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Federal Regulation of Ritalin in the Treatment of Hyperactive Children

Larry Padway*

INTRODUCTION

Between 500,000 and 1,000,000 children\(^1\) receive daily or twice-daily doses of stimulant drugs to control "hyperactive" behavior.\(^2\) Methylphenidate hydrochloride, marketed by CIBA-Geigy Corporation under the brand name "Ritalin,"\(^3\) is the most widely prescribed\(^4\) of these drugs, and is considered by some to be the most effective.\(^5\)

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1. P. SCHRAE & D. DIVOKY, THE MYTH OF THE HYPERACTIVE CHILD, at xii (1975). The authors note that the number of children now receiving such psychostimulants may well exceed this 1975 estimate, "since their numbers have been doubling every two or three years." \(\text{Id.}\) The estimates of the number of hyperactive children vary widely. A federal report conservatively placed the figure at three percent of all school children. U.S. Dep't of Health, Education, and Welfare, Report of the Conference on the Use of Stimulant Drugs in the Treatment of Behaviorally Disordered Children 2 (1971).

2. To explain why stimulant drugs are administered to control the behavior of hyperactive children, one commentator notes that "in adults the stimulant drugs act as so-called pep pills. When used on children, however, they have a paradoxical calming effect. The physiological reasons for this calming effect are not known." Messinger, Ritalin and MBD: A Cure in Search of a Disease, HEALTH POLICY CENTER BULL., Nov.-Dec., 1975, at 1, 2. But see Weithorn & Ross, Stimulant Drugs for Hyperactivity: Some Additional Disturbing Questions, 46 AM. J. ORTHOPSYCH. 168, 169 (1976) ("[D]espite the widespread misconception that stimulants have a paradoxical effect on hyperactive children, there really is no evidence that these drugs act differently on the central nervous systems of hyperactive children than on the central nervous systems of anyone else. Studies conducted with normal adults have indicated that stimulants enhance attention, prolong concentration, and counteract the effects of fatigue.").

3. While many of the studies cited in the Article refer to the drug only by its generic name, methylphenidate hydrochloride, this Article will use the proprietary name, Ritalin, exclusively.


5. See Connors, Recent Drug Studies with Hyperkinetic Children, 4 J. LEARNING DISABILITIES 476, 481-82 (1971) (noting that methylphenidate and Dextroamphetamine appeared to be equally efficacious, but the former has fewer side effects) [hereinafter cited as Connors, Recent Drug Studies].
The use of Ritalin in the treatment of hyperactive children is the subject of a great deal of debate in educational and medical literature. Ritalin is characterized, at the extremes, as either a miracle drug that allows otherwise disruptive and destructive children to learn or a "cure in search of a disease." There are obvious and severe hazards associated with the improper use of drugs. For a variety of reasons discussed in this Article, the use of Ritalin illustrates these hazards and their potential mitigation by appropriate governmental regulation.

New drugs, including Ritalin, cannot be distributed in interstate commerce without first being approved by the Food and Drug Administration (FDA). Federal drug regulation restricts interstate distribution to those drugs: (1) that have been demonstrated to be safe; and (2) for which there is substantial evidence of effectiveness when used in the treatment of a specific syndrome. Safety and effectiveness must be demonstrated by, among other things, clinical research.

One of the major difficulties encountered in establishing the efficacy of a drug is the problem of distinguishing those persons who will benefit from the use of the drug from those who will not. Human fallibility insures that the distinction will never be perfect. Nevertheless, federal law requires the manufacturer of a drug to specify a "label" that states the use or uses for which the drug is claimed to be safe and effective; the manufacturer must demonstrate to FDA the relative safety and efficacy of the use of the drug for that group of persons identified in the drug label as persons who will benefit by taking the drug. Ritalin regulation presents unique problems and issues because of its pediatric nature and because of the relative inability of researchers to isolate the persons to be benefited by the use of Ritalin, i.e., "hyperactive" children, which results in difficulty in prescribing a proper label for the drug.

This Article investigates the difficulty of identifying the hyperactive child, the resulting overinclusiveness of the diagnostic criteria used in the drug label, and the issues thereby raised for federal drug regulators who must decide if Ritalin is safe and if there is substantial evidence of its effectiveness as a treatment for "hyperactive" children. As will be shown, Ritalin's efficacy as a treatment for hyperactive behavior is measured by the subjective evaluation of a wide range of symptoms, with the judgments of

6. "Hyperactivity" is also known as minimal brain dysfunction, minimal cerebral dysfunction, hyperkinesia, hyperkinetic behavior disorder, and by a host of other terms. All of these refer to the same syndrome. One writer has identified 38 terms of similar usage which describe this syndrome. S. Clements, Minimal Brain Dysfunction in Children 9 (National Institute of Neurological Diseases and Blindness Monograph No. 3, 1966).

7. Ritalin is utilized in the treatment of adults for disorders other than hyperactivity. This Article concerns only the use of Ritalin in the treatment of hyperactive children.


parents, teachers, and physicians as to the social acceptability of a child’s behavior playing a dominant role in determining the presence and severity of the syndrome. In many respects, the regulation of Ritalin has much in common with the regulation of psychiatric drugs. The difficulty in determining when a patient is “depressed,” is similar to the difficulty in measuring the extent and existence of a child’s “hyperactivity.” This subjective element in the diagnosis of hyperactivity raises substantial questions regarding: (1) the type of clinical testing and evidence that should be required to demonstrate Ritalin’s safety and effectiveness in order to secure FDA approval of its distribution; and (2) the kind of labeling that should be employed in the distribution of Ritalin to guide physicians in its use.

Ritalin is administered to hyperactive children. Since a child is unable to consent to treatment, the decision to treat is made by a parent. The complexity of this parental decision is increased due to the behavior modification aspects of Ritalin treatment, the unusual role played by the parent in diagnosing the child’s hyperactive behavior, and the subjective nature of the hyperactive syndrome and its symptomatology. The parent may face conflicting interests as a decision-maker on behalf of the child, since the child’s interests may best be served by substantial environmental changes in lieu of drug treatment, while the parent may be discomfited by those changes. This conflict may produce a wholly unconscious parental bias which results in an inappropriate treatment decision for the child. The issue thus arises whether the parent, as a participant in the diagnostic process, should be formally provided with information concerning this potential conflict. Further questions arise as to when and how the information should be delivered to the parent.

The civil liberties and privacy issues concerning prescription of Ritalin over the objection of the parents are adequately dealt with elsewhere, and are not considered here. This Article focuses on the federal regulation of Ritalin in situations where the patient’s parents do not object to its use.

I

HYPERACTIVE BEHAVIOR DEFINED

Hyperactivity is not a disease with discrete, objectively verifiable symptoms; it is a syndrome whose presence is subject to uncertainty in many cases and whose broad symptomatology is often quite vague. One monograph identifies ninety-nine symptoms which tend to indicate hyperactivity, but no combination of which definitely determines the presence of

10. In one recent child custody case, for example, it was found that a hyperactive child who did not respond well to drug therapy improved greatly when removed from his mother’s care and placed in another home environment. See text accompanying note 202 infra.

the syndrome.\textsuperscript{12} This uncertainty in the identification of hyperactive characteristics in children reflects not only the lack of an objective symptomatology, but also the diverse theories of the cause of hyperactivity. Thus, the variety of names by which the disorder is known\textsuperscript{13} are derived from terms describing its functional characteristics \textit{e.g.} "hyperactivity" or "hyperkinetic behavior disorder," and its supposed organic cause, \textit{e.g.}, "minimal brain dysfunction." Despite the large numbers of labels attached to the disorder, research has not disclosed unique subgroups of "hyperactive" children that might be separately identified by these varying designations.\textsuperscript{14} Nonetheless, the probability remains that diagnoses of "hyperactivity" are being used to label children with a variety of syndromes.

Hyperactivity is frequently considered more an environmental or social problem than a medical one.\textsuperscript{15} This view finds support in the vague definition of hyperactivity,\textsuperscript{16} the contradictory results of the studies described below\textsuperscript{17} and the failure to determine its etiological nature.\textsuperscript{18} One researcher found that differing diagnoses of the syndrome were largely due to the etiological biases of the diagnosticians.\textsuperscript{19}

Perhaps the most accurate definition of hyperactivity is one that does not pretend to embrace the traditional scientific nomenclature, but defines the disorder medically in terms of what it is not, and socially in terms of what it is:

Most often, the designation of "hyperkinesis," minimal cerebral dysfunction, or other preferred terms used to label this complex of behavioral and medical difficulties, is defined by the presence of hyperactive behavior and the \textit{absence} of such other conditions as cerebral palsy, epilepsy, gross brain damage, psychosis, or mental retardation.\textsuperscript{20}

Hyperactivity is frequently defined in terms of its outward behavioral manifestations, such as "fidgeting," \textsuperscript{21} and "restless" \textsuperscript{22} and "impulsive" \textsuperscript{23} behavior. These terms are of little assistance because they do not signifi-
cantly narrow the broad range of characteristics that might be termed "hyperactive" behavior. One researcher, defining hyperactivity in terms of the relationship between the child and his environment, describes it as a "chronic, sustained, excessive level of motor activity which is the cause of significant and continued complaint both at home and at school," while another notes that the diagnosis is "partially a social value judgment." Although hyperactivity is frequently thought to be associated with learning disabilities, studies covering a wide range of intelligence tests have not borne this out. Even where teachers rate the child's hyperactive behavior as "improved" during Ritalin therapy, there is often no improvement in scholarship as measured by standardized tests.

The use of subjective social judgments to define a disequilibrium between a child's behavior and behavior acceptable in his social environment does not necessarily require labeling the child as someone in need of treatment. The problem may lie with: (1) the child; (2) his environment; or (3) the perceptions of those making the diagnosis. Unless a means exists for distinguishing which of the three possibilities is correct, severe moral and legal questions are raised for the drug regulation. How can medication be administered to a child in order to treat his environment? How can one prescribe or allow the child to take the drug when there are severe hazards connected with its use and there may be no corresponding benefits for the him? These issues are examined in detail elsewhere in this Article.

Researchers attempting to identify the symptoms and etiology of hyperactive behavior have examined both physical and behavioral characteristics of hyperactive children. Because the approved drug label for Ritalin claims that the drug is effective in the treatment of hyperactivity the attempts of these researchers to refine our knowledge concerning the nature

27. See note 58 infra, and text accompanying note 86 infra.
28. See text accompanying notes 200-215 infra.
29. See text accompanying note 183 infra.
of hyperactive behavior must be reviewed to determine whether such a broad drug label denotes a sufficiently specific group of children for whom the drug is effective.

A. Organic Definitions

There is much speculation as to possible organic causes of hyperactivity, including claims that hyperactivity is caused by birth complications, allergies to certain food additives, heredity, biochemical abnormalities


32. Cantwell, Psychiatric Illness in the Families of Hyperactive Children, 27 ARCHIVES GENERAL PSYCH. 414 (1972) (finding that male hyperactive children have relatives with a high incidence of alcoholism, sociopathy, and hysteria); Morrison & Stewart, A Family Study of the Hyperactive Child Syndrome, 3 BIOLOGICAL PSYCH. 189 (1971); Silver & Brunwick, Familial Patterns in Children with Neurologically-Based Learning Disabilities, 4 J. LEARNING DISABILITIES 349 (1971). See also Menkes, Rowe, & Menkes, A Twenty-Five Year Follow Up Study on the Hyperkinetic Child with Minimal Brain Dysfunction, 39 J. PEDIATRICS 393 (1967) (finding that, as adults, three individuals were still hyperactive, four institutionalized or psychotic, two retarded, and eight were self-supporting). Note that one could interpret these studies to mean that the primary cause of hyperactivity in children is the presence in the family of alcoholism and other psychosocial disorders, rather than interpreting them to mean that the presence of these disorders in adults and hyperactivity in children are the effects of a common genetic disorder. The former contention is made plausible by findings revealing no chromosomal abnormalities in hyperactive children. Warre, The Hyperactive Child Syndrome, 24 ARCHIVES GENERAL PSYCH. 161 (1971).

