the plaintiff's expert's analysis as "an accurate interpretation of the data."[82] The court seems either to have misunderstood the concept of statistical significance or to have decided simply to ignore it. The court instead stressed the reliability of this testimony as determined by the expert's experience, education, and other professional qualifications.[83] This manner of departure leaves litigants with little certainty as to what standards will be used and how they will operate. It also has implications for *Daubert* standards in general, as the discrepancies created by cases like *Linnen* may lead to improper avoidance of the objective standards for introduction of scientific evidence.[84] Furthermore, differences in standards from one jurisdiction to another may present difficulties for large drug manufacturers who may have to make inconsistent arguments as a result of the lack of uniformity. The analysis in the products liability cases binds together the question of meaning and the question of methods of determination of clinical significance. However, it is still worthwhile to attempt to answer the two questions separately in order to better understand how they relate to one another and thus what the phrase means in this context.

1. What Does "Clinical Significance" Mean?

Because they fall within the field of torts, the products liability cases are necessarily very concerned with the analysis of causation. Thus, in some of these cases, the use of the phrase "clinical significance" involves the idea of causation to some extent, but they still provide little or no definition of the phrase. A Vaccine Act[85] case, for example, associates "clinical significance"

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82. *Linnen*, 2000 WL 145758, at *4.

83. *Id.* at *4-*5.

84. *See supra* note 17 and accompanying text (introducing relationship to *Daubert* standards). This particular effect would manifest itself primarily in products liability cases. The judge in *Linnen* had in fact, only the month before this decision, ruled on a different *Daubert* motion to exclude a plaintiff's expert, disallowing testimony of another expert for the plaintiff because he failed to demonstrate the requisite statistically significant association between the disease and the exposure. *See* Linnen v. A. H. Robins Co., No. CIV.A.97-2307, 2000 WL 16769, *passim* (Mass. Super. Ct. Dec. 14, 1999) (citing testimony of prospective expert that "I can't point to a single study which would give me a statistically significant result" as well as citing testimony of another expert that process for determining causation involves finding statistically significant association between disease and exposure, and allowing motion to exclude witness for failing to meet *Daubert* standards for reliable scientific evidence). Judge Brassard was also very concerned in deciding this motion about the certainty with which the expert holds the opinion, requiring a "reasonable degree of medical certainty," a standard which Judge Brassard did not believe Dr. Wellmann met. *Id.* at *14.

85. The National Childhood Vaccine Injury Act of 1986 includes the National Vaccine Injury Compensation program, which allows, under certain conditions, for compensation for injuries sustained as a result of vaccines. 42 U.S.C.A. § 300aa-1 et seq. (2002). One of the

and correlation without causation.[86] The physician in that case found that a vomiting episode was "not clinically significant" and further stated that any association between the vaccine and the child's death was coincidental.[87] Especially in light of the court's requirement of a "reasonable degree of medical certainty" for this statement, it appears that the court understands clinical significance to relate directly to causation, so that it cannot exist when multiple possible causes have not been precluded.[88] Another Vaccine Act case reinforces this understanding by indicating that clinical significance is something that would point to a cause, or perhaps more accurately, would eliminate other possible causes.[89] Thus, while a definition is not forthcoming, there is at least a basic possibility that clinical significance relates to an effect and implicates causation analysis, perhaps at the level of a "reasonable degree of medical certainty."

On the other hand, there are also many uses of the phrase "clinical significance" in the products liability context that provide little or no meaning at all. Keeping to the context of Vaccine Act cases, for example, one case, which mentions clinical significance only in passing, defines the phrase "significant aggravation" as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness, accompanied by substantial deterioration of health."[90] It is arguable that the understanding of "significant" in one context within a case may be indicative of the understanding of "significant" in another within the same opinion. The two concepts, while not equated in the opinion, do seem by virtue of their shared vocabulary to coincide at some level. This perhaps suggests a meaning for "significant" in the phrase "clinical significance" beyond denoting simply *any*

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purposes of the program is to provide expedited and simplified procedures in lieu of litigation against each physician and drug company potentially involved. Russell G. Donaldson, Annotation, *Construction and Application of National Childhood Vaccine Injury Act (42 U.S.C.A. § 300aa-1 et seq.)*, 129 A.L.R. FED. 1, 47-48 (1996).

86. *See* Shepard v. Sec'y of Dep't of Health & Human Servs., No. 90-889V, 1991 WL 220282, at *4-*5 (Cl. Ct. Oct. 11, 1991) (discussing causation element in case of death of child following DPT vaccine).

87. *See id.* (summarizing physician's testimony that no association existed between vaccine and death of child).

88. *Id.* at *4.

89. *See* Vinyard v. Sec'y of Dep't of Health & Human Servs., No. 89-55V, 1990 WL 293374, at *4 (Cl. Ct. June 29, 1990) (citing doctor's testimony that given condition or symptom had no clinical significance that would point to alternative cause of injuries at issue).

90. Duffield v. Sec'y of Dep't of Health & Human Servs., No. 90-827V, 1991 WL 275005, at *9 (Cl. Ct. Dec. 2, 1991) (quoting definition from 42 U.S.C.A. § 300aa-33(4) (West 1991)). The court mentions "clinical significance" only as being unknown for a particular physical condition. *Id.*

change, and instead pointing toward a requirement of somewhat more substantiality.[91]

2. Where Does It Come From and How Can It Be Determined?

One might consider that the sources or requirements for determining clinical significance are more uniform in these cases than in the advertising context, but such uniformity exists only in their lack of objectivity and standardization.[92] That is, the standard is no standard. One case allowed that clinical significance may be based on clinical studies or experiments conducted on an individual patient, involving no controls or comparisons with others.[93] Similarly, the majority in *Glaser* deems analysis at an individual level, with no showing of statistical significance, to be clinically significant.[94] In effect, these cases allow a physician's subjective opinion as an adequate basis for a finding of clinical significance. The only clear conclusion here is that, apparently, formal testing or studies, while certainly permissible, are wholly unnecessary to findings of clinical significance in the products liability context.

The meaning of "clinical significance" in these cases remains unclear. The method of determining clinical significance allows for great subjectivity. As long as a court may allow clinical significance by such a standard to be determinative of a causation question, this level of subjectivity, coupled with ambiguity of meaning, will frustrate *Daubert*-type attempts to maintain objective, consistent, and accurate standards for reliable scientific evidence.[95]

D. Evaluation

This discussion demonstrates the degree of confusion in the usage and meaning of the phrase "clinical significance," both across drug litigation as a

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91. *See id. passim* (discussing possibility of "significant aggravation" of underlying condition by DPT vaccine throughout opinion, and mentioning unknown "clinical significance" of a truncated limb).

92. That is, the cases are uniform in not requiring that specific standards be met.

93. *See* Carmichael v. Reitz, 17 Cal. App. 3d 958, 960-61 (1971) (stating that "the testimony of a specialist in hematology . . . was sufficient, for the purposes of nonsuit, on the element of causation, where the specialist's conclusion was based on a series of clinical studies or experiments he had conducted on plaintiff over a 24-day period . . . .").

94. *See* Glaser v. Thompson Med. Co., 32 F.3d 969, 975 (6th Cir. 1994) (discussing prior opinion, in *Turpin v. Merrell Dow Pharmaceuticals, Inc.*, 959 F.2d 1349 (6th Cir. 1992), in which Sixth Circuit had considered same type of problem, had examined epidemiological studies, etc., and had concluded that individual type of determination was inadequate and invalid, but coming to different conclusion in this case, allowing individual over broader study results).

