MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : ALL REGIONAL FOOD & DRUG DIRECTORS
AND DISTRICT DIRECTORS
ATTN: NAS/NRC COORDINATORS
COMPLIANCE BRANCH CHIEFS

DATE: January 13, 1978

DLC-Rx Drug Study
Bulletin #233

FROM : Prescription Drug Compliance Branch (HFD-313)
Division of Drug Labeling Compliance

SUBJECT: Drug Products Containing Adrenal Cortex Extract or Adrenal Cortex Injection

On January 9, 1978, Regulatory Letters were issued to firms believed to be manufacturers, repackers, or distributors of parenteral drug products for human use containing adrenal cortex extract or adrenal cortex injection. The letter requested the firms' intentions regarding discontinuance of marketing and removal of outstanding stocks from trade channels down to the retail level.

For numerous years parenteral drugs containing adrenal cortex extract or adrenal cortex injection have been marketed with labeled indications for human use in the treatment of various conditions including adrenal cortical insufficiency, burns, trauma, and hypoglycemia. There is, however, a lack of substantial evidence of these drugs' safety and effectiveness for these labeled indications.

Adrenal cortex extract and adrenal cortex injection have a low corticosteroid potency which presents a substantial risk of undertreatment and thereby a hazard to the patients. It should be noted that in the AMA Drug Evaluations, 1971 First Edition, the adrenal cortex injection (adrenal cortex extract) is considered "an obsolete preparation for treatment of adrenal cortical insufficiency." The AMA Drug Evaluations, 1973 Second Edition considers that "there is no known medical use for this drug." Our medical advisers concur that these drug products are not generally recognized as safe and effective for labeled indications for human use.

In view of these facts, parenteral drugs for human use containing adrenal cortex extract or adrenal cortex injection are considered as new drugs for which there have been no New Drug Applications approved. The FDA considers these preparations to be new drugs within the meaning of Section 201(p) and their marketing without an approved New Drug Application is regarded as a violation of Section 505 of the Federal Food, Drug, and Cosmetic Act.

Although there may be drugs containing adrenal cortex extract or adrenal cortex injection which were marketed before 1938, it is the responsibility of the manufacturer/distributor to provide evidence that their specific drug enjoys the status of a "grandfathered" drug by demonstrating that there are sufficient data or information to justify such status. (See also Title 21 CFR Part 310.100.)

Attached are copies of the letters issued to firms in your District, and an information copy of the form letter to those Districts with no applicable firms. The Division of Drug Labeling Compliance will monitor the firms' replies, furnish the District with copies of such replies, and issue assignments where indicated. Although this is not a DESI drug, the same procedures for follow-up will be utilized.

Please submit labeling and FD-3033's for any additional parenteral drug products for human use containing adrenal cortex extract or adrenal cortex injection so that we may institute follow-up where indicated.

Albert Lavender

Albert Lavender, Chief
Prescription Drug Compliance Branch

PRIORITY : HIGH
PAC CODE : 52D001
PROJECT CODE : 52
ESTIMATED TIME : TWO HOURS
PROJECT OFFICER : DOROTHY L. OLSON, Telephone: 8-443-4206

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

REGULATORY LETTER

CERTIFIED

PRODUCT:

Gentlemen:

This letter is in reference to the drug product listed above which you market containing adrenal cortex extract or adrenal cortex injection alone or in combination with other ingredients.

The Food and Drug Administration has reviewed available data concerning the use of adrenal cortex extract and injection in various conditions such as adrenal cortical insufficiency, shock, burns, and hypoglycemia, and concluded that the low level of corticosteroid contained in these drugs presents a substantial risk that these serious conditions will be undertreated. These drugs therefore pose a significant potential hazard to patients. We note that such drugs are described in the AMA Drug Evaluations 1971 First Edition and 1973 Second Edition as obsolete and of no known medical use.

In view of the above, and in the absence of substantial scientific evidence which demonstrates that a drug containing adrenal cortex extract or adrenal cortex injection is generally recognized as safe and effective, we consider your product to be a new drug that is in violation of the Federal Food, Drug, and Cosmetic Act as follows:

SECTION	VIOLATION
505(a)	The article is a new drug which may not be introduced or delivered for introduction into interstate commerce, under Section 505(a) of the Federal Food, Drug, and Cosmetic Act, since it is a new drug within the meaning of Section 201(p) of the Act and no approval of application filed pursuant to Section 505(b) is effective for such drug, and no notice of claimed investigational exemption under Section 505(i) and regulation 312.1 is on file for such drug.

We request that you reply within ten (10) days of the receipt of this letter stating the action you will take to discontinue the marketing of your product listed above, and any identical or similar products containing adrenal cortex extract or injection which you may market. If such corrective action is not promptly undertaken, the Food and Drug Administration is prepared to initiate legal action to enforce the law. The Federal Food, Drug, and Cosmetic Act provides for seizure of illegal products and/or injunction against the manufacturer and/or distributor of illegal products, 21 U.S.C. 332 and 334.

We request that your reply include (1) an estimate of the quantity of the drug manufactured within the past 12 months; (2) an estimate of the size and frequency of shipments made by you within the past 12 months; (3) an estimate of the amount of the drug listed above that is in inventory under your control and that which remains in channels of distribution outside of your control; (4) in the event that you have already discontinued marketing this drug product, the date of discontinuance; and (5) your intentions with respect to the disposition of your inventory and the withdrawal of outstanding stocks from trade channels down to the retail level. Your reply should be directed to Dorothy L. Olson, Project Officer, Prescription Drug Compliance Branch (HFD-313), Division of Drug Labeling Compliance, Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland, 20857.

Sincerely yours,

Adr

T. E. Byers
Associate Director for Compliance
Bureau of Drugs

BY THE COMPTROLLER GENERAL

Report To The Honorable Barry M. Goldwater, Jr. House Of Representatives

OF THE UNITED STATES

Adrenal Cortical Extract Taken Off Drug Market

In January 1978, the Food and Drug Administration (FDA) sent regulatory letters to drug firms involved in the marketing of adrenal cortical extract products advising them that it considered these products to be unapproved new drugs and in violation of the Federal Food, Drug, and Cosmetic Act. FDA's action resulted in the removal of these products from the market.

GAO could not find any medical support for using this drug in the treatment of either Addison's disease or hypoglycemia and concludes that FDA's regulatory actions against this drug were within the agency's legal authority and were not unreasonable.

HRD-81-61
APRIL 20, 1981

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COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON D.C. 20548

B-202706

The Honorable Barry M. Goldwater, Jr.
House of Representatives

Dear Mr. Goldwater:

In response to your request of February 20, 1980, we have reviewed the circumstances surrounding the removal of adrenal cortical extract (ACE) products from the market by the Food and Drug Administration (FDA).

Our review was directed toward determining (1) FDA's basis for concluding that ACE products should be removed from the market, (2) medical opinions on the treatment of Addison's disease and hypoglycemia, including the usefulness of ACE products, and (3) the procedures followed by FDA to remove these products from the market.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from its issue date. At that time we will send copies to interested parties and make copies available to others upon request.

Sincerely yours,

Milton J. Socolar

Acting Comptroller General
of the United States

COMPTROLLER GENERAL'S
REPORT TO THE HONORABLE
BARRY M. GOLDWATER, JR.
HOUSE OF REPRESENTATIVES

ADRENAL CORTICAL EXTRACT
TAKEN OFF DRUG MARKET

D I G E S T

In January 1978, the Food and Drug Administration (FDA) advised drug firms marketing adrenal cortical extract (ACE) products that the drug represented a substantial risk of undertreatment because of its low potency and resulting potential hazard to patients. FDA noted that these products, now described as obsolete by the American Medical Association (see p. 5), were once recommended for treating Addison's disease. GAO's review of current well-known textbooks on medicine and endocrinology showed a unanimous preference for using synthetic compounds in the treatment of both the chronic and acute phases of this disease. (See p. 6.)