33. Silver, A Proposed View on the Etiology of the Neurological Learning Disability Syndrome, 4 J. LEARNING DISABILITIES 123 (1971) (suggesting that hyperactivity is caused by an inability to metabolize norepinephrine); P. Wendel, Minimal Brain Dysfunction in Children 163-91 (1971) (tentatively supporting this viewpoint); Rapoport, Lott, Alexander, & Abramson, Urinary Noradrenaline and Playroom Behavior in Hyperactive Boys, LANCET, Nov. 28, 1970, at 1141 (finding a relation between catecholamine levels and hyperactivity); Coleman, Serotonin Concentration in Whole Blood of Hyperactive Children, 78 J. PEDIATRICS 985 (1971) (finding below normal platelet serotonin levels in the blood of 22 of the 25 hyperactive children tested, although finding some indication that platelet serotonin levels are affected by environment). However, in a later study, Wender did not find any differences between hyperactive and nonhyperactive children in the levels of another neurotransmitter, monoamine, in the brain, although the indirect method used to measure the monoamine level, urine analysis, renders the findings inconclusive. Wender, Urinary Monoamine Metabolites of Children with Minimal Brain Dysfunction, 127 AM. J. PSYCH. 1411 (1971). Rapoport later found normal platelet
lead poisoning, and even sensitivity to radiation from fluorescent lighting.

In studies proceeding on an organic etiological assumption, hyperactivity has sometimes been defined in terms of the presence of various "soft" neurological signs. "Neurological signs are considered 'soft,' as opposed to 'hard,' when their actual presence is uncertain or when the relationship between their presence and specific central nervous system damage is unclear." Impairment of motor functions, such as a lack of coordination or "immature" reflexes, are considered "soft" signs.

The presence of soft signs alone may lead to a diagnosis of hyperactivity. Under some definitions, the presence of "hard" neurological signs removes the child from the vague "hyperactive" diagnosis and places the child into a distinguishable "organic brain damage" category.

However, doubt remains as to whether the child with soft signs has suffered any real organic damage. "Soft" signs are highly age-dependent and may reflect only the immature development of nervous system structures. Another problem with the use of "soft" signs is that these symptoms may be found not just in hyperactive children, but also in many other children who are behavior-disordered but not hyperactive.

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34. David, *Association Between Lower Lead Level Concentrations and Hyperactivity in Children*, Envt'l Health Perspectives, May, 1974, at 14 (finding that urban hyperactive children had significantly higher lead levels in their bones, blood, and urine than did the control group). See also Needleman, *Lead Poisoning in Children: Neurological Implications of Widespread Subclinical Intoxication*, in *Minimal Cerebral Dysfunction in Children* 47-55 (S. Walzer & P. Walf eds. 1973).

35. One researcher theorized that soft x-rays from standard fluorescent lights caused or at least aggravated hyperactivity. Ott, *Influence of Fluorescent Lights on Hyperactivity and Learning Disabilities*, 9 J. Learning Disabilities 417 (1976). By changing the lights to full-spectrum fluorescent lights and wrapping aluminum foil around the cathode ends of the tubes, Ott claims that hyperactive behavior improved.


37. Id.

38. The variance in the definitions of hyperactive behavior used by researchers reflects a major area of difficulty in the development of standardized criteria for the diagnosis of the disorder. One researcher, theorizing that hyperactive children suffer from minor brain lesions not directly detectable by the use of hard neurological signs, uses measurement of impaired motor activity as a diagnostic tool. Millichap, *Neuropharmacology of Hyperkinetic Behavior: Response to Methylphenidate Correlated with Degree of Activity and Brain Damage*, in *Advances in Behavioral Biology* 475 (A. Vernadikas & N. Weiner eds. 1974). Another study noted that the patient under scrutiny, a presumably "hyperactive" adolescent who was unable to spend any appreciable amount of time at any one activity, had a "well-developed repertoire of motor, social and intellectual skills." Allen, Henke, Harris, Baer, & Reynolds, *Control of Hyperactivity by Social Reinforcement of Attending Behavior*, 58 J. Educ. Psych. 231, 232 (1967).


40. See, e.g., Wilker, Dixon, & Parker, *Brain Function in Problem Children and Controls: Psychometric, Neurological, and Electroencephalographic Comparisons*, 127 Am. J. Psych. 634 (1970) ("excess" numbers of soft signs were discovered in both hyperactive and nonhy-
Some studies support a correlation between EEG abnormalities and hyperactivity, but a number of these studies do not compare hyperactive children with control groups. When hyperactive children are compared with a control group, the results are equivocal. One commentator notes that the absence of a relationship between EEG abnormality and hyperkinesis is further suggested by the failure to note differences between those hyperkinetic children who demonstrate the abnormality and those hyperkinetic children who show normal EEG tracings. The failure to find such differences in the areas of clinical symptomatology, severity of disturbances, and psychological test performance suggest strongly that the presence of an EEG abnormality in some hyperkinetic children may be more of an irrelevant association than an etiological factor.

peractive children with scholastic-behavioral problems). But see Minde, The Hyperactive Child VII, supra note 30 (finding hyperactive children to have more soft signs than behavior-disordered nonhyperactive children and normal children).


42. Kenny, supra note 41; Klinkerfuss, supra note 41; Satterfield, Response to Stimulant Drug Treatment, supra note 41; Satterfield, EEG Abnormalities, supra note 41.

Even EEG results may reflect subjective elements. See Hanvick, Nelson, Hanson, Anderson, Dressler, & Zarling, Diagnosis of Cerebral Dysfunction in Children, 101 AM. J. DISTURBED CHILD 364 (1961) (two independent, trained raters disagreed about EEG tracings in 29% of the cases). One study revealed that children with learning disabilities had significantly more muscle artifact when not taking Ritalin. Knights & Hinton, supra note 26, at 649-50. Muscle artifact is usually regarded as a nuisance by the electroencephalographer.

43. Minde, The Hyperactive Child VII, supra note 30. One study found hyperactive children with both greater and lesser EEG abnormalities than members of the control group had. However, hyperactive subjects whose central nervous system (CNS) arousal was lower than that of the control group's generally responded better to Ritalin than hyperactive subjects whose CNS arousal was higher than that of the control group's. Satterfield, Cantwell, Lesser, & Podosin, Physiological Studies of the Hyperkinetic Child: I, 128 AM. J. PSYCH. 1418 (1973) [hereinafter cited as Satterfield, Physiological Studies]. Another study found that while the hyperactive group had a larger percentage of abnormal EEG tracings, the control group also had an unusually high number of abnormalities. Werry, The Hyperactive Child I, supra note 24, at 127. The study also explained that the EEG abnormalities could be due to "the overactive temperament of the hyperactive child," rather than any brain dysfunction. Id. at 128. A third study found no difference in EEGs taken during sleep between hyperactive children and the control group. Small, Hibi, & Feinberg, Effects of Dextroamphetamine Sulfate on EEG Sleep Patterns of Hyperactive Children, 25 ARCHIVES GENERAL PSYCH. 369 (1971).

44. Dubey, supra note 36, at 355 (citations omitted). See also Knights & Hinton, supra
Another researcher asserts that there are different subgroups of hyperactive children and that some of these subgroups present specific types of EEG responses as well as certain behavioral symptoms.45

There is some evidence that minor physical abnormalities are associated with one type of hyperactive child.46 Yet the only claim of a relationship between hyperactivity and physical characteristics that has consistently held true is that of sex. Hyperactivity is much more prevalent in males than in females, with ratios varying between five-to-one and nine-to-one.47

The failure to establish a firm organic basis for hyperactivity is due to the fact either that the nonspecific label of "hyperactivity" encompasses numerous organically different syndromes or that the syndrome is not organic at all. The positive effects of placebo treatment on hyperactive behavior found in the drug treatment studies are so substantial as to cast doubt on the presence of any organic syndrome.48

B. Phenomenological Definitions

Those favoring a phenomenological approach to the diagnosis of hyperactivity also encounter substantial problems. Relatively little discussion is found in the literature as to what constitutes a "hyperactive" child. Generally, research studies list a number of behavioral characteristics that are found in greater or lesser degree in each "hyperactive" child. Hyperactivity is thereby identified by a totally subjective method similar to Justice Stewart's method of identifying pornography, i.e., "I know it when I see it."49

Children rarely complain about their behavior.50 Usually, parents or teachers complain about the child's behavior.51 Where hyperactivity is defined as activity that is the cause of significant and continued complaint

note 26, at 652 (finding no differences in responses to Ritalin treatment between learning-disordered children with and without probable brain damage); Sroufe & Stewart, Treating Problem Children with Stimulant Drugs, 289 NEW ENGLAND J. MED. 407, 408 (1973) ("To date, no neurologic sign or test or combination of tests has been established through cross-validation to differentiate hyperactive children or those with minimal brain dysfunction from normal control subjects.").

45. Connors, Recent Drug Studies, supra note 5, at 482 (summarizing conclusions reported in Connors, Stimulant Drugs and Cortical Evoked Responses in Learning Behavior Disorders in Children (1970) (paper presented to the Second Annual Cerebral Function Symposium, Denver)).


47. Silver, supra note 33, at 126.

48. See note 83 infra and accompanying text.


51. Minde & Weiss, supra note 50, at 129.
both at home and at school, the principal diagnostic finding must be that the child is not coping with his environment or his environment is not coping with him. This judgment is as much moral and social as medical. In the absence of objective laboratory tests, the distinction between a hyperactive child and one who is merely perceived as such is unclear.

Virtually all phenomenological studies assume that the child has an adequate environment, and that his environment does not contribute to the child's hyperactive behavior. The child's perception of himself or his environment does not contribute to the diagnosis of his "disease." Instead, he is diagnosed in accordance with the way in which his parents or teachers measure his behavior. Therefore, hyperactive behavior is measured either by intrinsic or by overt comparisons of the hyperactive child's behavior with the behavior of other children.

52. See, e.g., Werry, The Hyperactive Child I, supra note 24, at 121 (in selecting hyperactive subjects for study, the investigators preferred a functional "continued complaint" criterion over a more detailed behavioral diagnosis). An emphasis on complaints both from the home and school leads to significantly differing opinions as to a child's hyperactivity. In a review of various behavior rating scales used to measure hyperactivity, one commentator found that while teachers' rating scales generally had higher "interrater reliability" (degree of agreement among raters) than did parents' rating scales, the interrater reliability even among teachers varied in one study from .15 to .71. Sandoval, The Measurement of the Hyperactive Syndrome in Children, 47 REV. EDUC. RESEARCH 293, 297-303 (1977).