95. *See supra* notes 13-17 and accompanying text (discussing potential ramifications of continued confusion in this area).

whole and in each particular type of case. Even when uniformity may emerge in a given context, there is often little to explain how to apply that uniformity. Often, the explicit indications simply run in circular reasoning and meaning. Thus, no clear indication of a standard emerges from these attempts to find a meaning from the context in which the phrase appears.

IV. Comparison with Uses of Statistical Significance

Another approach to the process of deriving a definition from context is to examine more closely the relationship between clinical significance and statistical significance. However, there is considerable disagreement as to the nature of this relationship, even at the most general level.[96] This disagreement is due primarily to the uncertainty surrounding the meaning of "clinical significance" because it is clear, or certainly ought to be, to courts, to lawyers, and to scholars, what statistical significance means.[97] The following discussion will attempt to pull apart the different understandings of the two concepts and their relationship to each other. The following arguments represent the wide range of possible relationships that courts and parties have posited, as examined by type of case,[98] by manner of determination,[99] and by the nature of the relationship between them.[100]

A. General Comparison of Uses in Case Law

The FDA approval cases provide an excellent starting point in this discussion, as the FDA regulations require that a proponent of a new drug

96. *See infra* Part IV (discussing this disagreement).

97. *See* Zeneca Inc. v. Eli Lilly & Co., No. 99CIV.1452(JGK), 1999 WL 509471, at **25-26 (S.D.N.Y. July 19, 1999) (referring to typical *p* value requirement of less than .05, but noting expert's explanation of appropriateness of altering *p* value to account for alternate endpoints in given study); McNeil-P.P.C., Inc. v. Bristol-Myers Squibb Co., 755 F. Supp. 1206, 1214 n.7 (S.D.N.Y. 1990) (describing statistical significance as 95% certainty that results are not due to chance). To find statistical significance requires a substantial number of subjects in the study, to avoid type II errors (false negatives) and still yield positive results. SILVERMAN, *supra* note 6, at 199. As Silverman has remarked, the level of "significance" in a given study is arbitrarily determined based on the level of risk of type I error (false positives) that will be accepted. *Id.* at 119. As certain and meaningful as a finding of statistical significance may seem, it is important to remember that the statistical significance of accumulating data, repeatedly tested, is inevitable. *Id.* at 123. Thus, there is a level at which statistical significance does not necessarily have a great deal of meaning.

98. *See infra* Part IV.A (examining relationship between statistical and clinical significance by type of case).

99. *See infra* Part IV.B (examining relationship between statistical and clinical significance by manner of determination).

100. *See infra* Part IV.C (examining range of possible nature of relationship between statistical and clinical significance).

produce evidence of *both* clinical and statistical significance of each component of the drug, and that each component of a combination drug make a "statistically significant clinical contribution" to the effects claimed.[101] The cases in this area largely contrast the two types of significance. In addressing issues related to the safety of a color additive, the court in *Simpson v. Young*[102] deemed "clinically significant" changes to be non-statistical and even possibly illusory differences and demanded deference instead to statistical evidence.[103] The *Warner-Lambert* court similarly contrasted the two, although without any positive associations, stating that "[t]herapeutic or clinical significance is contrasted for this purpose with statistical significance, which ARW accurately characterizes as based on a premise of the elimination of chance results."[104] This may mean that clinical significance is purely concerned with a doctor's observation, based on his own experience and expertise, of effects on an individual patient or on a small group of patients, without any formal testing at all. On the other hand, it may mean that statistical significance (which comes from the more formal studies) is a necessary base and that clinical significance must be above and beyond that.

Along the same lines, in the context of false advertising, the *McNeil* court stated categorically that no clinical significance can exist in the absence of statistical significance.[105] Thus, the *McNeil* court appeared to define clinical significance as a difference that is *at least* statistically significant, but that must include something further.[106] However, the court gave no real indication of what that further element might be.

Other courts, even in the same context, leave the relationship between these two types of significance unexamined and unclear, simply mentioning the two types in parallel.[107] For instance, when a court found both types to be absent, there was no further explanation to define, compare, or contrast the two types.[108] The most one could take from that example is that the discussion

101. 225 Cartons II, 871 F.2d 409, 419 (3d Cir. 1989).

102. 854 F.2d 1429 (D.C. Cir. 1988).

103. Simpson v. Young, 854 F.2d 1429, 1436 (D.C. Cir. 1988).

104. *See* Warner-Lambert Co. v. Heckler, 787 F.2d 147, 154 (3d Cir. 1986) (treating clinical and statistical significance as distinct). It is important to remember that this case particularly stresses the need for both types of significance to be present. *Id.*

105. McNeil-P.P.C. v. Bristol-Myers Squibb Co., 755 F. Supp. 1206, 1219 n.12 (S.D.N.Y. 1990).

106. *Id.*

107. *See* Johnson & Johnson-Merck Pharm. Co. v. Rhone-Poulenc Rorer Pharm. Co., CIV.A.No.91-7099, 1993 WL 21239, at *3-*4 (E.D. Pa. Jan. 29, 1993) (noting lack of "statistically or clinically significant difference" between two products).

108. *See id.* at *4 (using these two phrases in parallel, but failing to clarify definition or difference because neither was proven).

involved an assessment, by means of statistical analysis, of differences in "symptomatic relief" (which one might take to be a "clinical" type of evaluation).[109] Thus, it is possible that clinical and statistical significance could simply be intertwined so that they necessarily are involved with each other and always come as a pair. At any rate, the reader of these cases is still left largely with only speculation as to the relation or the relative weight of these two types of significance in the false advertising cases.

A variation on this treatment occurs in cases that may mention both types of significance, but do not discuss the relationship between them at all. That is, the phrases appear in entirely separate parts of the analysis, and for the most part only in passing. In *Diet Drugs*, for example, the court mentions statistical significance in the context of controlled clinical studies.[110] The fact that there is no mention of clinical significance in this scenario indicates perhaps a lack of concern on the part of the court about the relationship between the two, or perhaps an idea that only statistical significance is important. An isolated reference to clinical significance at another point in the opinion, however, does indicate an awareness of the phrase and presumably some understanding of what it means, making yet more intriguing its absence in the earlier part of the discussion.[111]

The *Linnen* case discussed earlier in the products liability context also serves as an important case in this context.[112] In *Linnen*, in effect, the court allowed clinical significance, in the explicit absence of statistical significance, to determine causation by allowing the testimony of an expert on this point.[113] Thus, the *Linnen* court implicitly agreed with the *Glaser* court that statistical significance may hide clinical significance.[114] However, it is still worth noting that the court in *Linnen* was contradicting its previous decision to exclude an expert's testimony when it failed to show statistically significant association between the drug and the disease.[115]

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109. *See id.* at *3 (employing statistical analysis on data concerning symptomatic relief).

110. *See In re* Diet Drugs, Nos. 1203, 99-20593, 2000 WL 1222042, at *15 (E.D. Pa. Aug. 28, 2000) (discussing statistical significance of controlled clinical studies).

111. *See id.* at *29 (referring to "clinical insignificance" in different portion of opinion).

112. *See supra* notes 79-84 and accompanying text (discussing *Linnen*).