Discussions with four endocrinologists showed that all would use synthetic compounds today as opposed to ACE for treating patients suffering from Addison's disease. (See p. 7.)

GAO could not find any medical support for using ACE products in the treatment of hypoglycemia. (See p. 9.)

FDA'S REGULATORY ACTIONS

FDA's concern about the use of ACE products first appeared with complaints made in the early 1970s about the use of these products for Addison's disease. (See p. 14.)

Based on an internal review, FDA concluded that ACE products were not generally recognized as safe or effective and therefore were "new drug" products within the meaning of the Federal Food, Drug, and Cosmetic Act. (See p. 15.)

FDA began actions against these products as new drugs because, among other things, it had concluded that there was little possibility that even one drug firm's product could meet the criteria for exemption under the grandfather

provisions of the act. (See p. 2.) Although two firms claimed that their products had grandfather status, neither formally submitted evidence in support of its claim. (See p. 18.)

After its initial internal review, FDA deliberated over which regulatory actions to take in regard to the removal of these products from the market. In January 1978, FDA sent regulatory letters to 78 drug firms that had marketed ACE products. The letters said that FDA considered these products to be unapproved new drugs and in violation of the Federal Food, Drug, and Cosmetic Act. This action by FDA had the effect of removing all such products from the market. (See p. 18.)

CONCLUSIONS

Although ACE represented at one time the best known treatment for Addison's disease, the newer synthetic corticosteroids are now the drugs of choice in treating Addison's disease. The newer compounds are preferred because they have several advantages over their predecessors. GAO could not find any medical support for using ACE in the treatment of hypoglycemia.

The regulatory actions taken by FDA against ACE were within its legal authority under the Food, Drug, and Cosmetic Act and were not unreasonable. Although the use of alternative procedures would have afforded all interested parties a better opportunity to comment on FDA's findings and proposed actions, the affected drug firms had an opportunity to challenge FDA's findings, but did not. (See p. 26.)

AGENCY COMMENTS

The Department of Health and Human Services reviewed a draft of this report and had no comments. FDA offered technical suggestions to improve the accuracy of the report.

Contents

		Page
DIGEST		i
CHAPTER		
1	INTRODUCTION	1
	What is Addison's disease?	1
	ACE products and their uses	1
	FDA's responsibilities for regulating drugs	2
	Objectives, scope, and methodology	3
2	FDA'S CONCLUSIONS AND MEDICAL OPINIONS ON USING ACE PRODUCTS	5
	FDA's basis for concluding that ACE should be removed from the market	5
	Medical opinions on the treatment of Addison's disease	6
	Adverse reactions from corticosteroids	9
	Medical opinions on treatment of hypoglycemia	9
3	FDA'S REGULATORY ACTIONS AGAINST ACE AND OTHER OLDER DRUGS	14
	FDA's initial concern with ACE products	14
	FDA takes action against ACE under new drug provisions of the FD&C Act	15
	Consideration of possible grandfather status of ACE products	16
	FDA decision to issue regulatory letter on ACE	18
	Federal Register approach considered and rejected	19
	Old drug monograph considered and rejected	20
	FDA's rationale for not taking action under misbranding provisions of the FD&C Act	22
	FDA procedures for evaluating safety and effectiveness of older drugs	23
4	CONCLUSIONS	26
	Agency comments	26
APPENDIX		
I	Recommended treatment regimens for Addison's disease from current medical textbooks	27
II	Letter dated March 20, 1981, from the Acting Inspector General, Department of Health and Human Services	28
III	Letter dated February 20, 1980, from Congressman Barry M. Goldwater, Jr.	29

ABBREVIATIONS

ACE	adrenal cortical extract
AMA	American Medical Association
DESI	Drug Efficacy Study Implementation
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GAO	General Accounting Office
NDA	new drug application

CHAPTER 1

INTRODUCTION

In a February 20, 1980, letter, Congressman Barry M. Goldwater, Jr., requested that we examine the propriety of the Food and Drug Administration's (FDA's) actions which, in effect, removed adrenal cortical extract (ACE) products from the market. This drug, which had been marketed from the early 1930s until 1978, had been used for treating potentially fatal Addison's disease and for several other indications including hypoglycemia (low blood sugar).

WHAT IS ADDISON'S DISEASE?

Addison's disease (adrenal cortical insufficiency), when unrecognized and untreated, characteristically runs a chronic and relentless course. In some patients, its advancement is relatively slow, but in all cases the patient's condition may rapidly deteriorate into adrenal crisis. The disease is relatively rare, and its incidence is about 1 case per 100,000 population.

Adrenal destruction is a gradual process. When more than 90 percent of the adrenal cortex has been destroyed, the patient develops an "Addisonian crisis." Addisonian crisis occurs when the patient's hypotension progresses to shock and, if untreated, to death.

ACE PRODUCTS AND THEIR USES

ACE is obtained from the cortex of the adrenal glands of healthy domestic food animals (usually cattle, sheep, or swine). The major active component is the hormone hydrocortisone. For many years, ACE was recommended for treating Addison's disease. It was also labeled for use in preventing surgical shock, treating acute shock, burns, and loss of strength due to Addison's disease. More recently, ACE was offered by its distributors for acute and chronic drug addiction, hypotension, muscular fatigue, and control of hypoglycemia. The typical marketed product was an injectable formulation containing in each milliliter an amount of extract equivalent to the biological activity of 0.1 to 0.2 mg (milligrams) hydrocortisone.

According to Goodman and Gilman's "Pharmacological Basis of Therapeutics" the preparation of ACE with a reasonable degree of activity was first accomplished by investigators in 1930. Harrison's "Principles of Internal Medicine" states that in 1937 the first natural corticosteroid was synthesized. The synthesis of several other compounds, including cortisone and hydrocortisone, was achieved from 1940 to 1950. Aldosterone, the principal salt-retaining hormone of the adrenal cortex was identified in 1954.

Harrison's publication also states that several advances followed, including refinements in the ease and accuracy with which steroids and their metabolic products may be measured.

FDA'S RESPONSIBILITIES FOR REGULATING DRUGS

FDA is responsible for protecting the public from unsafe and/or ineffective drugs. In carrying out its mission, FDA is responsible for approving new drugs for safety and efficacy and for taking action to remove from the market drugs which are found to be unsafe or ineffective. FDA derives its legal authority and responsibility from the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended, (21 U.S.C. 301).

New drug application provisions

Section 505(a) of the act prohibits new drugs from being introduced into interstate commerce unless a new drug application (NDA) has been filed and approved. Section 505(b) specifies that the application shall include (1) full reports of investigations which have been made to show the drug is safe and effective; (2) a full list of the articles used as components of the drug; (3) a full statement of the composition of the drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of the drug; (5) samples of the drug and of the articles used as components; and (6) specimens of the labeling proposed to be used for the drug.

A new drug is defined by the act (section 201(p)) as any drug not generally recognized, among qualified experts, as safe and effective for use under the conditions prescribed, recommended, or suggested in the drug's labeling. An exemption is provided to drugs deemed to be "grandfathered" drugs.

Grandfather provisons

The 1938 Grandfather Clause, contained in section 201(p)(1) of the act, reads, in pertinent part, as follows:

> "Any drug * * * shall not be deemed to be a 'new drug' if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use * * *."