53. See Weithorn & Ross, supra note 2, at 171.

54. Generally, it is not the physician's medical examination, or even the child's complaints, which constitute the primary basis for the diagnosis, but the reported failure of the child to cope with the complex demands of his life situation. This life situation may include a number of variables intervening between observed hyperactivity and possible dysfunctioning of the central nervous system. Among these are the child-teacher ratio in the classroom, the frustration tolerance of the teacher or parent, the type and appropriateness of the instructional materials, the degree of disorganization in the child's home life, emotional stress, inadequacy of nutrition and diet, boredom, and even, possibly, the existence of extraneous agents such as lead in the atmosphere or additives in packaged foods.

Id. at 170 (citations omitted). To the same effect is the following observation:

What we actually observe is not a deficit in the process of learning but rather a failure of the child in the complex social matrix of the school world. Failure therefore is partially a social value judgment and not a statement of a scientific fact.

Connors & Rothschild, supra note 25, at 199.

55. At least one team of researchers claims that socio-economic status and parenting styles influence the severity of secondary characteristics of hyperactivity, although not the primary characteristics. Paternite, Loney, & Langhorne, Relationships Between Symptomatology and SES-related Factors in Hyperkinetic/MBD Boys, 46 AM. J. ORTHOPSYCH. 291 (1976). Primary characteristics are those symptoms directly attributable to the syndrome (e.g., excitability and impulsivity), whereas secondary characteristics (e.g., aggressiveness and loss of self-esteem) are caused by interacting with the environment while suffering from the primary characteristics. In general, secondary characteristics are relatively more serious among patients with lower socio-economic status. The researchers found, however, that differences in parenting styles (rated on such relative bases as, for example, loving/hostile, easy-going/firm, short-tempered/patient) contributed far more significantly to a reliable prediction of hyperactivity in a child than did socio-economic factors. Id. at 295.

On other possible effects of parental characteristics on hyperactive children, see note 32 supra and accompanying text.

56. See, e.g., Paternite, Loney, & Langhorne, supra note 55, at 294 (rating of symptom severity by raters reviewing medical, social, psychological, and educational reports); Rie, A
Most studies purport to measure a number of behavioral characteristics. Parents, teachers, and sometimes researchers commonly rate the children observed with respect to these characteristics (e.g., "destructive" or "easily frustrated") before the children are given treatment. The children then undergo Ritalin therapy, usually accompanied by a double-blind control group on placebo therapy. In some studies a "cross-over" design is utilized and the Ritalin and placebo groups switch therapies at some point in the course of the study. During treatment, changes in the level of "hyperactivity" are measured by the changes in the ratings of the parents, teachers, and researchers, thus measuring the efficacy of the drug therapy. However, the rating scales do not take into account the fact that the change the raters perceive in a child is significantly affected by their expectation of the child's improvement. According to dissonance theory, there is a psychological need to justify the enduring of difficulties or the expending of effort by developing a positive attitude toward the end result. Even the use of a double-blind experiment does not eliminate such possible bias from the results of the study; a teacher or parent may be able to distinguish the Ritalin...
subject from the placebo subject by the marked side effects\textsuperscript{60} of Ritalin. Even if the measurement of a subject's hyperactive behavior by one parent or teacher is accurate, the statistical nature of the studies, which compute the level of hyperactive behavior in terms of averaged ratings, demand significant "interrater reliability"—a marked degree of consistency among the raters in the scoring of behavioral symptoms. Few of the studies even attempt to establish this reliability. While in some studies professional observers,\textsuperscript{61} and occasionally teachers\textsuperscript{62} have established interrater reliability, parents have not demonstrated this trait.\textsuperscript{63}

Some researchers attempt to resolve this problem of subjectivity in the measurement of changes in behavior by using an "actometer" to measure relative levels of activity, a Porteus maze to measure distractibility, or similar devices.\textsuperscript{64} However, the failure to standardize the measurements between children currently makes the use of this type of measurement an ineffective diagnostic tool.

Even without the dissonance and interrater reliability problems, there are substantial problems in translating these methods of measuring the behavioral changes in drugged children into usable criteria for everyday, clinical diagnosis and for use in drug regulation. First, there is difficulty in converting a researcher's criteria into a manufacturer's drug label. The diagnostic criteria that have been employed by researchers are not sufficiently standardized to guide a physician in the use of the drug.\textsuperscript{65} From one home or school, the physician may hear continued complaints concerning the

\textsuperscript{60} For a discussion of Ritalin's side effects, see text accompanying notes 91-102 infra.

\textsuperscript{61} See, e.g., Schleifer, supra note 56, at 43.

\textsuperscript{62} See Sandoral, supra note 52, at 297-300.

\textsuperscript{63} See id. at 300-02.

\textsuperscript{64} See generally id. Devices used to measure activity level include: the actometer, Schulman & Reisman, An Objective Measure of Hyperactivity, 64 AM. J. MENTAL DEFICIENCY 455 (1959); the ballistograph, McConnel, Cromwell, & Bialet, Studies in Activity Level: VII, 68 AM. J. MENTAL DEFICIENCY 647, 648 (1964); the accelerometer, Pope, Motor Activity in Brain-Injured Children, 40 AM. J. PSYCHOL. 783 (1970); Johnson, Hyperactivity and the Machine: The Actometer, 42 CHILD DEV. 2105 (1971); the activity recorder, Rapoport, Abramson, Alexander, & Loff, Playroom Observation of Hyperactive Children on Medication, 10 J. CHILD PSYCH. 524 (1971); and the stabilimetric cushion, Sprague, Barnes, & Werry, Methylphenidate and Thoridizine; Learning Reaction Time, Activity, and Classroom Behavior in Disturbed Children, 40 AM. J. PSYCH. 615 (1970). See also Connors, Recent Drug Studies, supra note 5, at 14 (claiming Ritalin improvement measured by tremorgraph); Blacklidge & Ekbal, supra note 26, at 925 (noting no improvement on Porteus maze); Campbell, Douglas, & Morgenstern, Cognitive Styles in Hyperactive Children and the Effect of Methylphenidate, 12 J. CHILD PSYCH. 55 (1971) (maintaining that the subjects' reaction times increased but the subjects had fewer errors with Ritalin, but that "embedded figures" test show no change and "speed naming" test showed no change); Sykes, Douglas, & Morgenstern, The Effect of Methylphenidate (Ritalin) on Sustained Attention in Hyperactive Children, 25 PSYCHOPHARMACOLOGIA 262 (1972) (claiming that the Ritalin group showed improvements in reaction time and sustained attention performance measured by "serial" and "choice" reaction time tests).

\textsuperscript{65} Aside from the problem of a lack of standardized criteria, the typical pediatrician may lack the time, training, and interest necessary for the proper use of behavioral science measurements. Rie, Hyperactivity, supra note 26, at 787.
child's activity, while the same activity may have a far different effect in another home or school; one person's hyperactivity may be another's creativity or an indication of a free spirit. The measurements may well indicate as much about the parents and teachers as they do about the child.

A second problem lies in the fact that the existence of the disease is defined by response to the drug. If parents, teachers, and doctors perceive the child's behavior as having improved while on Ritalin, then the child is deemed "cured." Since the child is cured by Ritalin, then he must have had the disease. This circular method of diagnosis requires the use of Ritalin to determine whether such use is necessary. This raises severe regulatory problems, since physicians presumably use the information disclosed by the drug label to identify—before the drug is administered—those children that will benefit from the drug. The problems encountered in regulating a drug that treats an ill-defined syndrome, and the impact of vague diagnostic criteria on the evaluation of the relative safety and efficacy of a drug are considered in the final section of this Article.

C. Conclusion

Substantial difficulties permeate all of these studies. There is no uniform, reliable, and independently verifiable means of identifying hyperactive subjects. Often, referral or assignment to remedial classes by a parent, teacher, or physician is sufficient for inclusion of the referred child in a study. This methodology substantially undermines the integrity of the results. Not only does it provide little assurance of accuracy in the diagnosis of the referred subject, but it blindly leaves open the probability that researchers are studying, under the single designated category of "hyperactivity," several different disorders. This may be one of the reasons there are no established relationships between the results of neurological examinations,

66. The dubious nature of the diagnostic criteria is well illustrated by one study. When the double-blind experiment showed that Ritalin had no significant positive effects, the authors suggested, among other reasons, that the aggressive and disturbed natures of the study's subjects reflected only temporary symptoms, not psychopathological disturbances. Connors, Kramer, Rothschild, Schwartz, & Stone, Treatment of Young Delinquent Boys with Diphenylhydantoin Sodium and Methylphenidate, 24 ARCHIVES GENERAL PSYCH. 156, 159 (1971) [hereinafter cited as Connors, Methylphenidate].

67. This phenomenon has led one writer to call Ritalin a "cure in search of a disease." Messinger, supra note 2.

68. See text accompanying notes 183-193 infra.

69. For an analysis of the diagnostic problems with drug studies and some suggestions for refining the categories of hyperactive children, see Fish, The "One Child, One Drug" Myth of Stimulants in Hyperkinesis, 25 ARCHIVES GENERAL PSYCH. 193 (1971).

70. Even high interrater reliability within a study does not insure that different studies will not utilize substantially different hyperactive subjects. Children that are recognized as hyperactive in, for example, a rural environment, might not be recognized as such in an urban environment; teachers in structured schools might classify children as hyperactive who would not be so characterized in an individualized school.

71. See, e.g., Paine, Werry, & Quay, A Study of Minimal Cerebral Dysfunction, 10 DEV. MED. & CHILD NEUROLOGY 505 (1968) (finding that abnormal neurological exams, abnormal
EEGs, symptom ratings, and psychological evaluation for individual "hyperactive" children.

Virtually no effort is made by investigators to evaluate home environments and determine if some or all of the subjects studied actually suffer from a purely environmental or social disorder. Although socio-economic status can be accounted for in an attempt to screen out environmentally influenced "hyperactive" behavior, such gross environmental criteria are clearly inadequate to eliminate all environmental causes in the diagnosis of hyperactivity. The failure of the experimenters to successfully segregate various types of hyperactive children and to provide a means of distinguishing children who are in need of medical intervention from those who are perceived as hyperactive because of inadequacies in their social environment creates severe difficulties for those seeking to demonstrate to FDA the safety and effectiveness of drugs for the treatment of hyperactivity. A drug's proponent cannot show which (if any) of the subgroups of "hyperactive" children would benefit by the use of Ritalin. Since these treatable subgroups cannot be identified, and since even the manufacturer does not claim that the use of Ritalin is safe and effective for treatment of all "hyperactive" children, should the use of Ritalin for the treatment of hyperactivity be approved at all? Before that question can be answered, the alternatives to Ritalin therapy must be considered.

II
TREATMENTS FOR HYPERACTIVE BEHAVIOR

A. Non-Drug Treatments

Among the methods of treatment for hyperactivity are two modes which do not involve drugs. The first method is diet control. The diet treatment proceeds on the theory that certain food additives, particularly those containing salicylate radicals, cause allergic reactions in some children which are evidenced by hyperactive behavior. With proper dieting, some studies claim that improvement is seen in a few weeks, although there is evidence to the contrary. The second method involves behavior modification techniques, i.e., simple punishment-reward systems. These show considerable efficacy.
B. Drug Treatments

Another of the principal means of treatment for hyperactivity is the use of drugs. Ritalin, Dextroamphetamine, and Chlorpromazine are the principal drugs used for such treatment. Chlorpromazine is claimed to reduce "hyperactivity" or "fidgeting," but it is said to reduce distractibility, aggressiveness, or excitability. There is a dispute as to whether Chlorpromazine is more effective than placebo therapy.