113. *See* Linnen v. A.H. Robins Co., CIV.A.No. 97-2307, 2000 WL 145758, at *4 (Mass. Super. Ct. Jan. 4, 2000) (citing and following testimony of expert that "while an odds ratio of less than 2.0 is not statistically significant, it is clinically and diagnostically significant . . . .").

114. *See* Glaser v. Thompson Med. Co., 32 F.3d 969, 975 (6th Cir. 1994) (citing testimony of expert that statistical significance may obscure clinical significance).

115. *Compare* Linnen v. A.H. Robins, CIV.A.No. 97-2307, 2000 WL 16769, at *3, *14 (Mass. Super. Ct. Dec. 14, 1999) (stating, first, rule explained by one expert that to have scientifically valid basis for assertions in this field, generally accepted scientific methodology requires examination of controlled human studies to determine whether statistically significant

The foregoing discussion is likely to have left the reader in a state of some confusion. This is entirely appropriate as that is exactly where the relationship between clinical and statistical significance stands. Several possibilities have emerged to explain the relationship. First, statistical significance may be required and may be adequate in the absence of clinical significance, which would thus be fairly irrelevant. Second, clinical significance may be something that statistical significance only obscures and that ought to be allowed in the absence of statistical significance as meeting reliability standards under *Daubert*. Third, the relationship between these two simply may be unknown and unexamined. None of these standards is a clear favorite among courts (or even, apparently, within the same court).

B. Comparison of Ways in Which Clinical Significance and Statistical Significance May Be Determined

A comparison of the ways in which clinical and statistical significance are found may help one to understand how the two might compare in terms of reliability and, therefore, in relative weight or admissibility. This understanding may in turn lead to a clear meaning and a proper standard of use for clinical significance.

The views concerning assessments of statistical significance are overwhelmingly uniform. Statistical significance can come only from formal trials or studies, not from individual physicians' experience and expertise with regard to observations of individuals or small groups.[116] The typical requirements for a study are that the study be of sufficient size, that it be controlled and preferably either blind or double-blind, that it be of sufficient duration, and, in some cases, that it be published or otherwise subject to some sort of

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association exists, and if such association has been demonstrated, evaluation of whether relationship is causal; then stating that "[a]lthough an expert's opinion . . . may be offered on the basis of probability, reasonableness and likelihood, the scientific principles or knowledge on which those opinions are based must be held with a reasonable degree of scientific certainty. That level of certainty, while it need not be absolute, must be greater than "more likely than not.") *with* Linnen v. A.H. Robins Co., CIV.A.No. 97-2307, 2000 WL 145758, at *3-*5 (Mass. Super. Ct. Jan. 4, 2000) (allowing expert testimony that failed to show statistical significance when expert found clinical significance and when court deemed expert otherwise to meet *Daubert* standards for "experience, qualifications, education and training").

116. *See, e.g., Glaser*, 32 F.3d at 975, 986 (Boggs J. dissenting) (making clear that "you cannot get statistical significance from 'some' individuals"); Simpson v. Young, 854 F.2d 1429, 1436 (D.C. Cir. 1988) (stating that "statistical significance cannot be discerned by the comparison that petitioners make among individual animals, but only be a comparison of averages according to accepted statistical methods . . . ."); Warner-Lambert Co. v. Heckler, 787 F.2d 147, 154 (3d Cir. 1986) (referring to formal studies to find evidence of statistical significance); *In re* Diet Drugs, Nos. 1203, 99-20593, 2000 WL 1222042, at *15 (E.D. Pa. Aug. 28, 2000) (looking for statistical significance in controlled clinical studies).

peer review to show that it was performed in accordance with accepted practices and standards.[117] Although statistical significance itself is definable by each researcher performing a new study, there is a generally accepted normal level, set at 95% confidence, which maintains a further level of uniformity.[118] However, when it comes to clinical significance, this uniformity evaporates. One set of cases would have the standards or sources for finding clinical significance identical to those for statistical significance.[119] Another set of cases contrasts the two standards by allowing that clinical significance may come from observations of and opinions about individual subjects, rather than from formal studies.[120] Somewhere in the middle of these standards is one yet less defined – that a finding of clinical significance must be supported by "scientific evidence."[121]

As far as re-analysis of, or extrapolation from, previous studies, records, or literature, there is some indication that these are not permissible manners in which to find clinical significance.[122] For instance, the court in one prod-

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117. *See, e.g.*, Edison Pharm. Co. v. FDA, 513 F.2d 1063, 1070 (D.C. Cir. 1975) (citing CFR requirement for controlled studies (as explained, for purposes of that case, in 38 Fed. Reg. 17029 (June 28, 1973) which requires "well-controlled studies using blind and double-blind cross-over and randomization techniques or any other kind of control specified in 21 C.F.R. 130.12(a)(5)(ii) . . . ."), failure to meet which requirement means "neither the clinical nor the statistical significance of the reported results can be evaluated"); Zeneca Inc. v. Eli Lilly & Co., No. 99CIV.1452(JGK), 1999 WL 509471, at *29 (S.D.N.Y. July 19, 1999) (noting dependence of reliability of statistical significance on study size); 225 Cartons I, 687 F. Supp. 946, 961 (D.N.J. 1988) (requiring evidence of "published, well-controlled clinical studies").

118. *See supra* note 81 (noting standard confidence intervals).

119. *See supra* notes 115-117 (discussing these requirements); *see also* 225 Cartons II, 871 F.2d 409, 416 (3d Cir. 1989) (using "statistical" and "clinical" in parallel in stating requirements); *225 Cartons I*, 687 F. Supp. at 961 (stating same requirement slightly differently).

120. *See, e.g.*, Glaser v. Thompson Med. Co., 32 F.3d 969, 975 (6th Cir. 1994) (citing expert opinion that averages involved in finding statistical significance "can really hide clinically significant differences to things" and referring to those clinically significant differences as "variations from the mean that could influence one or two patients"); Warner-Lambert Co. v. Heckler, 787 F.2d 147, 155-56 (3d Cir. 1986) (never explicitly defining source of finding of clinical significance, but contrasting it with formal studies needed to find statistical significance, implying that clinical significance is determination made based on observation of individual); Linnen v. A.H. Robins Co., No. CIV.A.97-2307, 2000 WL 145758, at *4 (Mass. Super. Ct. Jan. 4, 2000) (allowing expert to base conclusion of clinical significance on plaintiff's medical record, expert's own career experience, and clinical observations, rather than relying on controlled studies).

121. *See* Mead Johnson & Co. v. Abbott Labs., 41 F. Supp. 2d 879, 883 (S.D. Ind. 1999), (" . . . Abbott makes no claim to medical superiority because it could not support such a claim with scientific evidence. There is no scientific evidence showing a clinically significant difference between these products . . . ."), *rev'd on other grounds*, 201 F.3d 883 (7th Cir. 2000).

122. *See supra* text accompanying note 58 (discussing requirements for extrapolation from previous studies); *see also* Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 584-85 (1993)

ucts liability action against the manufacturer of Bendectin held that re-analysis of epidemiological studies was not permitted to show causation, regardless of the credibility of the methodology used.[123]

C. Dependence, Exclusivity, or Hierarchy?

One view is that clinical significance cannot exist in the absence of statistical significance.[124] This may mean that a finding of clinical significance really does not add anything to what we know if something is already statistically significant because the "clinically significant" differences in this theory may be simply "illusory."[125] Or it may mean that having reached the threshold finding of statistical significance, a finding of clinical significance denotes something beyond that, making the finding somehow more meaningful.[126] There is no indication, however, that a finding of statistical significance depends on a finding of clinical significance. Thus, the relationship

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(disallowing results from reanalysis of previous epidemiological studies as unreliable because not subject to peer review or publication).