The grandfather provisions of the 1962 amendments read as follows:

> "In the case of any drug which on the first day immediately preceding the enactment date (October 9, 1962) (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of the Act, the amendments to section 201(p) made by this Act (i.e. that drugs be shown to be effective as well as safe) shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

Misbranding provisions

Section 502(a) of the act states that a drug shall be deemed to be misbranded if its labeling is false or misleading. Section 502(f) states that a drug shall be deemed to be misbranded unless its labeling bears (1) adequate directions for use and (2) such adequate warnings against use when it may be dangerous to health, or against unsafe dosage or methods of administration needed to protect users. Section 502(j) states that a drug shall be deemed to be misbranded if it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling.

OBJECTIVES, SCOPE, AND METHODOLOGY

Our review's objectives were to examine (1) FDA's basis for concluding that ACE products should be removed from the market; (2) medical opinions on the treatment of Addison's disease and hypoglycemia, including the usefulness of ACE products; and (3) the procedures followed by FDA to remove ACE products and other older drugs from the market.

To objectively address the medical aspects of ACE products, we reviewed several medical textbooks on endocrinology. We then asked the opinions of others, including FDA, as to what were considered the most prominent textbooks in endocrinology to determine whether it was necessary to supplement our original selection. In addition, we researched and reviewed opinions of medical consultants and experts outside the Government. We also discussed the medical aspects of ACE with four nongovernment endocrinologists who have been involved in the management of patients with Addison's disease and who were recommended by the Endocrine Society.

By design, our review of the medical aspects of ACE was concentrated on current medical literature and opinion. However, we also reviewed medical textbooks and opinions of the 1940s and 1950s to determine how ACE was viewed at that time. Likewise, we discussed with medical authorities information on the earliest uses of ACE products.

The medical aspects of ACE were also discussed with senior management and medical officers at FDA and the National Institutes of Health. Our findings were discussed with and reviewed by our chief medical advisor. We also reviewed and considered the publications of proponents of using ACE products for the management of hypoglycemia.

In regard to the legal aspects of this review, we examined FDA's procedures for regulating drugs in general and the particular circumstances involved in the removal of ACE products from the market. We focused on the period from FDA's initial awareness of complaints against ACE products in 1972 to its regulatory action in 1978 which, in effect, removed these products from the market.

We reviewed applicable sections of the FD&C Act, FDA regulations, relevant court actions, and regulatory action material and correspondence available at FDA headquarters. We also requested from FDA, and we were given, detailed written responses to a series of questions on its regulatory actions against ACE.

CHAPTER 2

FDA'S CONCLUSIONS AND MEDICAL OPINIONS ON USING ACE PRODUCTS

In instituting its regulatory action, FDA said it had concluded that ACE products represented a substantial risk in that serious conditions would be undertreated through their use. Our review showed a unanimous preference--in the medical literature and by endocrinologists recommended by the Endocrine Society--for using synthetic compounds as opposed to ACE products in treating Addison's disease. Our review did not disclose any medical support for using ACE products in the treatment of hypoglycemia. The endocrinologists with whom we discussed these matters agreed with FDA actions--which, in effect, removed ACE products from the market. This medical preference appears to be related to the availability of newer, more potent preparations.

FDA'S BASIS FOR CONCLUDING THAT ACE SHOULD BE REMOVED FROM THE MARKET

In January 1978, FDA sent regulatory letters to 78 drug firms in which it said that ACE products represented a substantial risk of undertreatment because of the drug's low potency and therefore posed a significant potential hazard to patients. Through this action, ACE products which had been marketed since the 1930s were in effect removed from the market.

In acting to remove ACE from the market, FDA contended that ACE represented a substantial risk to patients if taken as recommended in its labeling for the treatment of Addison's disease. According to FDA, danger to patients treated with ACE for Addison's disease involved the inability of the drug to provide an adequate amount of hydrocortisone. At the dosages recommended in ACE labeling, only 0.5 to 5 mg per day would be provided to a patient compared to the 15 to 30 mg considered by experts to be necessary for adequate therapy. FDA maintained that this inadequate dosage of ACE was even more significant if ACE was used in Addisonian crisis or acute Addison's disease precipitated in a patient by stress, surgery, or shock. According to authoritative medical literature, the amount of intravenous hydrocortisone recommended for this condition initially is 100 mg or more. It was for this reason that FDA said it used the term "undertreatment" to explain the lack of effectiveness of ACE for Addison's disease.

FDA maintained that not only was treatment with ACE as labeled inadequate to provide the amount of hydrocortisone needed, but because of the nature and mechanism of delivering the drug, even its administration at dosages exceeding those recommended in the labeling would not provide an adequate amount of hydrocortisone. According to FDA, the daily volume of ACE required to be injected to provide effective therapy would be so large (150 to 300 cc (cubic centimeter) of most preparations) that such administration would be impracticable.

FDA told us that it is impossible to justify a medical practice that subjects patients to such onerous therapy daily when a readily available effective oral therapy exists. Further, in an Addisonian crisis, FDA told us that even continuous intravenous administration of ACE would provide hydrocortisone at a rate too slow to be effective. Also, the agency said the 1973 edition of "AMA Drug Evaluations" states that ACE is "of no known medical use." Based on such evidence as this, FDA concluded that ACE is not known to be safe or effective for any claimed medical use.

FDA said it knows of no specific studies performed with ACE to show that it poses a significant potential hazard if used to treat patients with Addison's disease. According to FDA, this type of study would be unethical since it would require demonstrating clinical deterioration in patients treated with ACE. Moreover, FDA maintains that such a study is unnecessary because ACE cannot supply the replacement needs of corticosteroid-deficient individuals.

MEDICAL OPINIONS ON THE TREATMENT OF ADDISON'S DISEASE

The treatment of Addison's disease has undergone somewhat of an evolution over the years. Medical textbooks of the 1940s and early 1950s advocated using ACE products in conjunction with salt therapy in treating this disease. This form of therapy became outmoded when the newer more potent synthetic compounds were developed.

For example, Soffer's "Disease of the Adrenals" (1948) recommended using ACE in the treatment of Addison's disease. Cecil's "Textbook of Medicine" (1951 edition) stated that once the diagnosis of Addison's disease had been established, the patients' condition improved if they were given hormone therapy through using whole ACE. This version also stated that, for acute emergencies (adrenal crisis), large amounts of whole adrenal extract or cortisone represented the treatment of choice.

A review of four current, well-known textbooks 1/ on medicine and endocrinology shows a unanimous preference for the use of synthetic compounds in treating both phases (chronic and acute) of this disease.

Generally, these textbooks recommend the oral administration of synthetic hydrocortisone in multiple doses daily--for example, 25 mg in the early morning and 12.5 mg later in the day--for replacement purposes in maintenance therapy in chronic situations. These are supplemented with a daily dose of about 0.1 mg of fludrocortisone.

For treatment of the acute or "crisis" stages of adrenal insufficiency, these textbooks generally recommend a rapid administration of 100 mg of hydrocortisone intravenously. This is to be followed by intramuscular injections until the patient is capable of taking the drug orally. (See app. I for a list of recommended treatments.)

Furthermore, our review of other independent medical opinions, such as the "Medical Letter," Modell's "Drugs of Choice," and American Medical Association (AMA) publications showed the synthetics as the preferred method of treatment.

Views of endocrinologists on Addison's disease and its treatment

Our discussions with four nongovernment endocrinologists who were recommended by the Endocrine Society and one who was employed by the National Institutes of Health indicated that all would unequivocally use synthetic compounds as opposed to adrenal extracts for treating patients with Addison's disease.

According to two of these experts, ACE would be theoretically effective in the treatment of primary adrenal insufficiency in both the chronic and acute crisis states. However, in all cases, the endocrinologists we talked to preferred using synthetic corticosteroids in the treatment of Addison's disease and considered ACE to be an obsolete drug for treating this disease.