Dextroamphetamine is generally seen as somewhat less effective than Ritalin and as having somewhat more undesirable side effects. It is the second most frequently prescribed drug. The design of those experiments studying the effectiveness of Chlorpromazine and Dextroamphetamine for the treatment of hyperactivity suffer from the same use of vague diagnostic criteria as those studying the use of Ritalin therapy.

1. Ritalin Therapy: Questionable Evidence of Efficacy

Although Ritalin is the most widely prescribed drug for hyperactivity (probably due, in part, to the advertising campaign which accompanied its introduction), there is a dispute as to whether or not it is more effective than placebo therapy. The only study dealing exclusively with pre-school
children concluded that Ritalin therapy was ineffective in certain respects, and its benefits were not worth the cost of its side-effects among that age group. As previously discussed, there is disagreement as to whether Ritalin affects learning or only behavior. Studies indicated that Ritalin is sometimes effective in producing improvements on a symptom rating scale (using criteria such as “attention span” or “excitability”) but at the same time may not be effective in producing improvements in learning ability evaluated by batteries of standardized tests (such as the Iowa Basic Skills test and the Wechsler Intelligence Scale for Children), even though some of these standardized tests are also considered subjective. The symptom rating scales’ use of vague criteria which do not really measure an improved ability to learn (such as when parents are asked to rate their children on whether they are doing more or less “wriggling”) may produce this discrepancy.

Current studies indicate that no one is reliably able to identify from individual characteristics which children are more likely to respond to the drug. Furthermore, drug efficacy does not reliably correlate with the severity or quality of symptomatology. Clearly, no readily observable specific symptomatology enables a physician to identify cases where the drug is effective. Also, the use of the drug is not result-specific, that is, the drug does not consistently cause the same type of improvement in symptomatology.

2. The Side-Effects

Ritalin produces significant acute side effects. In one study, thirty

For a discussion on how an inadequate diagnosis of hyperactivity influences this dispute over the effects of drug therapy, see Fish, supra note 69.
85. See text accompanying note 26-27 supra.
86. Rie, Hyperactivity, supra note 26, at 788; Rie, A Replication, supra note 26, at 320-21 (claiming some improvement in learning measured by attention skills, but not on standardized tests); Knights & Hinton, supra note 26, at 647-48, 650. But see Weiss, Chlorpromazine, Dextroamphetamine, and Methylphenidate, supra note 76, at 23-24 (maintaining that Ritalin improved test scores, but hypothesizing that that improvement in I.Q. scores was possibly an “indirect” positive effect, the result of improved concentration).
87. The Werry-Weiss-Peters scale, for example, measures “wriggling.” See Werry, Developmental Hyperactivity, supra note 21, at 588.
88. See, e.g., Weiss, Chlorpromazine, Dextroamphetamine, and Methylphenidate, supra note 76, at 24; Sroufe & Stewart, supra note 44, at 407.
89. See, e.g., Weiss, Chlorpromazine, Dextroamphetamine, and Methylphenidate, supra note 76, at 24. But see Satterfield, Physiological Studies, supra note 43, at 1423 (finding the best response to Ritalin among children with the lowest central nervous system arousal states); Connors, Recent Drug Studies, supra note 5, at 482 (finding that patients with different behavioral profiles responded differently to drug treatment, showing improvements on different kinds of behavioral and learning tests) (summarizing conclusions reported in Connors, Stimulant Drugs and Cortical Evoked Responses in Learning Behavior Disorders in Children (1970) (paper presented to the Second Annual Cerebral Function Symposium, Denver)).
90. Weiss, Chlorpromazine, Dextroamphetamine, and Methylphenidate, supra note 76, at 24.
percent of the children treated with Ritalin suffered from insomnia; the same percentage suffered from anorexia as a consequence of treatment. In one of the studies used by the Food and Drug Administration (FDA) to evaluate the effectiveness of Ritalin, the figures were approximately seventy-nine percent and eighteen percent, respectively. In another study, weight loss due to anorexia was significant, but was found to decrease with continued use of the drug. In this study, reports of stomach aches were also common. Other reported side effects included irritability, sadness, dazed-ness, and bedwetting. Increasingly serious symptoms also appeared. One child screamed for hours after being administered the drug, and then fell asleep exhausted. Another went into a "world of his own" and became agitated on the first day of medication, suffered visual and tactile hallucinations the next day, and then returned to normal when medication was discontinued. Other cases of hallucinations have been reported.

Ritalin has been shown to cause a significant elevation of diastolic blood pressure and increase in the heart rate. There is insufficient data to ascertain what, if any, long-range effects might appear from continued use of the drug, although the Ritalin drug label states that Ritalin may impair normal height and weight gain.

Prescribed dosage of Ritalin varies widely. The standard dosage is five to twenty milligrams, twice-daily. However, at least one writer advocates continual increases in dosages until beneficial results are achieved, reporting that "the medication can be increased to seemingly alarming amounts before becoming effective, such as 160 [milligrams per day]."

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91. See Connors, Recent Drug Studies, supra note 5, at 17 fig. 8.
92. See text accompanying notes 160-173 infra.
93. See Connors & Eisenberg, supra note 26, at 460.
94. Weiss, Chlorpromazine, Dextroamphetamine, and Methylphenidate, supra note 76, at 24.
95. Id.
96. Id.
97. Id.
98. Id.
99. Lucas & Weiss, Methylphenidate Hallucinosis, 217 AM. MED. A. J. 1079 (1971). Dosage levels were modest, one subject taking not more than 15 milligrams per day, another taking 10 milligrams per day, and a third taking 40 milligrams per day, all well within the maximum dosage of 60 milligrams per day recommended in the FDA label for Ritalin. There is also a report of psychosis caused by Dextroamphetamine, another drug used to treat hyperactive children. Ney, Psychosis in a Child Associated with Amphetamine Administration, 97 CAN. MED. A. J. 1026 (1967).
100. Knights & Hinton, supra note 26, at 648-49.
104. Id. Current labeling guidelines call for small doses of 10 milligrams per day, gradually increasing to a maximum of 60 milligrams per day. CIBA Pharmaceutical Co., Ritalin Package Insert (rev. March, 1973). These guidelines are recommendations only, and the physician is free to exceed or disregard them.
The researcher reported using a dosage of 200 milligrams per day. 105

3. **The Failure to Reliably Identify those Children Who Will Benefit from Ritalin Therapy**

Despite flaws in the research designs of these studies from a drug regulation perspective, 106 the literature supporting Ritalin use provides substantial expert opinion suggesting that there are individual children: (1) who exhibit specific characteristics that parents, teachers, and physicians, acting independently, can agree upon as constituting "hyperactive" behavior (despite the vagueness of the diagnostic criteria and the capacity for variation in judgments among parents, teachers, and physicians); and (2) who are not significantly affected by the side effects of Ritalin; and (3) whose behavioral and other symptoms are significantly more improved by Ritalin therapy than by a placebo. To establish the safety and effectiveness of the drug for the treatment of hyperactivity, it would be necessary to conduct a study that identifies these children with reasonable specificity, i.e., children with reliably recognizable symptoms who demonstrate a low rate of side effects and significant improvement under Ritalin therapy. However, no such study has been conducted. The studies reviewed here do not demonstrate the existence of such children. 107

Since the studies undertaken to date fail to develop adequate criteria for the identification of "hyperactive" children who are significantly more

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106. For a description of the testing methodology required by FDA, see text accompanying notes 153-159 infra.

107. This result is not surprising, since these studies examine groups of children on a statistical whole, and do not report the relationship between the specific symptomatology and Ritalin responses of individual subjects. Examining the specific symptomatology of those who respond best to Ritalin might reveal a more useful set of criteria for the identification of those likely to improve under Ritalin therapy. The use of a group statistical approach, where the data for all the subjects are averaged, could obscure such very important relationships. For example, certain test subjects with a certain set of characteristics—some characteristics tested for as symptoms of hyperactivity and some not tested for—might respond very positively to drug treatment. The subjects who do not show a significant positive response—while classed as "hyperactive" because they display all of the symptoms tested for—might have some untested characteristics different from those of the first group. In the final analysis, one would conclude from a general statistical study that this large group of "hyperactive" children revealed no significant positive response to drug treatment, since only a small percentage of the total "hyperactive" group improved. See Marholin & Phillips, *Methodological Issues in Psychopharmacological Research: Chlorpromazine—A Case in Point*, 46 AM. J. ORTHOPSYCH. 477 (1976). Marholin and Phillips list the following advantages of single-subject investigations over group-statistical procedures:

[Single-subject investigations] allow the researcher to 1) evaluate effects of drugs on specific, clinically relevant problem behaviors; 2) determine individual differences in effect due to differing dosage levels; 3) evaluate specific drug effects on a range of clinically relevant behaviors for each individual; 4) assess systematically the interaction between drugs and other therapeutic endeavors; . . . [and] 6) evaluate systematically drug dosage curves, latencies, duration of effects, and peak effectiveness dosages . . . .

Id. at 490 (citations omitted).
improved by Ritalin therapy than by treatment with placebos, and who are not more significantly affected by Ritalin's side effects, serious questions are raised concerning: (1) FDA's approval of Ritalin as safe and effective for use in the treatment of "hyperactive" children; and (2) the accuracy and usefulness of the diagnostic criteria currently listed on the federally required drug label. These questions will be more fully treated after an examination of the current federal statutes and regulations governing the use of Ritalin.

III

THE CURRENT REGULATION OF RITALIN UNDER FEDERAL STATUTES

Ritalin, as a drug with a potential for abuse for non-medical drug uses, is currently regulated under three federal statutes. The first is the Controlled Substances Act of 1970, which is primarily a drug abuse control act. Regulation under this act is designed to prevent the diversion of Ritalin and other dangerous drugs into illicit channels and is not concerned with the regulation of their medical uses. Second, the Federal Trade Commission Act gives the Federal Trade Commission general authority to regulate drug advertising, but this statute has little effect on prescription drug advertising. Finally, the Food, Drug, and Cosmetic Act requires that the Food and Drug Administration review and approve a new drug as safe and effective before the drug can be introduced into interstate commerce. This statute is the primary mechanism for the regulation of Ritalin and the principal means of drug control that will be discussed.

A. Regulation Under the Controlled Substances Act

Under the Controlled Substances Act of 1970, the United States Attorney General is given the authority to classify drugs that have a "potential for abuse" into one of five schedules. These schedules range from one for drugs that have a relatively low potential for abuse, current domestically accepted medical uses, and limited physical or psychological dependence side-effects (designated as Schedule V) to one for drugs that have a high potential for abuse, no currently domestically accepted medical use, and lack acceptance as safe when used under medical supervision (Schedule I).