123. Lynch v. Merrell-Nat'l Labs., 646 F. Supp. 856, 865 (D. Mass. 1986). Similarly, reanalysis using changed p-values for statistical significance is generally not permissible either. Kelley v. Am. Heyer-Schulte Corp., 957 F. Supp. 873, 879 (W.D. Tex. 1997). The use of p-values occurs when there is (at least there is assumed to be) no effect in the given population. It also assumes a fixed level for the test – usually 5%. That means that results are significant at the 5% level. A p-value is the smallest fixed level at which the null hypothesis can be rejected. Put another way, a p-value represents the probability of something more extreme than a given correlation, either positive or negative – that is, the probability that results are due to chance. A p-value of less than 5% denotes statistical significance, while a p-value of greater than 5% denotes no statistical significance. For further discussion of p-values and statistical significance, see American College of Physicians, *Effective Clinical Practice: Primer on Statistical Significance and* P *Values* (July/Aug. 2001), *available at* http://www.acponline.org/journals/ecp/julaug01/primer.htm (last visited Mar. 28, 2002).

124. In *McNeil-P.P.C. Inc., v. Bristol-Myers Squibb Co.*, 755 F. Supp. 1206, 1219 n.12 (S.D.N.Y. 1990), *aff'd*, 938 F.2d 1544 (2d Cir. 1991), the court stated the following:

> McNeil also argues that even if a statistically significant difference exists, the advertising claim is nonetheless false because no clinically significant difference exists. Bristol-Myers contends that its advertising does not claim a clinically significant difference between the two products. In light of the Court's determination that no statistically significant difference exists, it follows that a clinically significant difference does not exist.

Id. Similarly, in a case involving fraud in the context of FDA approval of a laser device to treat angina pectoris, the plaintiffs argued that the results reported by the defendants were "so incomplete or so statistically flawed as to lack clinical significance." *In re* PLC Sys., Inc. Sec. Litig., 41 F. Supp. 2d 106, 115 (D. Mass. 1999).

125. *See* Simpson v. Young, 854 F.2d 1429, 1436 (D.C. Cir. 1988) (discussing "differences supposedly observed" between groups in study, belittling reliance on non-statistical evidence from observation when statistical analysis was available).

126. *See infra* Part IV.D. (discussing meaningful statistical significance).

may be one of dependence, but not of *mutual* dependence. Another view, however, as we have seen, would allow that clinical significance certainly may exist in the absence of statistical significance, that in fact relying on statistical significance as a threshold will only obscure findings of clinical significance.[127]

Are the two findings then entirely independent of each other? Or is there perhaps a hierarchy in terms of levels of significance, with clinical requiring a lower standard than statistical? Neither of these organizational schemes is entirely satisfactory. Indeed, there is remarkably little order.

D. "Meaningful" Statistical Significance

Some cases draw yet another distinction – that between statistical significance and *meaningful* statistical significance. This distinction returns to the idea already mentioned, that while a finding of statistical significance does not necessarily imply a finding of clinical significance, the finding of statistical significance alone may have more theoretical than practical meaning.[128] The FDA requires evidence of a new drug's significance both in statistical and clinical terms.[129] The FDA's phrase "statistically significant clinical contribution," describing the effects that manufacturers need to show to obtain approval for a combination drug, might suggest the view that the two types of significance together have meaning, but that alone either one might be deficient.[130] However, this analysis is, at best, only a guess.

It may seem that some of these arguments read a great deal into very little language. That may well be so, but these are the best indications that exist in the current case law. Far more references exist, in these and other contexts, that give no insight at all into the relationship between these con-

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127. *See* Glaser v. Thompson Med. Co., 32 F.3d 969, 975 n.11 (6th Cir. 1994) (discussing testimony of expert who noted that averages can hide clinically significant differences).

128. *See* SmithKline Beecham Consumer Healthcare, L.P. v. Johnson & Johnson-Merck Consumer Pharm. Co., 906 F. Supp. 178, 187 (S.D.N.Y. 1995) (referring to expert's testimony that "[y]ou can see statistically significant differences that aren't clinically meaningful"), *aff'd*, 100 F.3d 943 (2d Cir. 1996).

129. *See* Warner-Lambert Co. v. Heckler, 787 F.2d 147, 154-55 (3d Cir. 1986) (citing CFR requirement, explicitly contrasting these two types of significance without defining either, and supporting "[t]he Commissioner's interpretation of the statute as requiring a showing of clinical significance, rather than *merely* statistical significance" (emphasis added)). Note that this requirement potentially could eliminate the argument that either type of significance necessarily entails a finding of the other.

130. *See* 225 Cartons II, 871 F.2d 409, 416, 419 (3d Cir. 1989) (requiring both types of significance and associating them closely by expressing FDA requirement in quoted terms above as well as in terms of "showing that each ingredient is making a real clinical contribution of statistical significance").

cepts.[131] The less certain we are from the language we have, the clearer it is that there is a problem here. Thus, these interpretations of the language may not draw the correct conclusions about how the courts understand these terms, but the endeavor still shows that nothing about this is clear.

E. Evaluation

The foregoing analysis of the interaction between statistical and clinical significance demonstrates the degree to which this area remains unsettled. The meaning of statistical significance is well established, and its appropriate application and weight are also fairly clear. However, across jurisdictions and within individual courts, there is little, if any, uniformity as to the meaning or the appropriate application of the concept of clinical significance. When the two concepts appear in the same discussions, no clear pattern emerges to explain the relationship between them.

V. Looking for Definitions in Non-Caselaw Sources

A. Usage in the Code of Federal Regulations

"[W]e have traditionally left to legislators the task of defining terms of a medical nature that have legal significance."[132] The language of the Code of Federal Regulations (CFR) is in the background of much of the case law already discussed.[133] While the most relevant portions, Title 21 (Food and

131. One example of this is the type of passing reference in which both phrases appear in parallel, without any specific or explicit differentiation, mentioned only as both being absent. *See* Johnson & Johnson-Merck Consumer Pharm. Co. v. Rhone-Poulenc Rorer Pharm. Co., CIV.A.No.91-7099, 1993 WL 21239, at *4 (E.D. Pa. Jan. 29, 1993) ("Not one of the in vivo studies . . . demonstrated any statistically or clinically significant difference in the ability . . . to relieve symptoms . . . ."), *aff'd*, 19 F.3d 125 (3d Cir. 1994). It is simply not clear what the court's statement tells the reader, or how it furthers the court's analysis. One could make a tenuous argument from this language either that the court sees them as equivalent concepts, as if they were in apposition, or that they are different, and that is why the court mentioned both. Nor is it clear what the court would require of them if the court determined either one or both were present. At best, all that the reader can take from this opinion is that the language is vague and leaves us with no idea of the meaning or importance of "clinical significance."

132. *In re* Bailey, 740 N.E.2d 1146, 1153-55 (Ill. App. Ct. 2000) (quoting *Kansas v. Hendricks*, 521 U.S. 346, 359 (1997), in attempt to understand meaning of term "mental disorder," which respondent claimed to have "no clinically significant meaning," but which *Bailey* court held to be adequately defined by relevant statute).