1/Harrison's "Principles of Internal Medicine" (8th edition, 1977), Goodman and Gilman's "The Pharmacological Basis of Therapeutics" (5th edition, 1975), Cecil's "Textbook of Medicine" (15th edition, 1979), and Williams' "Textbook of Endocrinology" (5th edition, 1974).

According to one endocrinologist, ACE was used by physicians in the 1930s and 1940s to treat Addison's disease because it was the only drug then available for the treatment of this potentially fatal disease. Intravenous saline solutions containing ACE were the mode of treatment of patients undergoing an adrenal crisis during this period. At times, these saline solutions were enough to reverse the crisis.

Another endocrinologist told us that a salt-supplemented diet was the mode of treatment for Addisonian patients needing maintenance therapy. Later, deoxycorticosterone acetate injections and pellet implants became available to aid salt retention by Addisonian patients.

One endocrinologist ranked the forms of treatment of Addison's disease he preferred as: (1) synthetic corticosteroids, (2) purified natural cortisols, and (3) crude extracts (ACE).

Two endocrinologists told us that today synthetics are preferred by physicians for treating Addison's disease because it is (1) difficult to determine the exact potencies of the crude extracts and (2) easier to isolate the source of adverse reactions.

According to one endocrinologist, potency tests on these extracts normally could only be performed by the manufacturer. Potencies also would vary from lot to lot further compounding the problem. However, synthetic corticosteroids have a known measurable potency level and can be given in relatively more potent doses than the crude extracts. Because of the varying potencies of crude extracts, it was difficult for physicians who used ACE to determine whether a patient's response was attributable to the crude extract or to the body's natural responses.

One endocrinologist told us that the synthetic corticosteroids can cause certain anticipated and known side effects. On the other hand, the crude extracts contain a number of impurities, and it is difficult for the physician to discern whether a patient's adverse reaction is attributable to the extract or some other cause.

Severe side effects can be expected with excessive use of synthetic corticosteroids, especially if they are abruptly withdrawn from therapy. However, one endocrinologist told us that the same adverse reactions could occur whether the physician used ACE or a synthetic compound, and that the adverse reactions would be dose related. This endocrinologist said that larger doses of crude extract could produce the same adverse reactions as the more potent synthetics.

All of the endocrinologists fully endorsed FDA's actions which, in effect, removed ACE from the market. They did not believe that FDA's action would result in an increased use of corticosteroids since they told us that reputable physicians would have already been using the corticosteriods for the treatment of Addisonian patients and other therapies for the treatment of hypoglycemia.

None of the endocrinologists were aware of any "supplemental" benefits that could be derived from using the whole crude extract. Similarly, none were aware of any relatively recent studies that had been performed to show ACE's effectiveness in treating Addison's disease or other disorders.

ADVERSE REACTIONS FROM CORTICOSTEROIDS

Goodman and Gilman's "The Pharmacological Basis of Therapeutics" states that a single dose of corticosteroid, even a large one, is virtually without harmful effects. According to this source, a few days of corticosteroid therapy, in the absence of specific contraindications, is unlikely to produce harmful results except at the most extreme dosages. As corticosteroid therapy is prolonged over periods of months and dosages are increased, Goodman and Gilman maintain that the incidence of disabling and potentially lethal effects increases.

The November 7, 1975, "Medical Letter" states,

> "Prolonged daily treatment with more than replacement dosage of adrenocortical steroids produces major complications sooner or later in virtually all patients. Some of these complications, such as suppression of hypothalamic-pituitary-adrenal responsiveness and gastrointestinal hemorrhage, may be life-threatening; other effects, such as Cushing's disease, severe osteoporosis, or suppression of growth in children, are also serious. Administration of corticosteroids in a single dose every other day, instead of the usual divided daily doses, may avoid or minimize these adverse effects."

MEDICAL OPINIONS ON TREATMENT OF HYPOGLYCEMIA

The third edition of "Clinical Endocrinology," defines hypoglycemia as low blood sugar. It is not a disease, but it is a condition brought on by diverse causes. "Clinical Endocrinology" states that some of the early manifestations of hypoglycemia may

include flushing, sweating, pallor, tremor, headache, dizziness, hunger, increased blood pressure, and palpitation. If the hypoglycemia is of extreme degree or long duration, "Clinical Endocrinology" states that convulsions and coma can follow.

According to "Clinical Endocrinology," if the symptoms are mild, the attack may be aborted by giving fruit juice or candy. This source also indicates that, if the attack is severe and has progressed to unconsciousness, glucose should be administered intravenously.

Cecil's "Textbook of Medicine" states that after the hypoglycemia attacks have been brought under control a thorough examination should be performed to determine whether, in fact, the patient is truly a hypoglycemic and the possible underlying cause of the hypoglycemia.

According to Cecil's publication, the most common form of hypoglycemia is reactive hypoglycemia. Hypoglycemia, however, can be an induced form resulting from insulin excess or drugs. In the latter cases, Cecil states that no special therapy is required other than attempts to modify exposure to the offending agent.

Williams' "Textbook of Endocrinolgy" states that most causes of hypoglycemia are directly related to food ingestion, with the symptoms appearing at varying intervals within 5 hours after eating. Of these, according to Williams, the majority (about 70 percent) are apparently healthy young adults who exhibit a low plasma sugar level about 2 to 4 hours after food intake for which the underlying mechanism is unknown. Williams states that these individuals tend to be thin, emotionally unstable, tense, anxious, and have a compulsive personality.

The 1980 edition of Harrison's "Principles of Internal Medicine" points out that it is well known that the diagnosis of reactive hypoglycemia has reached epidemic proportions in this country. According to Harrison, some persons who appear to be subject to reactive hypoglycemia are not true hypoglycemics because either low blood sugar does not occur or low levels do not occur when the symptoms are present. Rather, Harrison states that many of these patients may be subjected to other factors brought on by anxiety or stress.

Cecil's "Textbook of Medicine" states that the treatment of reactive hypoglycemia may entail multiple small feedings or regular meals with diets high in protein, low in carbohydrates, and sufficient in fats. According to Cecil, this could be supplemented with other specific therapy related to the possible cause, such as drugs to slow gastrointestinal movement or mild sedatives and tranquilizers for the "functional hypoglycemic." Cecil also

stated that adrenal cortical steroids are not found to have a place in the treatment of these hypoglycemic disorders.

"Clinical Endocrinology" states that the multiple causes of hypoglycemia associated with the fasting state usually are indicative of a disease process. According to this source, fasting produces hypoglycemia in patients with hypopituitarism, Addison's disease, forms of hepatic disease, and severe liver function impairment. According to Cecil's publication, tumors of the pancreas are the most frequent cause of fasting hypoglycemia, and surgery is the treatment of choice.

Using ACE for hypoglycemia

The FDA medical officer responsible for the initial actions against ACE said that there have not been adequate controlled scientific tests performed with ACE to determine if it is safe and effective for the treatment of such conditions as hypoglycemia. He said that the drug had been studied for the treatment of hypoglycemia by Dr. Tintera, 1/ but that the study was inadequate because it did not use controls, and it used a glucose tolerance test. According to this medical officer, the giving of a glucose test and the administration of the extract will show that the body returned to normal. The medical officer indicated, however, that this change in condition is not due to the administration of the extract, but rather to the body's normal interaction with cortisol which automatically returns the body to its normal condition. According to the medical officer, a glucose tolerance test induces reactive hypoglycemia (a condition found in healthy people when they become tired or are under stress) as opposed to the fasting hypoglycemia associated with Addison's disease.