112. Id. § 811. The Attorney General must consider the following factors: (1) actual or relative potential for abuse; (2) scientific evidence of pharmacological effect; (3) the state of current scientific knowledge regarding the drug; (4) history and pattern of abuse; (5) scope, duration, and significance of abuse; (6) risk to public health; (7) likelihood of psychic or physiological dependence; (8) whether the substance is an immediate precursor to another controlled substance. Id. § 811(c). The recommendations of the Secretary of Health, Education, and Welfare are binding on the Attorney General as to scientific and medical aspects. Id. § 811(b).
113. Id. § 812(b)(5).
114. Id. § 812(b)(1).
In order to add a drug to a schedule or to transfer a drug from one schedule to another, the Attorney General must consult the Secretary of Health, Education, and Welfare. The Secretary must evaluate the drug from a medical and scientific viewpoint and make recommendations for control. The Attorney General cannot control a drug or transfer it among the schedules if the Secretary recommends that the drug not be controlled or transferred.\textsuperscript{115}

Ritalin was originally classified as a Schedule III drug,\textsuperscript{116} meaning that its abuse could lead to moderate or low physical dependence and that it had a current domestically accepted medical use.\textsuperscript{117} Subsequently, on October 28, 1971, Ritalin was reclassified to Schedule II\textsuperscript{118} in order to provide tighter controls on the drug, \textit{i.e.}, a prohibition on the refilling of prescriptions,\textsuperscript{119} and tighter restrictions on manufacturing and distribution.\textsuperscript{120} Schedule II has the tightest controls of any schedule for a drug made available for treatment purposes.\textsuperscript{121}

The regulation of Ritalin under the Controlled Substances Act is basically designed to prevent its diversion into non-medical channels. No attempt is made to regulate medical use. While physicians must register under the Act in order to dispense the drug,\textsuperscript{122} the physician is free under federal law to decide what medical uses to make of the drug.\textsuperscript{123} The only labeling requirement imposed by the Act is the requirement that a label be included warning that any transfer of the drug to another person is a crime and placing a symbol on the container identifying the drug as a controlled substance.\textsuperscript{124}

\textbf{B. Regulation Under the Federal Trade Commission Act}

Under the Federal Trade Commission Act (FTCA),\textsuperscript{125} the Federal Trade Commission (FTC) has the authority to enjoin the false and misleading advertising of drugs.\textsuperscript{126} Since the Food and Drug Administration (FDA) has authority to regulate labeling,\textsuperscript{127} there is considerable jurisdictional

\textsuperscript{115} \textit{Id.} \textsection{811(b).
}\textsuperscript{116} \textit{Id.} \textsection{812(c) (Sched. III) (a)(4) (1970).
}\textsuperscript{117} \textit{Id.} \textsection{812(c).
\textsuperscript{119} Although the drug classifications were originally determined by statute, see note 116 supra and accompanying text, the classifications can be altered by regulation. See note 112 supra and accompanying text.
\textsuperscript{119} 21 U.S.C. \textsection{829(a) (1970).
}\textsuperscript{120} \textit{Id.} \textsection{826.
}\textsuperscript{121} \textit{Id.} \textsec{811. 828.
}\textsuperscript{122} \textit{Id.} \textsection{822(a).
}\textsuperscript{123} Subject, of course, to whatever limits are imposed by state law. \textit{Id.} \textsection{823(f).
}\textsuperscript{124} \textit{Id.} \textsection{825.
}\textsuperscript{126} \textit{Id.} \textsection{53.
overlap between the two agencies. Conflict between the two agencies is minimized, however, by both statute and agreement.

Prescription drug advertisements must comply with Food, Drug, and Cosmetic Act (FDCA) standards,\(^{128}\) which require that the advertisement include basic information concerning the drug.\(^{129}\) Advertisements that comply with the FDCA standards are exempted from the false advertising provisions of the FTCA. Advertisements that do not comply are in violation of the FDCA and the drug is subject to the false advertising sanctions of the FTCA.

To minimize conflict in the regulation of over-the-counter drugs, the agencies entered into a formal agreement in 1968,\(^{130}\) under which FTC accepts FDA's evaluation of the safety and effectiveness of a drug if FDA has determined the drug's safety and efficacy. Where FDA has not fully exercised its regulatory powers concerning a nonprescription drug, FTC makes its own determinations.\(^{131}\)

The primary impact of the FTCA on prescription regulated drugs is in terms of the remedies made available for violation of the FDCA advertising rules. FTC has authority to issue cease and desist orders;\(^{132}\) FDA does not have this power. FDA, on the other hand, has the authority to seize drugs that are mislabeled.\(^{133}\) When a violation is found, the agencies can work together in order to determine the best statute under which to proceed. Aside from this use, the FTCA is of little importance in the federal regulatory scheme for Ritalin.

C. Regulation Under the Food, Drug, and Cosmetic Act

1. Required Labeling and the Required Showing of Safety and Effectiveness

The FDCA divides drugs into three main categories for purposes of regulation. Drugs whose uses were established prior to 1938 are exempt from regulation for those uses.\(^{134}\) So-called "new drugs" need FDA's approval as safe and effective before they can be distributed in interstate commerce.\(^{135}\) Drugs which are "generally recognized by experts qualified by scientific training and experience" as safe and effective for use under the


\(^{129}\) The information required includes the name, formula, and a brief summary of the effectivenness, side effects, and contraindications. \textit{Id.}

\(^{130}\) \textit{Id.} at 18.

\(^{131}\) \textit{Id.} at 19.


\(^{134}\) \textit{Id.} § 355.

\(^{135}\) \textit{Id.} § 355(a). This section also prescribes the processing procedures for new drug applications. The required contents of the application are set out in § 355(b). FDA has 180 days following the application either to approve the application or to hold a hearing on the question. \textit{Id.} § 355(c). This period may be extended by agreement between the Secretary and the applicant. \textit{Id.}
conditions that are set forth in the label of the drug are, by statutory
definition, not "new drugs" and are exempt from regulation.136 Provisions
of the FDCA allow a new drug into interstate commerce if it is properly
labeled137 and if it is approved as safe and effective for at least one use.138 A
significant aspect of the regulatory scheme is the evaluation of drugs as safe
and effective for specific uses. Safe and effective treatment of one disease
with a particular drug does not guarantee similar results with the same drug
on another disease. Safety and efficacy are evaluated by FDA in terms of the
manufacturer's claims,139 all of which are contained in the label which must
accompany each container of the drug in interstate commerce.140 However,
once the drug is allowed into interstate commerce, federal law does not
regulate the medical uses that may be made of the drug (with the exception
of Methadone141). Thus, a physician may prescribe a drug for a medical use
for which it has not been federally approved, subject, of course, to potential
civil liability for malpractice.

FDA has primary jurisdiction to determine which drugs are "new drugs" and a manufac-
turer may not seek judicial relief from an FDA decision in a district court. Rather, the proper
procedure is to proceed through FDA and then appeal to a circuit court of appeals. The circuit
court will affirm FDA's decision if it is supported by substantial evidence. Weinberger v.
Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); CIBA Corp. v. Weinberger, 412 U.S.

136. 21 U.S.C. § 321(p) (1970). No amount of recognition or usage is sufficient to place a
drug in this exempt category if the drug cannot also meet the criteria for approval of new drugs.
This section does not provide a loophole in drug regulation for a drug that is widely used and
accepted by experts as safe and effective, but for which there is no substantial evidence of

Although judicial review of FDA's classification of a drug as either a new drug or a drug
generally recognized as safe and effective is available by appeal to a circuit court of appeals, the
decision is considered "peculiarly within the FDA's expertise" and the courts are "reluctant to
intrude into a medical matter we do not truly understand." Pfizer, Inc. v. Richardson, 434 F.2d
536, 546 (2d Cir. 1970) (dictum). *But see* Edison Pharmaceutical, Inc. v. FDA, 513 F.2d 1063
(D.C. Cir. 1975) (directing FDA to consider studies technically not in compliance with FDA
requirements), *rehearing denied*, 517 F.2d 164 (1975).

At one time, FDA attempted to exempt from new drug requirements those drugs that were
chemically equivalent to approved new drugs. These so-called "me-too" drugs were usually
produced by manufacturers other than the manufacturer whose drug was approved. This action
was held to be without authority. Hoffman-LaRoche, Inc. v. Weinberger, 425 F. Supp. 890


138. *Id.* § 355.

139. *See* text accompanying notes 140, 146, 151 *infra*.

140. One major shortcoming of labeling regulations is that the label, which must accom-
pany each container of a drug, need not accompany a drug repackaged by a pharmacist. 21
the drug label.

A container of drugs repackaged by a pharmacist must be labeled "Caution: Federal law
prevents dispensing without a prescription." In addition, the repackaged container must bear
the name and address of the dispenser, a serial number, the name of the prescriber, the date of
prescription or its filling, and if contained on the prescription, the name of the patient,
directions for use, and cautionary instructions. *Id.* In some circumstances, additional require-
ments apply. *Id.*

141. *See* note 215 *infra*.
In order to approve a drug, FDA must receive an application that contains: full reports of investigations regarding the safety and effectiveness of the drug; a list of ingredients and composition of the drug; a description of the methods used in, and the facilities and controls used for the manufacture, processing, and packing of the drug; samples of the drug; and labeling specimens. 142 FDA may either approve the drug for use or hold a hearing in order to allow the manufacturer to present evidence in favor of approval. 143 No hearing is required if use is approved. 144 FDA may withdraw approval when a drug no longer meets the criteria for approval. 145

a. The required showing of safety

The most important issue in the regulation of new drugs, and the one with which this Article is primarily concerned, is the requirement that the drug be shown to be safe and effective for use as directed by the label before it can be approved for distribution in interstate commerce. FDA may disapprove a new drug application if it finds that the data submitted "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 146

Safety and efficacy under the FDCA are relative concepts based upon a balancing of risks and benefits. A drug is not considered "safe" unless the benefits potentially resulting to society from the use of the drug to treat

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143. Id. § 355(c). While a manufacturer may contest whether FDA’s denial of a new drug application or a withdrawal of approval is supported by substantial evidence, Ubiotica Corp. v. FDA, 427 F.2d 376, 378 (6th Cir. 1970), there is no provision in the FDCA for an interested party such as a consumer group to challenge a decision to approve a drug. In fact, if FDA approves a new drug application, the statute does not require FDA to hold any hearing at all. See 21 U.S.C. § 355(c) (1970). However, the Administrative Procedure Act provides a means for challenging FDA rules. See 5 U.S.C. § 553 (1976). Whether an interested party has standing under the Administrative Procedure Act to challenge an approval decision is an open question. Even assuming standing, a successful challenge would be virtually impossible, give the reluctance of courts to overturn an FDA decision on a particular drug, see note 136 supra, and a party’s onerous burden on appeal. The challenging party would be likely to succeed only in the most exceptional circumstances, such as where the studies submitted to FDA indicate on their face that the challenged drug is unsafe and ineffective.

144. See note 143 supra.
145. Withdrawal is permitted on the basis of "new evidence," including "tests by methods not deemed reasonably applicable when such application was approved," if the new evidence evaluated with the original evidence shows that the drug is not safe or effective. 21 U.S.C. § 355(a) (Supp. V 1975). While the burden of proof in the initial approval proceeding is clearly on the manufacturer, Ubiotica Corp. v. FDA, 427 F.2d 376, 378 (6th Cir. 1970), the burden of adducing new evidence is on FDA upon withdrawal of approval. See Hess & Clark v. FDA, 495 F.2d 975, 992 (D.C. Cir. 1974). FDA may withdraw approval without a hearing if the evidence submitted by the manufacturer does not meet the tests mandated by the regulation set forth in note 154 infra. Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 620 (1973); CIBA-Geigy Corp. v. Richardson, 446 F.2d 466, 467 (2d Cir. 1971). Thereafter, to gain new approval, the burden is on the manufacturer to provide evidence indicating that the drug meets FDA standards.
disease outweigh the harms potentially caused by the drug.\textsuperscript{147} As FDA Commissioner George Larrick once stated:

The safety of a drug cannot be considered as an absolute value to be determined with a computing machine . . . . All potent drugs, old and new, have a potential for harm . . . . So the medical officer and other scientists must evaluate safety in light of the good inherent in the drug and balance it against the hazards. If the good in saving lives or alleviating suffering outweighs the hazards, he will permit the NDA (New Drug Application) to become effective under labeling which clearly sets forth the hazards, the contraindicated conditions, the side effects, cautions to be observed, warnings and directions for use which reduce to a minimum the danger inherent in the use of the drug.\textsuperscript{148}

Similarly, a drug is not considered effective when the improvement it provides in the treatment of a syndrome is either non-existent or substantially outweighed by its toxic side effects.