133. References to the CFR in case law in which the phrase "clinical significance" appears are rare, but, especially in the drug approval and patent infringement cases, the regulatory language is implicitly important due to the role that it plays in the earlier stages of the process, prior to litigation. Where it is mentioned, however, it is generally not for definition or clarification of the meaning of the phrase. *See supra* note 35 (noting that CFR definition of "effectiveness" incorporates "clinical significance"). While references in the Federal Register would of

Drugs) and Title 42 (Public Health), both contain many references to findings of "clinical significance," neither of these sections provides an explicit definition of the phrase.[134] This lack of clarity produces notable difficulties, considering the fact that a finding of clinical significance is a determinative factor in several different contexts within the regulations. The fact that the term appears, however, suggests that there is a proper meaning and, therefore, a proper use for the term, but it is extremely difficult, if not impossible, to glean from the context of these usages precisely what that proper meaning might be.[135]

Title 21 sets out in great detail the procedure and requirements for the investigation, approval, labeling, and advertising of both over-the-counter and prescription drugs.[136] Labeling requirements dictate that there must be an indication of specific guidance for the physician on preventing "clinically significant drug/drug and drug/food interactions that may occur."[137] They allow manufacturers to include any data that demonstrates effectiveness in *in vitro* or animal tests, but that does not prove by adequate and well-controlled clinical studies to be pertinent to clinical use, only on the condition that the following statement precedes the data: "The following *in vitro* data are available, but their clinical significance is unknown."[138] Without knowing what constitutes clinical significance, the drug manufacturer and marketer will be hard pressed to comply with these requirements. The same title of the regulations sets out specific and rigorous requirements for clinical testing of investigational new drugs.[139] In the context of these requirements, the code provides that in the case of a new protocol, the manufacturer must provide "a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols."[140] Again, the code also requires certain safety information on clinically significant drug/drug interactions.[141]

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course also be relevant here, none of these references adds enough meaning to contribute to this discussion. These references are made primarily only in passing.

134. Other CFR Titles, including Title 10 (Energy), Title 14 (Aeronautics & Space), Title 16 (Commercial Practices), Title 29 (Labor), and Title 32 (National Defense), also refer to "clinical significance" without defining the term in those contexts.

135. The method by which it may be possible to glean such a definition is the same as that attempted in relation to the case law in the preceding text – by analyzing it contextually.

136. *See, e.g.*, 21 C.F.R. §§ 201.57, 202, 312.10, 314.50, 320.1, 330.10, 601.25, 860.7, 868.1900 (2001).

137. *Id.* § 201.57(f)(4)(i).

138. *Id.* § 201.57(b)(2)(i).

139. *Id.* §§ 312.20-.38.

140. *Id.* § 312.30(d)(1)(i).

141. *See id.* § 314.50(d)(5)(vi)(a) (describing safety information from clinical investigations that manufacturers must provide on drug application form).

The definition of "effectiveness" in the context of over-the-counter drugs incorporates the concept of clinical significance as follows: "Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide *clinically significant* relief of the type claimed."[142] Perhaps most helpfully here, the regulation provides that proof of effectiveness "shall consist of controlled clinical investigations as defined in § 314.126(b)" unless the FDA waives such requirements.[143] This is the sort of meager indication that suggests clinical significance may be something that comes from controlled clinical investigations. However, it is heavily qualified by the fact that the FDA may waive the requirement.[144] There is a similar indication (from identical language) in the code section dealing with review of licensed biological products to ensure safety and effectiveness.[145] It refers to effectiveness as having a "clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man" and states that "proof of effectiveness shall consist of controlled clinical investigations" unless waived upon a reasonable showing of inapplicability or inessentiality.[146] On the other hand, however, the section does allow for corroboration of investigations by "partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing."[147] The section expressly disallows "isolated case reports, random experience, and reports lacking the details which permit scientific evaluation."[148] For comparison, these same requirements also exist, in largely the same language, in the context of approval of medical devices.[149]

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142. *Id.* § 330.10(a)(4)(ii) (emphasis added).

143. *Id.* § 330.10(a)(4)(ii). The referenced definition of controlled clinical investigations includes characteristics such as a clear statement of objectives and proposed methods of analysis, a study design permitting valid comparison with a control mechanism, careful selection of subjects, randomization of treatment to minimize bias, well-defined and reliable assessment of subject response, and analysis of results adequate to assess the effects of the drug. *Id.* § 314.126(b).

144. *See, e.g., id.* § 330.10(a)(4)(ii) (stating that FDA may waive requirement "on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness").

145. *See id.* § 601.25(d)(2) (providing identical definition of effectiveness and waiver option).

146. *Id.*

147. *Id.*

148. *Id.*

149. *Id.* § 860.7(c)(1)-(e)(2). There is also a clear example of recognized principles defining a well-controlled clinical investigation, which is essential to these requirements, at *id.* § 860.7(f).

Once the drug trial and approval process is complete, the requirements for advertising become relevant. Here, again, Title 21 addresses numerous details but does not define clinical significance. One of the criteria by which the FDA deems advertisements false or misleading is that the advertisement "contains favorable data or conclusions from nonclinical studies of a drug . . . in a way that suggests they have clinical significance when in fact no such clinical significance has been demonstrated."[150] The FDA *may* deem the advertisements false or misleading if, among other possibilities, they "use the concept of 'statistical significance' to support a claim that has not been demonstrated to have clinical significance or validity, or fails to reveal the range of variations around the quoted average results."[151] The code also provides that "[c]orrelation of in vivo bioavailability data with an acute pharmacological effect or clinical evidence of safety and effectiveness may be required if needed to establish the clinical significance of a special claim, e.g. in the case of a controlled release preparation."[152] These examples seem to indicate that there are situations in which one must establish clinical significance as determinative of something, but these examples do not explain what clinical significance *is*.

While the discussion so far has related to the approval and marketing areas, there is little or no relevant language in Title 21 relating specifically to products liability cases in the pharmaceutical context. However, the sections discussed above nevertheless may be relevant to products liability litigation because the clinical studies conducted for the purpose of obtaining FDA approval could easily later become a source of evidence as well as a source of dispute in products liability cases.

Title 42 of the CFR addresses issues involving Public Health. In the section devoted to "Drug Use Review and Electronic Claims Management System for Outpatient Drug Claims," the code provides definitions that

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150. *Id.* § 202.1(e)(6)(vii). One scholar has pointed out the degree to which this continues to be a problem, in that:

> [The] FDA continues to be troubled by the selection and poor quality of research or, conversely, the misuse of data from apparently adequate and well controlled studies, the extension or distortion of the claim for usefulness beyond those approved and the use of pharmacokinetic data or blood tissue levels that suggest clinical significance but are in fact unsupported by substantial clinical experience.

Milind Kale, *Monitoring the Regulatory Process of Prescription Drug Advertising*, 5 J. PHARM. & L. 229, 233 (1996) (quoting Lloyd Millstein, *The Regulation of Prescription Drug Advertising*, 23 AM. PHARMACY 491 (1983)).

151. 21 C.F.R. § 202.1(e)(7)(ii) (2001). As relates to determinations of bioequivalence or bioavailability, this code title refers to "medical []significance," but without any indication as to the relationship between that concept and "clinical significance." *Id.* § 320.23(b).