In its written response to our questions, FDA referred to Duncan's "Diseases of Metabolism" (1974) which states:

> "Although some of the patients with this syndrome have clear-cut hypoglycemia and physical disease, many patients who complain of tremulousness, weakness and other nonspecific problems occurring toward the end of the morning or afternoon prove not to have low blood glucose concentrations. These patients usually have severe psychosocial problems, and their symptoms are due to their emotional disturbance rather than to a reduced level of blood glucose. Unfortunately, they are often victimized by unscrupulous or misguided physicians who make a diagnosis of hypoglycemia without adequate evidence and treat the patient with a

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1/Dr. Tintera founded the Hypoglycemia Foundation in the 1950s.

variety of nostrums of little pharmacological or physiological value. The most indefensible approach in recent years has been to give minute amounts of adrenal cortical extract--a maneuver which cannot affect the carbohydrate metabolism because the amount of steroid given is too small to be of physiological significance, even if the patients actually were hypoglycemic."

Views of endocrinologists and others on hypoglycemia and its treatment

The endocrinologists believed that hypoglycemia is highly overdiagnosed in the United States and that only a small portion of the persons claiming to have it are true hypoglycemics. They said that the true cases of hypoglycemia associated with Addison's disease are a rarer event. They also believed that ACE would not have been prescribed by reputable physicians for hypoglycemia.

The January 21, 1972, issue of the "Medical Letter," in its discussion of hypoglycemia in adults, makes the following comments:

"Many persons believe that hypoglycemia can cause disorders such as arthritis, alcoholism, drug addiction, insomnia, chronic fatigue, loss of libido, and schizophrenia. This belief is backed by The Hypoglycemia Foundation, an organization that promotes the 'Endocrinologic Approach to the Etiology and Treatment of Functional Hypoglycemia.' * * * The treatment usually recommended is avoidance of coffee and sweets and injections of adrenocortical extract * * *

"If physicians lack enthusiasm for such therapy, it is with good reason; hypoglycemia has not been a common finding, and when it does occur, it demands quite different treatment. Many of the symptoms and disorders listed by the Foundation respond to placebo therapy (particularly injections, as of adrenocortical extract, an obsolete preparation), and favorable results in trials that are not well controlled cannot be accepted as convincing evidence for the claims."

The same issue of "Medical Letter" concludes:

> "Contrary to the belief of those who attribute many common ailments to hypoglycemia, it is an uncommon disorder. * * * When adrenal insufficiency is the cause of hypoglycemia, treatment calls for administration of sodium chloride, fluids, and either hydrocortisone or other glucocorticoids. In the treatment of hypoglycemia, there is no useful place for estrogens, testosterone or other anabolic agents, or adrenal cortical extract, an obsolete preparation once used for the treatment of Addison's disease."

CHAPTER 3

FDA'S REGULATORY ACTIONS AGAINST ACE AND OTHER OLDER DRUGS

FDA acted to remove ACE products from the market because it considered them to be "new drugs" that did not meet the exemptions of the grandfather provisions of the FD&C Act. (See p. 2.) FDA considered several possible forms of regulatory action from 1973 to 1978 and decided in January 1978 to send regulatory letters to drug firms distributing ACE declaring ACE products to be unapproved new drugs. This form of regulatory action, according to FDA, was the most expeditious way of removing ACE products from the market.

Thousands of prescription drugs marketed between 1938 and 1962 have been reviewed under the mandate of the 1962 amendments to the FD&C Act. This effort was formally known as the Drug Efficacy Study Implementation (DESI) review and was conducted in conjunction with the National Academy of Sciences. FDA has no specific mandate, however, to conduct similar reviews of drugs marketed before 1938 and does so only on a case-by-case basis as the need arises or as questions are raised about a specific drug's safety and/or efficacy.

FDA'S INITIAL CONCERN WITH ACE PRODUCTS

FDA's concern with the use of ACE appeared first in the early 1970s as a result of complaints from a University of California School of Medicine professor and an FDA medical officer who first became aware of the drug while working at the National Institutes of Health. Both believed that the labeled instructions contained on these products for their use in treating Addison's disease were inadequate.

According to FDA, after these complaints were raised, the Office of Compliance, within FDA's Bureau of Drugs, undertook a review of the recognized medical literature. Its review showed that reliable sources described ACE as an obsolete preparation, as a product with no known medical use, or as one promoted and improperly used for hypoglycemia and hypotension. Furthermore, it found that reputable medical textbooks did not mention ACE.

FDA stated that this review formed the basis for an initial determination that ACE was an ineffective drug presenting a serious safety issue because of the increased risk to the patient whose serious or life-threatening adrenal insufficiency would progress and worsen when treated with ineffective therapy. FDA

felt that permitting the continued dangerous use of ACE products was not justified, particularly in this case when alternative medical treatment, recognized as being effective, was available.

Although FDA contends that its Office of Compliance "undertook a review of the recognized medical literature," our review of the chronological developments in this situation indicates that the determinations were made on the basis of very limited documentation available to it at the time. We could find no evidence of any review for safety, effectiveness, risk-benefit assessment, labeling adequacy, and legal status by FDA personnel with the exception of two references to AMA publications and a reference to the lack of mention of ACE products in another medical textbook.

FDA TAKES ACTION AGAINST ACE UNDER NEW DRUG PROVISIONS OF THE FD&C ACT

FDA's actions against ACE products were based on its determination that these were "new drug" products because they were not generally recognized as safe and effective. Because of this, and in the absence of formal documentation that any of the products were exempt from "new drug" status under the grandfather provisions, FDA acted to remove all ACE products from the market as unapproved new drugs.

Until 1938, Federal law did not provide for any kind of administrative premarketing approval for drugs sold in interstate commerce. With the passage of the FD&C Act of 1938, section 505(a) of the act provided that no person shall introduce into interstate commerce any "new drug" unless an application was in effect. Unless FDA took affirmative action against the application, it automatically became effective within a specified time period. Such new drug applications became known as NDAs.

A "new drug" was defined in section 201(p) of the 1938 act as any drug, the composition of which is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for its intended use. Drugs could be exempt from the "new drug" provisions if they met the grandfather provision of the act. (See p. 2.)

The drug amendments of 1962 made four important changes with respect to the marketing of new drugs: (1) no new drugs could go on the market without affirmative approval by FDA, (2) effectiveness had to be proven in addition to safety, (3) "substantial evidence" was defined in terms of adequate and well-controlled trials, and (4) detailed transition provisions, including a grandfather clause, were included for the new effectiveness requirements.

Concerning FDA's decision to proceed against ACE as a "new drug," FDA said a new drug is one which is not generally recognized as safe and effective. The act does not define "generally recognized as safe and effective," but several Supreme Court cases have established that "general recognition" cannot exist without evidence from adequate and well-controlled clinical investigations and substantial support in the scientific literature. FDA told us that no adequate and well-controlled clinical studies which permit a conclusion that ACE is safe and effective have been located in the literature or presented by a firm or any person. Moreover, according to FDA, authoritative scientific texts indicated that the drug was generally regarded as ineffective for labeled indications including Addison's disease, for which treatment with ACE at the recommended dosages was viewed by FDA as unsafe.

FDA further stated that it is not required under the act or regulations to consult with outside experts before determining that a drug is a new drug and that the courts have sustained FDA's authority to make this determination. FDA believed it was sufficient that its experts and a review of recognized authoritative literature indicated to its satisfaction that ACE products could not reasonably be considered generally recognized as safe or effective.

CONSIDERATION OF POSSIBLE GRANDFATHER STATUS OF ACE PRODUCTS

FDA stated that it had proceeded against ACE products as new drugs because, among other things, it had concluded that there was little possibility that even one firm's product could meet the criteria for exemption under the grandfather provisions. In addition, although two firms had claimed that their products had grandfather status, neither formally submitted evidence in support of its claim.