\textbf{b. The required showing of effectiveness}

When Ritalin was approved in 1955,\textsuperscript{149} there was no requirement that a drug be shown to be effective. However, since a consideration of safety under the FDCA entails a consideration of benefits as well as risks, an evaluation of the effectiveness of the drug is necessary to develop the essential information. In 1962, the FDCA was amended to include a specific requirement of effectiveness.\textsuperscript{150} Disapproval of an application is required if “there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling thereof.”\textsuperscript{151}

Congress chose the “substantial evidence” standard for effectiveness instead of the more stringent “preponderance of the evidence” test required for a showing of safety because

in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion . . . .

[T]he existence of such a difference should not result in disapproval

\textsuperscript{147} This relative safety standard might operate, for example, to approve a drug that has a ten percent mortality rate, yet cures an invariably fatal disease.

In contradistinction to the relative standard for safety, an absolute safety standard is found in those sections of the FDCA that deal with the permissible risks of food additives. If tests show that the additive causes harm, use of the additive is proscribed. \textit{See generally} Freedman, \textit{Reasonable Certainty of No Harm: Reviving the Statutory Standard for Food Additives, Color Additives, and Animal Drugs}, 7 \textit{ECOLOGY} L.Q. 245 (1978).

\textsuperscript{148} \textit{Hearings on Administered Prices in the Drug Industries Before the Subcomm. on Antitrust and Monopoly of the Senate Committee on the Judiciary}, 86th Cong., 2nd Sess. 22 (1959-60).


of a claim of effectiveness if it is supported by substantial evidence

In approving a drug, FDA does not conclusively determine that the drug is effective. Rather, FDA can approve the drug even if there is a legitimate dispute as to effectiveness, thereby increasing the discretionary role of the physician in deciding whether a particular drug should be utilized as treatment.

In 1970, FDA developed the following criteria in order to more fully define "substantial evidence" of effectiveness. An application may be refused if

there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling.

The requirement of an "adequate and well controlled" clinical investigation

The FDA regulation further establishes specific criteria for an "adequate and well controlled" clinical investigation. The criteria require a plan or protocol that sets forth a method of selection of subjects for

152. S. REP. NO. 1744, 87th Cong., 2nd Sess. 6 (1962).
154. The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.

(a) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(1) A clear statement of the objectives of the study.
(2) A method of selection of the subjects that (i) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

(ii) Assigns the subjects to test groups in such a way as to minimize bias.
(iii) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.
(3) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjects [sic] response, and steps taken to minimize bias on the part of the subject and observer.
(4) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. Generally, four types of comparison are recognized:

(i) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.
(ii) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.
experimentation. The protocol must provide "adequate assurance that [the subjects] are suitable for purposes of the study, [and] diagnostic criteria of the condition to be treated or diagnosed, [with] confirmatory laboratory tests where appropriate."\textsuperscript{155} The regulation permits a waiver of the criteria in an investigation where they are not "reasonably applicable" and where alternative procedures will yield adequately reliable data.\textsuperscript{156}

The FDA regulation permits the use of several recognized methods for clinically measuring drug effectiveness. These methods compare the changes observed in patients using the drug with the changes, if any, observed in patients receiving: (1) no treatment; (2) placebos; or (3) non-drug therapy.\textsuperscript{157} In the case of drugs intended for use in the treatment of

(iii) Active treatment control: An effective regimen of therapy may be used for comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(iv) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(5) A summary of the methods of analysis and an evaluation of data derived from the study, including any appropriate statistical methods.

Provided, however, That any of the above criteria may be waived in whole or in part, . . . by the Director of the Bureau of Drugs with respect to a specific clinical investigation; . . . A petition for a waiver shall set forth clearly and concisely the specific provision or provisions in the criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been, employed, what results have been obtained, and the basis on which it can be, or has been, concluded that the clinical investigation will or has yielded substantial evidence of effectiveness, notwithstanding non-conformance with the criteria for which waiver is requested. . . .

(c) Uncontrolled studies or partially-controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.


These regulations have been upheld by the courts. See Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973); Upjohn Co. v. Finch, 422 F.2d 944 (6th Cir. 1971). When the regulations were first promulgated, FDA did not comply with the notice requirements of Section 4 of the Administrative Procedure Act, 5 U.S.C. § 553 (1976), and enforcement of the FDA regulation was enjoined. Pharmaceutical Mfrs. Ass'n v. Finch, 307 F. Supp. 858 (D. Del. 1970). After FDA complied with the Administrative Procedure Act, the same court approved the regulations. Pharmaceutical Mfrs. Ass'n v. Finch, 318 F. Supp. 301 (D. Del. 1971).


156. Id. § 314.111(a)(5)(ii)(a)(4), quoted at note 154 supra. See also Edison Pharmaceutical, Inc. v. FDA, 513 F.2d 1063 (D.C. Cir. 1975) (following the criteria would have endangered the health of clinical studies subjects).

high-mortality diseases, the progress of the disease in patients taking the new drug is compared with data "derived historically from the adequately documented natural history of the disease or condition." 158 Uncontrolled or partially controlled studies do not provide a sufficient basis for drug approvals, but they may provide corroborative support for controlled studies. 159

2. The Ritalin Effectiveness Review

As a result of the 1962 Drug Effectiveness Amendments 160 to the FDCA, FDA commissioned the National Academy of Sciences-National Research Council (NAS-NRC) to determine whether or not drugs that had been approved prior to the 1962 amendments were effective. 161 Ritalin was evaluated for use in the treatment of those diseases the manufacturer described in the drug label, including, inter alia, "functional behavior problems in children (hyperactivity, stuttering, etc.)." 162 The NAS-NRC panel found that the drug was "probably effective," but recommended that the words "stuttering" and "functional" be dropped because of a lack of controlled studies concerning stuttering and because the "'functional' as opposed to 'organic' nature of the hyperkinetic syndrome is highly controversial." 163 The review committee also recommended that a new label containing the phrase "hyperkinetic behavior disorders in children" replace the old label.

The NAS-NRC panel cited only two studies in documenting its conclusion that Ritalin was probably effective in the treatment of hyperactive children. 164 In the first study, 165 the children were selected at random from the population of a center for children awaiting foster homes. A drug therapy group performed significantly better than a placebo group on paired-associate learning tests, which require the test subject to anticipate the appropriate pairing of digits and symbols through the recognition of patterns in such pairings. Two low-I.Q. groups on Ritalin performed better on a maze test than did their low-I.Q. placebo counterparts. A high-I.Q. placebo group performed better on the maze test than their high-I.Q. drugged counterparts, but the difference was not statistically significant. The drug group suffered a high rate of loss of appetite (seventy percent), and seven of the thirty-nine subjects who took the drug reported insomnia. In contrast, about seven percent of the placebo group reported loss of appetite, and none

158. Id.
159. Id. § 314.111(a)(5)(ii)(c), quoted at note 154 supra.
160. See text accompanying notes 150-152 supra.
162. NAS-NRC Drug Efficacy Study, submitted to FDA.
163. Id. at 2 (psychiatric panel).
164. Id.
165. Connors, Eisenberg, & Sharpe, Effects of Methylphenidate (Ritalin) on Paired-Associate Learning and Porteus Maze Performance in Emotionally Disturbed Children, 28 J. CONSULTING PSYCH. 14 (1964).
reported difficulty sleeping. The two groups did not differ in a statistically
significant manner on a "symptom rating score" similar to the ones
described earlier.

The second study, performed by two of the same researchers, also
utilized a double-blind technique. The subjects were residents at two resi-
dential care institutions, one an institutional foster home for children unsuit-
able for care in individual foster homes, the other a psychiatric treatment
center. The study reports that none of the subjects were diagnosed as brain-
damaged, defective, or overtly psychotic, but the report does not indicate
that any testing was done that would have led to such a diagnosis. Signifi-
cant improvement in learning was demonstrated only in one of the two
paired-associate learning tests administered to the subjects after treatment
was begun.

The results of a Porteus maze test "showed significantly better per-
formance by the drug-treated subjects." However, "children of low and
average I.Q. displayed greater gains from drug therapy than did those of
high I.Q." Further, the validity of these results is unclear because there
were no pre-test maze scores for comparison. While the group as a whole
demonstrated a "moderately significant" improvement in behavior as
measured by symptom rating scales, there were "large individual differ-
ences in responsiveness to the drug."

The following section of this Article will show that the studies used in
the NAS-NRC evaluation do not satisfy the FDA regulation requiring
"adequate and well-controlled clinical investigations" to demonstrate drug
safety and effectiveness, because the studies lacked adequate diagnostic
criteria for the selection of study subjects. It is also submitted in the
following section that the diagnostic criteria set forth in the federally
approved drug label, by which FDA is required to evaluate the safety and
efficacy of Ritalin, are over-inclusive. The label's vague diagnostic criteria
suggest the advisability of treatment with Ritalin for "minimal brain dys-
function" where the patient may in reality suffer from any one of a variety

166. Id.
168. Id. at 458.
169. Id. at 460.
170. Id.
171. Id. Interestingly, improvements in learning as measured by the paired-associate tests
were analogously divided. On those tests, the presumably more disturbed children from the
psychiatric institution made greater gains than did the children from the foster home. Id.
172. See id. at 458.
173. Id. at 459. Conclusions based on such group statistical data can overlook important
individual responses to the drug and are potentially very misleading. See note 107 supra. The
researchers apparently recognized this defect of group-statistical approach in cautioning that
"the wide individual differences in responsiveness and the consequent smallness of overall
changes indicates that the practical or clinical significance of the drug . . . . must still be
determined." Id. at 462 (emphasis in the original).
of differing syndromes, and where the use of Ritalin therapy to treat the particular syndrome may be relatively unsafe and ineffective when compared to available alternative therapies. Hence, a more narrowly drawn set of diagnostic criteria may be necessary to support the required showing of Ritalin’s safety and effectiveness in the treatment of a medical disorder.

IV
THE REGULATION OF RITALIN: AN EVALUATION

Serious questions exist concerning the adequacy, under FDA regulations, of the studies used in the NAS-NRC Ritalin effectiveness review. Further, it is unlikely that these or any other studies conducted can demonstrate the relative safety and effectiveness of Ritalin under the broad conditions of use suggested in Ritalin’s present drug label. This section reviews these problems and suggests some possible solutions, including a more narrowly drawn set of diagnostic characteristics and a carefully delineated statement of the drug’s benefits. Some suggestions for requiring the development of data on the comparative effectiveness of Ritalin and non-drug therapies are also set forth. Finally, this section treats some of the special problems posed by the pediatric aspects of Ritalin treatment.

A. The Inadequacies in the Showing of Ritalin’s Safety and Effectiveness

1. The Inadequacies of the Studies Used in the NAS-NRC Review

It is doubtful that the two reports employed in the NAS-NRC evaluation provide “substantial evidence” through “adequate and well-controlled clinical investigations” that Ritalin will have the effect that it is purported to have under its current labeling. An “adequate and well-controlled” investigation must, under FDA regulations, provide “adequate assurance that [the subjects] are suitable for purposes of the study, [and] diagnostic criteria of the condition to be treated or diagnosed.” First, the subjects used were not suitable to demonstrate the efficacy of Ritalin for the treatment of hyperactivity in the general population. The studies were carried out among institutionalized patients. There is undoubtedly a difference in kind and degree of symptomatology between an institutionalized child and a child in a home environment.