152. *Id.* § 320.28.

incorporate the concept of "clinical significance," for which there is no separate definition.[153] For example, the regulation defines an "adverse medical result" as a "clinically significant undesirable effect, experienced by a patient, due to a course of drug therapy."[154] It defines "overutilization" alternatively as use "that is greater than necessary to achieve a desired therapeutic goal or that puts the recipient at risk of a clinically significant undesirable effect."[155] It defines "underutilization" in a similarly alternative fashion, but for insufficient, rather than excessive, dosage.[156] However, all of these uses of the phrase in this Title, as with those in Title 21, do not reveal a concrete definition. Thus, the next potential source for examination is the information dispensed by the agency that interprets these regulations.

B. Agency Website Information: Test Case on VHD Standards

The following discussion provides one example of data that an agency provides concerning a particular disease or drug. The FDA's Center for Drug Evaluation and Research has published and analyzed studies relating to Valvular Heart Disease (VHD), a condition alleged to be associated with the use of the diet drugs phentermine, fenfluramine, and dexfenfluramine.[157] In doing so, the FDA has promulgated standards for assessing "significant" VHD.[158] The word "significant" remains unqualified, but it is at least arguable that "clinical" significance is the type that best fits the concept here, based on the methodology set out in this study.[159] By reference to *In re Diet*

153. 42 C.F.R. § 456.702 (2001). (This section falls under the code title of Health Care Financing Administration, and the part title of Utilization Control).

154. *Id.*

155. *Id.*

156. *Id.*

157. *See* U.S. Food & Drug Administration Ctr. for Drug Evaluation and Research, *FDA Analysis of Cardiac Valvular Dysfunction with Use of Appetite Suppressants*, 1997 (providing information on case reports and survey and study results relating particularly to risk of valvulopathy), *available at* http://www.fda.gov/cder/news/slides/fenphendata.pdf (last visited Feb. 12, 2002).

158. The FDA provides a "'research' case definition of valvulopathy in the setting of appetite suppressant use" defining it as "aortic regurgitation of greater than trace/trivial/minimal severity and/or mitral regurgitation of greater than mild severity, as documented by echocardiography." *Id.* at 5. Thus the FDA has put forward a definition of the condition and the means for determining it. However, as this standard is only that of something more than minimal, it is unclear how much meaning this standard bears.

159. The information in this study consisted of reports from physicians about their small numbers of patients in their individual practices, from whom they have collected test results and "clinical data." *Id.* at 9. These results seem to be very much about individual responses. On the other hand, the reference to 95% confidence limits that the FDA gives for the study in the context of a discussion of absolute risk might suggest that the "significance" here is "statistical

Drugs,[160] in fact, this is precisely the type of significance intended.[161] Thus, perhaps one could argue that clinical significance *is* defined for this very precise issue regarding this particular disease.

However, perhaps that leap is premature. For there to be a certain, genuine connection between "clinical significance" as the statutes and the cases employ on the one hand, and these standards laid down by the FDA, the language should match with greater clarity (or indeed identity). Without identical language, we are left to make assumptions about the meaning of the words and phrases. Indeed, the apparent fact that only one case actually uses the phrase "clinical significance" with reference to these standards somewhat weakens any argument that there is a clear understanding of the relationship between them. In a subsequent publication, published by the Centers for Disease Control and Prevention (CDC), the FDA's Center for Drug Evaluation and Research (CDER) uses the phrase "clinical importance" in discussing the same subject matter.[162] Not only does this publication fail to define this

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significance." *Id.* at 12. At any rate, the FDA never explicitly identifies the "significant valvular regurgitation" with which the information here is concerned as "clinically significant." Nor, if the FDA were to do so, would this identification provide a clear objective standard for discussing the existence of the condition. These two factors demonstrate the relative uselessness of the use of "significance" here.

160. Nos. 1203, 99-20593, 2000 WL 1222042 (E.D. Pa. Aug. 28, 2000).

161. *See In re* Diet Drugs, Nos. 1203, 99-20593, 2000 WL 1222042, at *57 (E.D. Pa. Aug. 28, 2000) (using term "clinically significant" in discussion of FDA benchmark for VHD). *Diet Drugs* was part of a class action suit against American Home Products Corp. (AHP), regarding the effects of the appetite suppressants fenfluramine and dexfenfluranime, used together with the drug phentermine in the regimen known as "Fen-Phen." *Id.* at *1. In this case, AHP moved jointly with the class for certification and approval of a nationwide settlement. *Id.* The court granted the motion. *Id.* at *69. The court included among its findings of fact and conclusions of law a discussion of statistical significance and medical significance in controlled clinical studies, discussions of clinical significance of certain conditions as found in medical records, and arguments concerning the "appropriate benchmark for clinically significant VHD." *Id.* at *14-*15, *29, *57. Throughout the opinion, the court also often used "significance" without a qualifier, which makes it difficult to take very much from the discussion as a whole. *See id. passim.* The court mentioned, as a factor balancing in favor of approving the settlement, that it considered the sheer volume of studies on the subject of VHD and the studies' findings on the use of diet drugs to show that scientific knowledge is sufficiently developed in this area and thus to support the conclusions the parties had reached. *Id.* at *63. If the scientific knowledge is sufficiently developed, but there are still arguments concerning the "appropriate benchmark," it would seem as though we still have not reached an objective standard. Without an objective standard, it seems unlikely that "clinical significance" is a term that can add any meaning to the discussion.

162. *See Cardiac Valvulopathy Associated with Exposure to Fenfluramine or Dexfenfluramine: U.S. Department of Health and Human Services Interim Public Health Recommendations, November 1997*, MORBIDITY AND MORTALITY WEEKLY REPORT 1061 (1997) (summarizing data used by FDA in decision to request voluntary withdrawal of these drugs and presenting health recommendations for exposed persons), *available at* http://www.fda.gov/cder/news/

term, but after it notes that "clinical importance" could be an important factor to consider, it subsequently states only that the clinical importance of the given condition in this context is unknown.[163] If clinical significance is to play any meaningful role as a standard in these pharmaceutical contexts, the regulatory bodies involved must define and use the term consistently. These sparse examples demonstrate that even when there may be clearer standards promulgated by the regulatory bodies on a very precise issue, the meaning, both on the general and the specific levels, remains vague and ambiguous.

C. Medical Treatises, Scientific Manuals, and Scholarly Legal Articles

Medical treatises, scientific manuals, and scholarly legal articles are other potential sources of information regarding the general understanding of the meaning of clinical significance. In his treatise on human experimentation, William Silverman discusses significance, statistical and otherwise, and in doing so, expresses a serious disapproval of the use of the word "significance."[164] He begins a section on terminology by stating that "[if] it were possible to outlaw the word 'significant' when describing statistical inferences, the ban would go a long way in improving the clarity of our assertions about the state of evidence in medicine."[165] He refers to the typical reliance on the word "significance" as "desperate longing for anchors of certainty in a sea of doubt," and likens any attempt to define clinical significance to an attempt to catch a "greased pig."[166]

In his treatise, *Ethics and Regulation of Clinical Research*, Robert Levine points out the degree to which our culture affirms statistics as determinations of truth.[167] Further he reminds the reader that scientists, journal editors, and

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mmwr.pdf (last visited Feb. 12, 2002). While the FDA here refers to "clinical importance" rather than "clinical significance," there is no reason, from the context, to believe that the two are qualitatively or conceptually different in meaning and thus for the purposes of this Note they are interchangeable.