Section 201(p)(1) of the FD&C Act and section 107(c)(4) of the Drug Amendments of 1962 provide exemptions from the new drug provisions of the act for drugs that meet the labeling and marketing conditions specified in those sections. A drug that meets the exemption requirements is said to be "grandfathered."

A drug was not subject to the effectiveness requirements of the 1962 amendments if its labeling and formulation had not changed and it also met the following three grandfather provisions of the amendments: it was (1) commercially used or sold in the United States on October 9, 1962, (2) not subject to an effective NDA on October 9, 1962, and (3) not a "new drug" as defined by the 1938 act. Before 1962, a drug would <u>not</u> be deemed to be a new drug if

it was either (1) generally recognized as safe or (2) marketed before the 1938 act and contained the same labeling concerning the conditions of its use.

FDA regulations require a person asserting a claim of grandfather status to support such a claim through the submission of "evidence of past and present quantitative formulas, labeling, and evidence of marketing." The regulations further state that a failure to submit the required evidence in the required format constitutes a waiver of the claim.

During our review we asked FDA to comment on whether ACE products that had been on the market before 1938 were exempt under the grandfather provisions of the FD&C Act. We told FDA that we could find little evidence in its files to show that product labels had changed, which would have voided any grandfather claims by the manufacturers.

FDA told us that a drug not generally recognized as safe and effective is subject to the new drug provisions of the FD&C Act unless it is exempted by virtue of its grandfather status. The grandfather clause contained in the Drug Amendments of 1962 applies primarily to pre-1938 drugs and permits an exemption from the statute's effectiveness requirements for a drug meeting all three criteria set forth in that portion of the amendments.

FDA said that it did not make a formal determination that ACE products were or were not grandfathered because no manufacturer had presented evidence upon which to make such an evaluation. According to FDA, the simple assertion of grandfather status is not sufficient. FDA contends that, as indicated in the applicable regulations (21 CFR 314.200(e)(2)), a claim for grandfather status must be supported by submitting evidence of past and present quantitative formulas, labeling, and marketing data. The regulation also provides a format for organizing the information in the submission.

According to FDA, establishing a grandfather status is an obligation the law imposes on the manufacturer. A determination that a drug is entitled to the exemption is not actually made until a claim by the manufacturer is raised and documentation is given to FDA for evaluation. In short, a manufacturer seeking the protection of the exemption has the burden of showing that the drug product in question comes within its terms.

FDA told us that, in deciding what action to take on a drug, it may informally consider the possibility that it is grandfathered and make a preliminary evaluation of the factors relevant to grandfather status. But without clear evidence of grandfather status, FDA's responsibility is to apply the act and to grant

grandfather exemption only when a claim has been raised by an applicant who has demonstrated that all the applicable criteria are met. Furthermore, if such an exemption is established for one firm's product, it does not ordinarily provide a full exemption for other firms' products.

FDA said that a preliminary check by the agency showed that the drug was the subject of two existing NDAs on October 9, 1962. Thus, the conditions for grandfather status under the Drug Amendments of 1962 could not be met. (See p. 2.) According to FDA, the later withdrawal of approval of the NDAs because the manufacturers failed to submit required annual reports is irrelevant to the failure of the drug to meet the criteria for the grandfather exemption.

In addition, FDA maintained that the "conditions prescribed, recommended, or suggested in the labeling" have not remained unchanged, as required for exemption from the 1938 new drug provisions. FDA said that it normally maintains records of labeling for drugs approved through the NDA process, but that its records do not give a complete history of changes in labeling for ACE products. However, FDA officials said it was clear that conditions of labeling for ACE products have changed through the years.

The agency stated that, although two drug firms had asserted their belief in writing that their ACE products were not new drugs, neither chose to enter or support a claim for grandfather status with the necessary data. FDA said that the oldest labeling it has available is a 1940 product label which states that ACE is indicated for Addison's disease, prevention of surgical shock, acute shock, burns, and for weakness due to adrenal cortex deficiency. According to FDA, later labeling recommends the drug for such indications as alcoholism, drug addiction, hypoglycemia, muscular fatigue, mental illness, and hypotension.

FDA further told us that, although the information available to it is limited, it is sufficient to indicate that grandfather status could not be established by most manufacturers, and very likely, not by any. In effect, therefore, FDA said it determined, at least tentatively, that a grandfather claim for ACE would be difficult to sustain before it issued its regulatory letter to the drug firms.

FDA DECISION TO ISSUE REGULATORY LETTER ON ACE

In January 1978, FDA sent regulatory letters to 78 drug firms involved in the marketing of ACE products. The letters said that FDA considered ACE products to be unapproved new drugs and in violation of the FD&C Act. This action by FDA had the effect of removing all ACE products from the market.

Regulatory letters are intended to address violations for which FDA would take legal or administrative action, such as seizure, prosecution, injunction, civil penalties, revocation of license, or loss of certification if corrections were not made. Regulatory letters are viewed as an alternative to legal and administrative sanctions intended to effect correction of violations promptly and with a minimum expenditure of agency resources.

FDA said that the agency issued its regulatory letters on ACE at the end of an ongoing process under which various alternatives were considered and analyzed by FDA personnel. It said that, because many of FDA's actions are complex and interrelated and because frequently a variety of offices exist within the agency whose functions are associated with a given action, it is not unusual to develop a position through a broad exchange of ideas--in meetings, memoranda, and the like--by which possible actions are considered and discussed by staff in other offices.

FDA told us that any attempt to remove ACE products by formally publishing its proposed actions in the "Federal Register" (see below) would have deferred removal of the drug until the publication of a final regulation and could have resulted in further deferral if the agency's actions were challenged in court. As a result, and with the concurrence of the agency's lawyers, FDA decided that a direct class action using the regulatory letter would be the preferable approach because it would be faster, require fewer agency resources, and be within the agency's authority. Consequently, in January 1978, regulatory letters declaring ACE to be an unapproved new drug were sent to 78 drug firms involved in marketing ACE products.

FEDERAL REGISTER APPROACH CONSIDERED AND REJECTED

FDA's earliest considerations related to the removal of ACE products from the market centered on the "Federal Register" approach. Under this approach, FDA would have had to publish its findings about ACE and its proposed actions in the "Federal Register" and give drug firms and other interested parties the opportunity to comment on or submit evidence disputing FDA's findings.

This approach would have required all interested persons to submit their written comments to FDA within 60 days of the publication of the proposal. FDA would then have had to consider these comments in publishing its final regulations.

In August 1973, FDA prepared a draft "Federal Register" proposal on ACE products which stated that FDA concluded (1) parenteral drug products for human use containing ACE are not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling; (2) the drug products are misbranded under section 502(a), (f)(1) and (2), and (j) as currently labeled; and (3) the drug products are new drugs within the meaning of section 201(p) of the act. Interested parties were to be given 60 days to submit written comments to FDA regarding this proposal.

The draft proposal was reviewed by FDA's Office of General Counsel which decided that using an old drug monograph procedure (see p. 21) that was also being considered at that time would be a more appropriate action.

OLD DRUG MONOGRAPH CONSIDERED AND REJECTED

One of the procedures FDA considered using to remove ACE products from the market was the publication of an old drug monograph, a concept that FDA was considering that would have been applied over time to all older drugs. ACE was viewed as a primary candidate for such a monograph, which would have set forth conditions under which a drug, or category of drugs, would have been generally recognized as safe and effective and not misbranded. However, because of an adverse court decision in 1975 and FDA's realization that it would take many years to write monographs, this approach was not used. (See p. 21.)

In the 24 years between 1938 and 1962, the number of new drugs on the market had grown enormously. In addition to products for which an NDA had become effective, there were thousands of identical, related, and similar formulations for which manufacturers had not filed an NDA. Those manufacturers had either (1) concluded that their products were generally recognized as safe because an NDA was in effect for the "pioneer" drug, (2) received an advisory opinion from FDA that an NDA was not required because their products were generally recognized as safe, or (3) marketed their products illegally without being discovered.