Second, the reports lack adequate diagnostic criteria for the selection of suitable subjects for the study of the treatment of hyperactivity. There was

174. See text accompanying note 155 supra.

175. See Weithorn & Ross, supra note 2, at 170. A definite relationship between secondary characteristics of hyperactivity and home environment has been demonstrated. See note 55 supra. See also Solomons, supra note 103, at 474 (suggesting that “along with medication, other steps must be taken” in the treatment of hyperactivity, including changes in the treatment of hyperactive children at home). Other studies suggest a connection between the child’s home environment and the primary characteristics of hyperactive behavior. See note 32 supra.
no indication that the study subjects were hyperactive.\(^{176}\) The lack of any diagnostic criteria in the studies creates a basic impediment to their use as "substantial evidence of effectiveness" in the treatment of hyperactive children.\(^{177}\) While, in general, subjective evaluation may necessarily play a larger part in the study of psychiatric and pediatric drugs than for other drugs (and perhaps a different set of adequacy criteria should be used), the criteria should not be so vague that the test for the presence of the disease is to administer the drug and see if a "cure" is effected. There must be limits to the vagueness of the criteria used for diagnosis.\(^{178}\) Even under the very limited exceptions\(^ {179}\) to the FDA regulation governing "adequate and well-controlled" investigations (which ordinarily provides the exclusive means under which studies can meet FDCA standards\(^ {180}\)), the studies submitted are acceptable only if they are "as scientifically sound and objective as it [is] humanly possible" to make them.\(^ {181}\)

176. The subjects were, instead, "disturbed children."

177. In 1970, FDA reviewed the scientific literature on Ritalin. Twenty-six articles relating to pediatric use of Ritalin were reviewed. Several articles were not relevant to the use of Ritalin in the treatment of hyperactivity. Two of the articles cited in 1970 were the studies utilized in the original efficacy review. A third was a paper apparently describing the same study utilized for the first two articles.


One study used as diagnostic criteria persons who had a "behavior disorder of some sort." Lytton & Knobel, supra note 105, at 336. Two articles described possible objective measures of hyperactivity. The first study used modified, self-winding watches strapped on children to measure movement. Apparently, however, the sole purpose of the two page report of the study was to discuss the new measurement technique; no results of the study were given. Schulman & Reisman, supra note 64. The second study utilized an actometer, and indicated that activity increased with the use of Ritalin. The authors did not draw firm conclusions due to the short, two-day period of the experiment and low dosages used. Millichap & Boldrye, *Studies in Hyperkinetic Behavior: II—Laboratory and Clinical Evaluations of Drug Treatments*, 17 *Neurology* 467 (1967).

One of the two principal double-blind controlled studies relied on by FDA simply stated that the subjects selected had been diagnosed by a physician as having minimal brain dysfunction, following referral of the subjects for school problems. Knights & Hinton, supra note 26, at 644. A second study was Millichap, *Learning Disorders*, supra note 26.

It is difficult to appraise the effects of varying dosage rates on the results of the studies. In general, a wide range of dosages is found in use in pediatric drug therapy, due in part to the large relative differences in weight among children.

178. Pharmaceutical manufacturers have a strong economic interest in the use of vague diagnostic criteria because the use of vague criteria for the proper administration of the drug means that physicians will generally be more liberal in their prescription of the drug. See text accompanying notes 183-190 infra.


2. The Inadequacies of the Current Drug Label

As a result of the NAS-NRC study, Ritalin's label was changed, but the current language contains no more definite information than the prior language. The current label approves the use of Ritalin, in part, for the following:

Effective: Minimal Brain Dysfunction in Children—as adjunctive therapy to other remedial measures (psychological, educational, social).

Special Diagnostic Considerations
Specific etiology of Minimal Brain Dysfunction (MBD) is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

Characteristics commonly reported include: chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis of MBD must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with MBD. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

a. The lack of guidance for the prescribing physician

While federal law does not regulate the medical uses for which the physician may prescribe an approved drug, the physician should derive some guidance in making this choice from the claims of the manufacturer contained in the label which accompanies the drug and which was employed by FDA in evaluating the drug's efficacy. However, the information found in the Ritalin label provides very little, if any, meaningful guidance for the physician prescribing the drug. The broad language of the characteristics listed makes it impossible to determine exactly what groups of


182. See text accompanying note 163 supra.
184. See text following note 140 supra.
185. See text accompanying note 140 supra.
186. See text accompanying note 139 supra.)
"hyperactive" children are covered by this label. The label refers to both soft and hard neurological signs and to a host of other factors attributable to almost anything. The label does not specify the kind or kinds of EEG abnormality commonly encountered in hyperactive children; nor does it define "moderate to severe hyperactivity" or distinguish it from "minimal brain dysfunction." It does not distinguish learning problems from behavior problems or hyperactive-like behavior caused by anxiety. Nor does it indicate if Ritalin is effective for severe motor problems or only mild problems.

The label does not designate laboratory or other objective tests that can demonstrate or even substantially indicate whether a child is a proper subject for Ritalin therapy. The label states that "special psychological, educational, and social resources" are appropriate for use in ascertaining drug applicability. However, this instruction does not tell the physician what resources to use and how to use them. Some of the "characteristics commonly reported," such as distractibility or impulsivity, could apply to almost any child.187 This failure to provide adequate diagnostic criteria is unacceptable because it renders the drug label overinclusive. The greater the number of persons included within the label, the greater the risk that a physician will unnecessarily prescribe the drug.

The evidence submitted to FDA188 might have supported a more narrowly worded label reading: "For use in children not suffering from gross brain damage who have mild difficulty in sustained fine motor coordination based upon the Porteus maze tests." This description indicates a far more limited potential user population than does the actual label. The label should add that children in the mid- and lower-I.Q. range are more likely to respond to the drug.189 This type of labeling clearly indicates to the physician what symptomatology to look for in the child before prescribing the drug in the expectation that the child will be likely to benefit by such therapy.

b. The impact of the overinclusiveness of the label on the approval of Ritalin as safe and effective

Aside from the question of whether the present Ritalin label provides any meaningful guidance in the application of Ritalin therapy, the label's failure to define precisely the subjects for whom the drug is safe and efficacious has adverse consequences for the FDA approval of the drug, inasmuch as safety and efficacy are to be evaluated by FDA in terms of the label's suggested conditions of use.190

187. In one survey of elementary school teachers in a Midwestern town, the teachers indicated that the symptoms of distractibility, restlessness, disruptiveness, short attention span, and inattentiveness were present in just under half of the boys in the first three grades of elementary school. Werry & Quay, The Prevalence of Behavior Symptoms in Younger Elementary School Children, 40 AM. J. ORTHOPSYCH. 136 (1971).
188. See text accompanying notes 164-173 supra.
189. See text following note 165 supra, and text accompanying note 171 supra.
190. See text accompanying notes 140, 146, 151 supra.
(1.) The balancing of risks and benefits

Since it is doubtful that any drug can ever be completely safe and effective for the treatment of the disease specified in its drug label, the evaluation of the drug's safety and effectiveness involves a balancing of risks and benefits.\textsuperscript{191} The drug regulator must decide whether the dangers presented by the drug to the entire class of persons described in the label outweigh the efficacy of the drug for that subgroup which will be benefited by use of the drug. If the manufacturer cannot meet his statutory burden\textsuperscript{192} of demonstrating that the benefits of the drug outweigh the risks presented by its use, the drug cannot be approved for distribution.

While some overinclusiveness will always be present in a drug label, where the label is relatively overinclusive, \textit{i.e.}, where the class of persons for whom the drug is indicated by the label is relatively much larger than the class for whom it has been demonstrated to be safe and effective, it becomes likely that the drug is relatively unsafe and inefficacious. It seems very doubtful that the manufacturer of Ritalin has met its burden of establishing the efficacy of Ritalin for use in the broad patient population described in the drug's label. The fact that a drug is widely used and is believed to be efficacious by numerous physicians is not a substitute under federal law for approval under FDA procedures.\textsuperscript{193}

(2.) Other considerations

Beyond the required balancing of risks and benefits, there are other good reasons for requiring that the information provided by the drug label reflect the current state of the art. Since an overinclusive label means that more of the drug can be sold, the manufacturer has an economic interest in obtaining as broad a label as possible. FDA should, therefore, require the manufacturer to demonstrate that the drug label is reasonably narrow. This demonstration should require the manufacturer to subsidize studies designed

\begin{itemize}
\item \textsuperscript{191} See text accompanying notes 147-148 \textit{supra}.
\item \textsuperscript{192} Ubiotica Corp. v. FDA, 427 F.2d 376, 378 (6th Cir. 1970).
\item \textsuperscript{193} \textit{See, e.g.}, Upjohn Co. v. Finch, 422 F.2d 944 (6th Cir. 1970). In that case, an antibiotic sold by Upjohn was prescribed regularly by 23,000 physicians. Over 750,000,000 doses had been sold and FDA had approved 2,400 batches of the drug as safe and effective. When FDA reconsidered the effectiveness of the drug under new regulations, the agency withdrew its approval. The reviewing court held there was no substantial evidence of effectiveness. In explanation, the court cited Sir Arthur Bradford Hill, a distinguished British scientist:
\begin{quote}
In medicine, theories and therapeutic practices, including those espoused by the majority come and go. One generation bleeds the ill, another scoffs at bloodletting. One generation insists on prolonged bedrest, another preaches the dangers of immobilization and the benefits of early ambulation for everything from surgery to cardiac infarct. There thus can be no sense of confidence automatically generated by "traditional" practice; in therapeutics, as in many other areas of human endeavor, there is no magical safety in numbers.
\end{quote}
\end{itemize}
to find the proper limits of diagnostic criteria for listing on a drug label. This burden on the manufacturer is not too harsh, at least not in those situations where drug prescription is justified only by subjective measurement and the underlying syndrome is without an accepted etiological foundation.

The label should also specifically delineate those areas where Ritalin has demonstrated its effectiveness. The label might state that Ritalin may possibly help improve motor skills or attention span or other behavioral symptoms, but that research has not shown improvement on standardized intelligence test performance. The label might also distinguish the use of Ritalin in institutions from non-institutional use. In addition, the label should disclose that research does not indicate the length of time a child must take the drug in order to effect a cure. In the normal case, it is unnecessary for a drug label to be so explicit, because there will be a body of medical literature that will set forth generally accepted diagnostic tests for a disease, and the mere identification of the disease in the label will allow a drug to be safely and effectively used. The terminology applied to "hyperactivity" or "minimal brain dysfunction" is not sufficiently standardized or refined to justify such a label.

3. The Impact of Other Therapies on Ritalin Regulation: Some Suggestions for Requiring Efficacy Comparisons

To date, very little information exists comparing the efficacy of Ritalin therapy and non-drug therapies. For example, the efficacy of Ritalin therapy has not been compared with that of diet control. The development of efficacy comparisons could have several important ramifications. Chief among these is the effect of such information on the evaluation of the relative safety of Ritalin for use in the treatment of hyperactivity.