163. *Id.* at 1064-65.

164. *See* SILVERMAN, *supra* note 6, at 127 (discussing confusion over word "significance" and phrase "statistically significant").

165. *See id.* (expressing basic idea that "significance" is unhelpful and misleading word to use because word has no clear meaning at all).

166. *Id.* at 120, 127. The word is, in Silverman's assessment, completely subjective and, therefore, leads people to believe that they have found some level of certainty when objectively they have not. *Id.* At the very least it must be conceded that any objective standard for clinical significance necessarily would be limited to a very narrow context. *Id.* at 121. Silverman actually refers to a "clinically important difference," rather than "clinical significance" *Id.* at 120. However, as discussed *supra* note 162, rewordings of the concept do not command a conceptually different meaning.

167. *See* ROBERT J. LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 200 (1986) ("Our culture seems to affirm statistics as one way of determining what is true, i.e., what is

the FDA, among other authorities, all require statistical significance for the establishment of scientific claims.[168] This is acceptable because we all share a common understanding of what statistical significance is, and can thus rely on this understanding. However, for *clinical* significance to be meaningful and reliable to the extent that our culture might affirm it as it affirms statistical significance, a clearer definition or standard will have to emerge. Otherwise, clinical significance never will achieve the determinative force with which some attempt to credit it.

The scholarly legal articles that deal with medical, and particularly drug or pharmaceutical product topics, tend to use the phrase "clinical significance" only in passing, without any discussion of what it means.[169] It seems, in fact, that more often than not the author is noting a *lack* of clinical significance. This might explain, if not excuse, the absence of a definition, as perhaps there is less need to define something that is not there. Even so, as long as there are statements in this literature to the effect that, as one scholar has described it, clinical significance is "the relevant measuring stick for all studies," it is important to try to understand what clinical significance is.[170] Thus, however minimal the amount of material, it is worth an attempt to extract what definition one can from these academic, as opposed to legislative and judicial, uses of the phrase. In terms of positive contributions to the definition, there are a few isolated indications.

In their article on Lanham Act litigation, Charles Walsh and Marc Klein spare only a few lines for discussion of statistical and clinical significance.[171] These authors provide an appositive statement, containing what appears to be

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sufficiently true (or sufficiently proven) so that it may be revealed as an accepted fact, one that is worthy of disclosure."). The relevant portion of this book discusses Randomized Clinical Trials (RCTs). *Id.* at 185-212. Levine identifies major problems associated with their design and implementation. *Id.* Levine calls the RCT the "gold standard for evaluating therapeutic efficacy." *Id.* at 211.

168. *Id.* at 200.

169. *See* Beverly W. Lubit, Note, *The Time Has Come for Doing Science: A Call for the Rigorous Application of Daubert Standards for the Admissibility of Expert Evidence in the Impending Silicone Breast Implant Litigation*, 42 N.Y.L. SCH. L. REV. 147, 169-70 (1998) (demonstrating generic example of this type of usage, as follows: "Because the spectrum of effects is so wide, autoimmune processes are commonly invoked to explain many diseases of unknown etiology, and highly sensitive assays often reveal auto-antibodies even though they are of no clinical significance").

170. *See* Andrea C. Levine, *NAD Case Reports Voluntary Self-Regulation of National Advertising*, 808 PRAC. L. INST. COM. L. 73, 143 (2000) (placing quoted phrase in apposition to phrase "clinical significance").

171. *See* Charles J. Walsh & Marc S. Klein, *From Dog Food to Prescription Drug Advertising: Litigating False Scientific Establishment Claims Under the Lanham Act*, 22 SETON HALL L. REV. 389, 436 (1991) (devoting only twelve lines of text, in fifty-seven page article, to these two phrases).

a proposed meaning for the phrase "clinical significance."[172] They gloss clinical significance as meaning "that the perceived difference is relevant to the use of a medication for treatment."[173] It is not clear that this definition really tells the reader anything, but Walsh and Klein probe no further (if they have probed at all). At most, the reader learns from this that clinical significance entails some effect that has more than a theoretical impact on the patient's outcome.

In one instance, simple word association implicates a possible identity of meaning between "clinical" and "therapeutic."[174] Other references provide some information through examples. For instance, one reference states the following:

> The effectiveness of a drug is traditionally demonstrated by proving (in well-controlled, double blind clinical studies) that the drug affects some clinically significant endpoint. An example of a clinically significant endpoint is death – if the experimental drug reduces the number of patients who die from a particular disease, then it is deemed effective in treating that disease.[175]

The same discussion also refers to "the efficacy of a drug [being] proven by showing an effect on a non-clinically significant endpoint that indicated a likely clinical effect."[176] A similar analysis suggests that clinical significance should be defined in terms of potential harm to the patient.[177] Examined together, these references only reinforce the impression of ambiguity and vagueness that pervades the use of this phrase, with the possibility of a stress on the idea of something that will have a perceptible impact on the patient's condition or treatment.

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172. Note that they put clinical significance in quotation marks, but not statistical significance. *Id.*

173. *Id.* Walsh and Klein also distinguish between "clinically significant" and "clinically trivial," reinforcing the idea that a perceptible clinical difference may not necessarily be clinically significant. *Id.* at 436 n.228.

174. *See* Mary C. McCarron, *The Right to Refuse Antipsychotic Drugs: Safeguarding the Mentally Incompetent Patient's Right to Procedural Due Process*, 73 MARQ. L. REV. 477, 481 n.28 (1990) (referencing "clinically significant therapeutic effects").

175. Nancy K. Plant, *Adequate Well-Controlled Clinical Trials: Reopening the Black Box*, 1-SPG WIDENER L. SYMP. J. 267, 272 (1996).

176. *Id.*

177. *See* Laizure, *supra* note 13, at 537 n.130 (citing ARTHUR F. SHINN, EVALUATIONS OF DRUG INTERACTIONS, xii (Arthur F. Shinn & Mark J. Hogan, eds., 1988), in which Shinn rated drug interactions at different levels of clinical significance). Shinn describes drug interactions of "moderate" clinical significance, for example, as being "of moderate potential harm to the patient, [as] less predictable or [that] occur less frequently, or lack complete documentation," whereas those of "minimal" clinical significance are "of little potential harm to the patient, have variable predictability or occur infrequently, or have little documentation." *Id.*

When the foundation for clinical significance, or the way in which it is properly determined, is concerned, there is some indication that formality of testing and studies is at least preferred, if not necessary.[178] However, a contrast appears concerning the issue of the substantiality of the difference to be regarded as clinically significant. On the one hand, it is not the case that *any* deviation or difference is *necessarily* clinically significant.[179] On the other hand, a difference can have little or no clinical significance and still have costs to individuals and society.[180]

Thus, the references to clinical significance in the secondary materials add little to clarify an understanding of the proper use and meaning of that phrase in the drug litigation context. There is little indication of concern about the problem (or even recognition of the problem) on the part of individual authors. Therefore, it is only in looking at the broader array of possibili-

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178. *See* Ivan L. Preston, *Description and Analysis of FTC Order Provisions Resulting From References in Advertising to Tests or Surveys*, 14 PEPP. L. REV. 229, 276 n.207 (1987) (requiring that for test results to be clinically significant, test must be of sufficient duration); *see also* Levine, *supra* note 170, at 143 (requiring "sufficient test population" to achieve clinical significance).