By 1968, FDA had sent several thousand letters or verbally notified drug manufacturers that various types of drugs were no longer covered by the definition of a new drug in section 201(p) of the FD&C Act, because they had become generally recognized as safe and had been used to a material extent or for a material time period and thus, they had achieved "old drug" status.

An "old drug" monograph approach was proposed to establish procedures to fill a gap in regulating prescription drugs--those not considered to be new drugs. This approach could have encompassed virtually all drugs over time, but could have been first applied to pre-1938 drugs and then to DESI drugs. FDA believed that, in order to review these drugs, there was a need for criteria and procedures to determine the conditions under which a drug is generally recognized as safe and effective and not misbranded.

Under this proposed approach, all drugs were to be classified under three groups: (1) not new drugs (monograph drugs), (2) new drugs, and (3) banned drugs. All the drugs in the first category would be subject to monographs and all further agency action would involve assuring compliance with monograph standards. Drugs in the second category would be subject to the new drug requirements and would be more closely monitored to determine their safety and efficacy. Drugs in the last group would be banned from further marketing, and FDA would act to remove them from the market.

FDA believed that the legality of marketing identical, related, or similar drug products without an effective NDA, in the absence of an "old drug" determination from the agency, was questionable. Several products were consequently seized by FDA even though applications had been filed with FDA for drug products containing the same active ingredients as drugs produced by other manufacturers. The agency believed that its resources to prevent such products from being marketed were limited and it could not effectively police the market for identical, related, and similar drug products being marketed without an NDA, except by occasional random proceedings.

To comply with the 1962 amendments regarding effectiveness, FDA published a formal statement in the May 28, 1968, "Federal Register" revoking all previous opinions that certain drugs were not subject to the new drug provisions of the FD&C Act. However, the agency had no complete file or list of the oral and written opinions it had been given on such matters or the drugs they covered.

In June 1973, the Supreme Court upheld the agency's primary jurisdiction to determine the status of drugs under the act, subject to judicial reviews. On the basis of these court decisions, FDA proceeded with the development of an old drug monograph system for regulating human prescription drugs.

However, in July 1975, the courts prohibited FDA from implementing its policy of permitting the introduction of "new" prescription drugs into interstate commerce without an approved NDA. On September 16, 1975, FDA announced its decision to withdraw its previously published interim enforcement policy in the "Federal Register," which included provisions for the proposed old drug monograph approach.

According to FDA, ACE was to have been one of the first drugs to be considered when this program was implemented. FDA said that, when the decision was made to move against ACE, the agency was planning the use of old drug monographs to regulate prescription drugs that were generally recognized as safe and effective and not misbranded. Older drugs that could not qualify for an old drug monograph would, as part of the program, be removed from the market. The program, however, was never fully developed or implemented because of the July 1975 court decision.

FDA'S RATIONALE FOR NOT TAKING ACTION UNDER MISBRANDING PROVISIONS OF THE FD&C ACT

During its deliberations, FDA considered moving against ACE under the misbranding provisions of the FD&C Act. However, this action would have placed the burden of proof on the agency to show the drug was misbranded. FDA told us that although it could have done so, it is easier for it to proceed in such cases under the new drug provisions, and consequently, FDA took this action against ACE.

The FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any drug that is misbranded. The act states that a drug shall be deemed to be misbranded if its labeling is false or misleading. The act also states that a drug shall be deemed to be misbranded unless its labeling bears (1) adequate directions for use and (2) such adequate warnings against use when it may be dangerous to health, or against unsafe dosage or methods of administration as needed for the protection of users. The act also states that a drug shall be deemed to be misbranded if it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling.

FDA told us that, although it could not recall precisely the reasons why it recommended against proceeding against ACE products under the misbranding provisions, it believed that one reason might have been that such charges would have been superfluous in the context of the "Federal Register" announcement, which was based on a new drug violation. FDA considers a new drug violation, in itself, sufficient evidence to question a drug's safety and effectiveness.

According to FDA, using a new drug charge also offers advantages in terms of using agency resources. If the new drug charge is contested, the manufacturer seeking to avoid new drug status bears the burden of proof of establishing either that it is not new or that it is "grandfathered." (See p. 2.) If a misbranding charge is contested, however, the agency bears the burden of proof of establishing the violation.

FDA further stated that, had it been required to pursue the matter in court, it would not have been prevented from including a misbranding charge as an alternative basis for removal of the drug. According to FDA, it is for this reason that the agency advised the affected drug firms of the possibility of regulatory action based on misbranding.

FDA did not provide any information on the adequacy of its support for its references to misbranding in the regulatory letters sent to firms marketing ACE products.

FDA PROCEDURES FOR EVALUATING SAFETY AND EFFECTIVENESS OF OLDER DRUGS

Because of varying circumstances, several procedures have been used to evaluate the safety and efficacy of prescription drugs. Drugs marketed before 1938 would possibly be considered to be grandfathered drugs, but could be reevaluated for safety if dictated by new evidence. Thousands of prescription drugs marketed between 1938 and 1962 had their effectiveness evaluated retrospectively by experts for the National Academy of Sciences under DESI. (See p. 24.) Newer drugs marketed after 1962 have their safety and efficacy evaluated through data submitted with their NDAs.

Evaluations of pre-1938 prescription drugs

FDA told us that it does not have a formal process for reviewing the safety and effectiveness of so-called "old" prescription drugs for which no approval is in effect, but rather evaluates such drugs as the need arises and resources permit. At FDA's discretion, any pre-1962 drug, including pre-1938 drugs, may be subject to an indepth review to evaluate safety, effectiveness, the benefit-risk assessment in view of available therapy, labeling adequacy, and "legal status" to determine whether it is a new drug or whether evidence supports a manufacturer's claim, if any, that the product is generally regarded as safe and effective or grandfathered.

FDA stated that no specific report is required for this type of review. Rather the drug's sponsor can choose to submit studies, reports, medical literature, and other information to FDA. In addition to making its own review of old drugs, FDA could ask an advisory committee to review the data supporting an old drug's safety and efficacy.

Efficacy studies of pre-1962 drugs

Under the 1962 amendments to the FD&C Act, FDA was required to undertake a retrospective review of labeling claims made for the efficacy of drugs marketed under new drug procedures between 1938 and 1962. In 1966, FDA took its first step to review effectiveness claims for drugs that had been cleared for marketing before 1962 on the basis of safety only--that is, they were subject to an NDA before 1962. With assistance from the National Academy of Sciences, the DESI reviews were initiated to determine whether appropriate scientific evidence existed to support the effectiveness claims of pre-1962 drugs. Thirty panels, each composed of six experts in a particular field of drug therapy, reviewed the claims and evidence of effectiveness for the drugs in their field of expertise.

To facilitate this review, manufacturers holding NDAs were requested by notices in the July 9, 1966, and October 6, 1966, "Federal Register" to submit to the panels the best available evidence in support of the effectiveness claims of their products. Evidence was to include copies of labeling, publications pertinent to claims, and any unpublished data the manufacturer wished to submit.

The panels found that, of some 16,500 claims made for about 4,000 drug formulations marketed by 237 drug firms, only about 19 percent were supportable. Products were rated as less than effective for the other claims.

While panels reviewed more than 4,000 drug products for which NDAs were in effect, they did not specifically evaluate the then still unknown larger number of identical, related, or similar drug products which were also being marketed without an approved NDA.

In the July 1970 "Federal Register," FDA published uniform conditions for marketing all new drugs which were covered by a DESI notice. This provided that those firms not holding an approved NDA and marketing a drug covered by a DESI notice must submit a full NDA or an abbreviated NDA (applications not requiring clinical trials to support safety and efficacy).