Under the FDCA's relative concept of safety and efficacy, an "unsafe" drug is one whose harms outweigh the benefits resulting to society from its use. Therefore, the existence of a safer therapy found to be as effective as Ritalin in the treatment of all hyperactive children would render Ritalin relatively unsafe, since the use of Ritalin would produce no additional benefits to society, while harm would result from the side effects associated with the normal use of Ritalin, combined with its potential medical abuses. If the alternative treatment were somehow ineffective or inappropriate for a particular type of patient, the use of Ritalin would produce some additional benefits to society, but whether these benefits would outweigh the harms connected with its use would still have to be shown.

An ideal alternative to Ritalin treatment does not exist. However, non-drug alternatives, such as placebos, have shown substantial effectiveness.

194. See text accompanying notes 26-27, 84-87 supra.
195. See text accompanying notes 147-148 supra.
when compared with Ritalin. As placebos demonstrate consistently fewer side effects where they are effective, they are thus safer than Ritalin. These facts alone are insufficient grounds for declaring Ritalin unsafe or ineffica-

cious, since there are a substantial number of children for whom placebo therapy is not efficacious, and there are thus substantial benefits resulting to society from the use of other efficacious therapies for such children.

Nonetheless, the Ritalin label should include a note about the strong placebo effects noted. Absent a method of predicting which patients will respond to Ritalin therapy, sound medical practices would indicate that the initially preferred treatment should be the safer placebo therapy.

The efficacy of Ritalin should be compared with that of diet control, since one of the four FDA-recognized methods of evaluating drug effectiveness is by comparing patients who are undergoing drug therapy with patients who are utilizing an alternative therapy. Under FDA regulations, the manufacturer is not compelled to conduct an alternative therapy comparison if a placebo control group is used, but may undertake such studies independently. The FDA regulations are permissive in this respect. While the efficacy of diet control is uncertain, carrying out properly controlled tests could resolve the uncertainty. If diet control is proven sufficiently efficacious, the marked side effects of Ritalin would render the drug unsafe by comparison, since diet control has no side effects.

While Ritalin use is frequently discontinued as unnecessary during summer vacation, there are no studies comparing Ritalin effects with those of minimal environmental changes or parent and child counseling.

Comparisons of drug efficacy and safety among different drugs are generally not incorporated into the information found in the drug label because, among drugs, there are so many variables that such data is extremely difficult to develop. However, the present comparison is between drug therapy, with a high risk of adverse side effects, and non-drug alternatives, which have virtually no side effects. In this situation, comparative safety and efficacy information is relatively easy to develop. Thus, a showing of relative safety and efficacy with respect to other drugs, such as Dextroamphetamine, is desirable but less warranted than comparisons of Ritalin with non-drug alternatives. At the very least, FDA regulations should compel the manufacturer of Ritalin to produce substantial evidence that some children who are benefited by Ritalin would not benefit equally by use of less hazardous non-drug therapy.

196. See note 83 supra.
197. Of course, tests for the efficacy of placebo treatment are subject to the same methodological infirmities as those dealing with Ritalin.
199. Bosco, Behavior Modification Drugs and the Case of Ritalin, 56 PHIL DELTA KAPPAN 489, 489 (1975).
B. Special Considerations Relating to Pediatric Drug Regulation

1. The Nature of the Problem

Special considerations in the regulation of Ritalin arise because of the child’s inability to participate meaningfully in the diagnosis of the disorder and the decision to treat, and because there is evidence that environmental as well as medical factors may aggravate or cause hyperactivity. Normally, the child does not complain of hyperactivity; rather, the parent or teacher complains of the child’s behavior. In view of this absence of participation by the child in the diagnosis and of the lack of a symptomatology that can help in diagnosing the condition with certainty, the question arises as to whether the problem is with the child or with his environment.

This problem is illustrated by the facts in a recent California child custody case, In re Randy B. Randy was diagnosed as being hyperactive when in his mother’s charge. Drug therapy apparently was ineffective. Custody was given to a maternal aunt following the trial court’s finding that, despite the mother’s genuine love and concern for the boy, his negative interaction with his mother and her inability to control him meant that parental control was sufficiently detrimental to his welfare to deprive the mother of custody. The child was greatly improved as a result of the change. On appeal, the trial court’s finding was approved.

In such a situation, the parent who in some way is causing or contributing to the problem is probably unable to exercise sound judgment in giving or withholding informed consent on behalf of the child. Since the physician generally relies upon the parents or teachers for a description of the disorder, and is unable independently to analyze the disease by a medical examination, the child is essentially without objective protection from unneeded or harmful medication. Further, the physician may be influenced by the sociological phenomenon found in our society whereby organic defects are sought as a cause of behavior, thus placing the behavior in a blameless state in which no one is at fault; the child is not “bad,” he is

200. See notes 32, 55 supra.
201. See text accompanying notes 50-51 supra.
203. As judges of the subjective symptomatology of hyperactivity, parents have shown less “interrater reliability” than teachers and other professionals. See text accompanying notes 61-63 supra.
204. In a report of a physician survey, it was concluded that practically none of the routinely gathered physical examination findings, nor the evidence from the laboratory studies were judged to be important in making a diagnosis of hyperactivity. Behavioral indicators, information from the child’s personal medical history, as well as evidence from the family history constitute the group of medical findings which most of the randomly sampled physicians cited as being important in making the diagnosis of hyperactivity. Consistently there was a rejection of the importance of positive neurological findings in making a diagnosis of a hyperactive syndrome. The physicians view the disorder as a behavioral condition rather than one with a neurological basis...
"sick." Absent independent medical analysis, this reasoning can result in the prescription of Ritalin when there is nothing wrong with the child that the pill can correct or when the problem is correctable by less drastic and safer means. If the problem is environmental, Ritalin becomes a behavior modification drug and is likely to aggravate the environmental problem by masking its symptoms and thereby forestalling correction of the underlying problem.


Since the child cannot give informed consent to his treatment with Ritalin and the parents may be unable to evaluate objectively whether the problem rests with the child or with the child's environment, the state should intervene to protect the child. Despite its traditional reluctance to regulate the "who, when, where, and how" of drug treatment decisions, the state has an obvious interest in protecting the child in a situation where the parent is unable to exercise and fulfill the historic parental obligation to the child.

Because the parents play such a large role in the diagnosis of and decision to treat hyperactivity, it is important that parents be informed of the possibility of environmental causes, and of the effects and side effects of Ritalin. Full disclosure better enables them to avoid inadvertently sacrificing the child's best interests, and alerts them to carefully review the child's environment. By apprising them of the side effects, they will be encouraged to have the child closely monitored, and will be less likely to interpret insomnia or anorexia as a symptom of hyperactivity instead of as a side effect of the drug. Disclosure is possible by requiring the dispensing pharmacist or physician to deliver the FDA-approved label with the drug or by insisting that a separate fact sheet concerning the drug designed for parents be enclosed with every prescription. Such a requirement finds precedent in the regulation of oral contraceptives. In promulgating the disclosure regulation for oral contraceptives, FDA noted that it had a duty to assure physicians and patients of drug safety. The regulation provides that each

Sandoval, Lambert, & Yondell, supra note 20, at 333. See also Rie, Underachieving Children, supra note 26, at 785. ("Even [behavioral symptom] rating scales may be ignored in clinical practice . . . .")


206. See id. at 31.

207. See note 215 infra. See also text accompanying notes 122-123 supra.

208. There is an excellent discussion of the relative rights of parents and children in Doe v. Irwin, 428 F. Supp. 1198 (W.D. Mich. 1977) (holding that the state could not exclude parents of minor, unemancipated children from their children's decisions as to whether to consent to risks encountered in the use of contraceptives), vacated and remanded without opinion, 559 F.2d 1219 (1977).


210. Id.
patient receive such a notice with the drugs.211 While the existence of alternative means of preventing pregnancy was deemed important in enacting the regulation,212 alternate therapy is not required to be mentioned in the fact sheet.213 With respect to Ritalin, the best course is to give the parents access to such information before the child receives the drug so that the parent will have the opportunity to explore alternative therapy with the physician.

A more effective means for informing parents of the safety and efficacy problems of Ritalin is a requirement that parents sign a consent form similar to the one used in Methadone treatment.214 The consent form should list side effects and alternate therapies. If parents are required to read a consent form containing a proper description of the dangers of Ritalin use, they might opt for an alternate therapy. By requiring a higher quantum of proof of efficacy and safety in the prescription of Ritalin, and by requiring more specific information in the drug's labeling, protection of the child is enhanced with minimal intrusion into family life.215

CONCLUSION

Properly labeled and adequately tested drugs are essential to society's health. But with the plethora of drugs now on the market, it is no longer possible for physicians, much less patients, to keep themselves adequately informed of the dangers and uses of these drugs. The FDCA provides a meaningful opportunity for government regulation of drugs, and a means of disseminating drug information through detailed drug labels. By permitting drugs to be marketed without adequate testing, including an adequate means of selecting those who will be benefited by a drug, and by allowing broad

211. The oral contraceptive notice received by the patient along with the drug refers to a booklet that will supposedly explain the efficacy and safety problems. The booklet is not required to be given to the patient but is available on request from the doctor. However, the patient does not get the notice about the booklet until after she has seen the doctor and presumably purchased the drug, elsewhere. An additional trip to the doctor is necessary for the actual information. This problem could be alleviated by having the booklet delivered with the drug. This increases the chance that the patient will actually receive and read the booklet.

213. See note 211 supra.
215. In the alternative, FDA might attempt to closely regulate the distribution and usage of Ritalin, as it has attempted to do with Methadone. FDA regulates who can prescribe and who can receive Methadone, the amounts of the initial and subsequent dosages, and the treatment of minors and pregnant women with Methadone. 21 C.F.R. § 310.505 (1977). However, there appears to be no statutory authority for this detailed regulation of drug prescription and distribution. The courts invalidated those portions of the regulation that restricted distribution of Methadone. American Pharmaceutical Ass'n v. Weinberger, 377 F. Supp. 824 (D.D.C. 1974), aff'd sub nom. American Pharmaceutical Ass'n v. Mathews, 530 F.2d 1054 (D.C. Cir. 1976). The reasoning employed to invalidate the restrictions on distribution appears applicable to the regulation's other restrictions as well. This lack of statutory authority for such detailed regulation is attributable to Congress' reluctance to regulate medical practice. The regulation of medical practice is deferred to the states and the American Medical Association.
and overinclusive labels, FDA may bolster the economic status of drug manufacturers, but it does so at a societal cost which cannot, at present, even be estimated.

Ritalin, ingested by hundreds of thousands of children on a daily or twice-daily basis, is now marketed under a virtually meaningless drug label, to be administered to children who have no opportunity to assess its benefits and whose parents are confronted with the use of pseudo-scientific language (e.g., “minimal brain dysfunction”), but no real information about the drug. This problem is aggravated by the pediatric nature of the drug’s usage, the lack of a consistent and objective symptomatology, and a lack of knowledge concerning the etiology of hyperactivity. Despite the numerous considerations justifying a high quantum of proof of efficacy and a very detailed and narrow drug label, the drug efficacy studies utilized by FDA in approving the distribution of Ritalin employed a subject selection technique that was virtually one of random selection.

There are, however, indications of support for the use of Ritalin in treating certain specific groups of children. If the attempt were made, groups of children for whom Ritalin is safe and effective probably could be defined. FDA should take steps to insure that such research is begun. Meanwhile, FDA’s drug labeling powers will remain a powerful but under-used method of providing governmental assistance and protection for patients, while offering minimal state intervention in the doctor-patient and child-parent relationship.