179. One author has written about statistical significance in the FTC's regulation of advertising, first quoting from the opinion in *Thompson Medical*, 104 F.T.C. 648, 724 (1984), then adding his own analysis.

> "A danger in evaluating clinical trials is to misinterpret a failure to demonstrate a difference between two treatments as meaning that the treatments are in fact the same. When differences are statistically significant, the results can be said to be due to essential differences in the drugs. When differences are statistically insignificant," however, this does not rule out the possibility that real differences exist. Even when differences are statistically significant, they can be clinically insignificant. Bristol-Myers stated that a determination must be made concerning whether a statistically significant difference is clinically significant; this will not be so if scientists regard the difference as too small to matter.

Preston, *supra* note 178, at 283 (quoting *Thompson Medical*, 104 F.T.C. at 724). Another scholar warns:

> Statistical significance should not be confused with medical significance. A result that is statistically significant means only that chance has probably been excluded as an explanation. Whether the result has implications for health care is a medical or public health judgment, not a statistical one. A test of statistical significance is not determinative of medical or clinical significance, nor does it validate a result.

Charles Q. Socha, *All Journal Articles are Not Created Equal: Guidelines for Evaluating Medical Literature*, 67 DEF. COUNS. J. 61, 68-69 (2000). Note that these discussions tell us something about the relationship between the types of significance, but they still do not provide a definition of clinical significance.

180. *See* Lars Noah, *Pigeonholing Illness: Medical Diagnosis as a Legal Construct*, 50 HASTINGS L. J. 241, 305 (1999) (citing ROBERT A. ARONOWITZ, MAKING SENSE OF ILLNESS: SCIENCE, SOCIETY, AND DISEASE 107 (1998), who includes as among these costs iatrogenic harm, worry, stigma, and abuse of sick role).

ties that it becomes apparent how disparate, or at least how vague, the views on the problem can be.

D. Evaluation

In sum, the secondary sources beyond the case law add very little to any understanding of clinical significance. The regulatory language incorporates the phrase and gives it determinative importance, but never defines it. The agency's provision of more specific standards for a particular disease refers, although in inconsistent language, to the concept without explicit explanation. Academic usage, even when it ostensibly provides a definition or a description, fails to put forward a definitive statement. Academics more often use the phrase in passing, without paying particular attention to its meaning. Thus, once more, only confusion and ambiguity emerge from the use of the phrase in these sources.

VI. Final Evaluation and Conclusion

Having presented a survey of the various indications from case law, legislative materials, and academic sources, it is apparent how little clarity, and certainly how little consensus, there is concerning the meaning and appropriate usage of the phrase "clinical significance." It is possible without too much artificiality to organize the contextual indications into a few potentially coherent definitions. The two most basic of these understandings seem to be so different as to be irreconcilable. They are at opposite ends of the spectrum of possible meanings – whether there may be something else in between the two is something not yet worked out.

The first of these would require that a finding of clinical significance be based on formal studies of sufficient size, duration, controls, randomization, and so on, to make a scientifically sound generalizable determination. However, it is unclear what one would use the resulting finding to look for or to decide. Such a finding would likely produce only statistical significance. It is not clear that a finding from a study would aid the clinician who must apply it.[181] In fact, it appears that these requirements are so much like those for

181. One author has stated a clinician's perspective on diagnosis and treatment that implicates this issue: "Diagnosing disease is an act with consequences, not merely a cognitive exercise that matches the particular patient to specific disease criteria." ARONOWITZ, *supra* note 180, at 246 n.20. For the determination of clinical significance to be of practical use to those who will apply it to patients or who might look for it in studies of patients, there must be an observable effect on those patients. *See also* Cordis Corp. v. Advanced Cardiovascular Sys., Inc., No. CIV.A.97-550-SLR, 1998 WL 422300, at *3 n.4 (D. Del. July 17, 1998) (stating, in medical device case, that particular result from study, "while not statistically significant, has some clinical significance because doctors make decisions based upon such data").

finding statistical significance as to be simply redundant. The findings would be reliable and consistent, but would add little value that determining statistical significance did not gain already.

A second possible understanding of clinical significance involves observing the individual patient (or perhaps a few patients), drawing associations between two events (namely, use of a drug and an observable change in the patient's condition), and arguing for a causal link between the two. The major problem here is with the evidence of causation. Unless all other potential causes have been precluded, which is nearly impossible in a small sample or test group, this argument would be based purely on the experience and expertise of the individual clinician. When this judgment goes explicitly against the statistically significant results available from larger or more formal studies, its reliability becomes questionable. In short, "clinical significance" by this definition is simply not reliable. It represents only a guess based upon experience, with too small a sample and too many possibilities for other causes.

A third possibility, from an entirely different angle, might set very specific standards for clinical significance for each given drug or disease (like the FDA's standards for VHD, or the Black Lung test standards). However, in that scenario, the usefulness of a uniform phrase would be questionable. There is no need for generalization if the phrase cannot be generally applied. A fourth standard might be to define clinical significance as a statistically significant finding with an observable therapeutic effect. However, as compelling as this might sound, it still lacks any clear indication of the level to which such an effect must rise, and thus still is not a very meaningful or useful standard on which to rely.

At its worst, "clinical significance" is assigned no explicit meaning at all, but simply appears in passing. Of all of the pitfalls listed so far, this is perhaps the worst. Therefore, it makes sense either that the phrase should be endowed with some specific meaning or that it should not be used at all. This leads to the question of the purpose a definition might serve, if an adequate definition could be constructed. Admittedly, all that is statistically significant is not necessarily important in a clinical setting, either because there is no therapeutic effect on the individual patient, or because it is too undetectable a difference to be applied by the clinician.[182]

If "clinical significance" can be clearly defined in a way that differentiates it from statistical significance, I believe that the contrast would be a useful one. For the phrase to be useful, however, the definition must be both general enough to apply to a range of particular circumstances, and yet precise enough to be helpful in the particular context at issue, so it must retain a

182. *See supra* note 181 (remarking on diagnostic approach of clinician).

certain amount of flexibility. At the same time, it must be concrete enough to afford consistency of understanding and application. However, all of the options laid out in this final evaluative section demonstrate the shortcomings and potential pitfalls of the possible approaches.

If a definition cannot be formulated in a workable fashion – and the current mess suggests that it cannot – it would be much better to do away with the phrase at the general level and use it only when specifically defined for a narrow context. For that matter, it is unnecessary at the specific level to use the phrase at all. Instead, one might avoid the ambiguities and vagueness of both "clinical" and "significant" by defining threshold findings and determinations of causation in terms specific to the given disease, condition, or drug involved.

As the phrase stands now, it makes little if any positive contribution to drug-related litigation, while at the same time causing several important problems that will only grow worse with continued confusion and ambiguity. Discrepancies, like those among the *Linnen* orders, leave litigants unsure of what the phrase means and how courts will apply it.[183] This uncertainty may make room to accommodate avoidances of *Daubert*'s gatekeeping standards. Either there must be a uniform, objective understanding of the phrase "clinical significance" in drug-related litigation, or the phrase should not be used at all, but something must change to maintain an acceptable level of predictability and fairness in these cases.

183. *See supra* note 84 and accompanying text (explaining these discrepancies).