During our review, we noticed that ACE products were not included in the DESI review of effectiveness by the panels. According to FDA officials, data submissions to the DESI panels were on a voluntary basis, and no submissions were received from firms marketing ACE.

Also, according to FDA officials, after the DESI panels had completed their work and had been dissolved, FDA found that an additional 35 drugs should have been covered under the DESI reviews. These drugs were given DESI-type reviews by the FDA staff, but no ACE products were included.

FDA had been told by the only two firms which had held NDAs for ACE products that neither was still marketing ACE products. FDA correspondence indicated that one firm, which had an NDA for ACE, had dropped the product from its line before 1954. FDA said that an employee of the other firm with an approved NDA for ACE said he did not recall that his company had marketed the drug during his 20 years of employment. Moreover, neither firm had filed annual reports on ACE as required by FDA regulations, thus causing the NDAs to become inactive.

The NDAs, along with others, were withdrawn for these products by FDA because of the firms' failure to submit required reports. Therefore, according to FDA, these two NDAs were not included in the review of DESI drugs by agency personnel.

CHAPTER 4

CONCLUSIONS

Although ACE products represented the best known treatment for Addisonian patients during the 1940s and 1950s, the newer synthetic corticosteroids are currently the drugs of choice for treating Addison's disease. In fact, current medical opinion does not now offer any justification for using the older extracts for the treatment of Addison's disease. Moreover, it is readily apparent that the medical community considers the newer synthetic corticosteroids to be the generally accepted and preferred method of treating Addisonian patients because of several advantages these compounds offer over their predecessors--the crude adrenal extracts.

In regard to hypoglycemia, endocrinologists we interviewed said that reputable physicians would not have been prescribing ACE products for this condition. Treatment for the most prevalent complaints of "hypoglycemics" may simply involve dietary control. Actual cases of hypoglycemia, with more serious underlying causes, such as tumors or Addison's disease, may require other forms of therapy.

The regulatory actions taken by FDA against ACE were within its legal authority under the Food, Drug, and Cosmetic Act and were not unreasonable.

AGENCY COMMENTS

The Department of Health and Human Services reviewed a draft of this report and had no comments. FDA provided us with technical suggestions which we have included in the report where appropriate.

RECOMMENDED TREATMENT

REGIMENS FOR ADDISON'S DISEASE

FROM CURRENT MEDICAL TEXTBOOKS

Textbook source	Drug	Form of administration	Dosage	Frequency
	Acute			
Harrison	Hydrocortisone	Intravenous	100 to 200 mg	4- to 8-hour period
	Hydrocortisone	Intravenous	100 mg	First few minutes (in extreme cases)
Goodman	Hydrocortisone, Hemisuccinate, or Phosphate	Intravenous	100 mg	Rapidly
Cecil	Hydrocortisone phosphate with physiologic sodium chloride	Intravenous	100 mg	Rapidly
Williams	Hydrocortisone phosphate with 3 liters of saline (or 4 mg of Dexamethasone phosphate)	Intravenous	100 mg	Single dose
	Chronic			
Cecil	Hydrocortisone	Oral/ Injection	20 mg	Single or divided doses
	Fludrocortisone	Oral	0.1 mg	Once daily
Goodman	Cortisone acetate	Oral	25 to 37.5 mg	Single or divided dose (25 mg in the morning and 12.5 mg in the afternoon)
Harrison	Cortisone	Oral	12.5 to 50 mg (generally 37.5 mg)	Single or divided dose (25 mg in the morning and 12.5 mg in the afternoon)
	or			
	Hydrocortisone		30 mg	Daily
	Prednisone		7.5 mg	Daily
	Flurohydrocortisone	Oral	0.1 to 0.2 mg	Daily
	or			
	Deoxycorticosterone	Intra-muscular	2 to 5 mg	Daily
	or			
	Deoxycorticosterone	Injection/ Intramuscular	25 to 50 mg	Every 3 to 4 weeks
Williams	Cortisol		30 mg	20 mg in the morning 10 mg in the evening
	Fludrocortisone		0.1 mg	Daily

APPENDIX II

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

MAR 20 1981

Mr. Gregory J. Ahart
Director, Human Resources Division
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report, "FDA's Actions Regarding the Drug Adrenal Cortical Extract". We have carefully reviewed the report and have no comments to make at this time.

Thank you for the opportunity to comment on this report before its final publication.

Sincerely,

for P. Kropatkin
Bryan B. Mitchell
Acting Inspector General

BARRY M. GOLDWATER, JR.
20TH DISTRICT OF CALIFORNIA

COMMITTEE ON PUBLIC WORKS AND TRANSPORTATION
COMMITTEE ON SCIENCE AND TECHNOLOGY

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February 20, 1980

Mr. Elmer B. Staats
Comprtoller General
General Accounting Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Mr. Staats:

The issue of Adrenal Cortical Extract (ACE) first came to my attention approximately two years ago, shortly after the Food and Drug Administration ordered that new drug applications be filed for its further manufacture. At that time, a constituent wrote to me to complain about the decision and stated her need for continued therapy with the drug. My investigation of this matter revealed substantial evidence that the FDA acted without sufficient medical data; without sufficient understanding of the drug itself; and without an understanding of one of the major symptoms of Addison's Disease, namely hypoglycemia (independent of an actual diagnosis of Addison's Disease per se).

Adrenal Cortical Extract is used to treat the progressive stages of Addison's Disease and its hypoglycemic manifestations. For over thirty years, application of the extract resulted in unquestionably positive therapeutic results, and its safety was well established. The cost of obtaining the extract predicated the development of synthetic hormones, which, in spite of evidence supporting ACE's safety over them, became ever more popular with the medical community. Eventually, based largely upon opinion and a narrow field of references, the FDA claimed ACE posed health hazards.

Enclosed are hard scientific reports that were either unknown to or ignored by the FDA before the decision was made to effectively stop the manufacture of ACE. Also enclosed is a summary copy of my file on this subject, for your use and information.

I hereby request that you investigate the following:

1. The propriety of the FDA action in requiring a new drug application for ACE, effectively banning it, based upon stated FDA

concerns that the original use (Addison's Disease) differed from the then current use (primarily hypoglycemia). This action was taken although there was and is substantial evidence that a direct, if not incontrovertible, link exists between Addison's Disease and hypoglycemia. Scientific research has been done which gives sound basis for the contention that the efficacy of ACE in the treatment of Addison's Disease is proven even if it is not the modern drug of choice in many cases.

2. The effect of the FDA action on the use of corticosteroids: does the removal of natural ACE (which was free of damaging side-effects) increase the use of corticosteroids which have numerous, sometimes dangerous, contraindications? This is not only eliminating freedom of choice, but more crucially, encouraging dependence upon a potentially hazardous alternative. Certainly, the FDA position that available ACE dosages were not high enough to correct Addison's Disease deficiencies is contradicted by reputable scientific documentation. And certainly the FDA's contention that ACE was improperly labeled is specious considering the relationship between Addison's Disease and hypoglycemia.

3. The FDA's internal procedure that led to the decision. What prompted the decision, and what empirical method has been used to gather evidence on the use and efficacy of ACE? What documentation forms the basis for the decision? What commonality is there in drug efficacy labeling reviews routinely conducted by the FDA and how much is enough when it comes to documented evidence?

Your findings will help us all in determining whether or not there are serious deficiencies and misdirections within the FDA's procedural regulations and statutes. These areas should corrected to reinstill the intent of Congress in creating the FDA guidelines.

Thank you for your assistance in this matter.

Best regards,

Barry M. Goldwater

BARRY M. GOLDWATER, JR.
Member of Congress

BMG/ff/sm

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