

evidence in the administrative record. Whether or not fully audited, and regardless of the validity of its findings, the UGDP study was not relied on by me in withdrawing approval of the phenformin NDA's.

Finally, I note that the CCD petition for reconsideration, dated December 22, 1978, is untimely. Although the notice of availability of the final decision was published in the *Federal Register* of November 24, 1978, the decision was dated and effective on November 15, 1978. That is the "date of the decision involved" within the meaning of 21 CFR 10.33(g), which requires that a petition be filed within 30 days. Counsel for CCD was aware of the November 15 date because of their involvement in a lawsuit concerning the Secretary's imminent hazard determination on phenformin, *Forsham v. Califano* (D.D.C. No. 77-1478; D.C. Cir. No. 77-2072). In that suit, FDA made a specific representation to the Court that the withdrawal order would be issued on or before November 15.

I conclude that the petition for reconsideration does not merit reconsideration of my decision to withdraw the NDA's for phenformin and that the grounds presented in the petition do not meet the criteria for reconsideration set forth in the regulations, 21 CFR 10.33(d). Accordingly, the petition is denied.

Dated: February 5, 1979.

Donald Kennedy,
Commissioner of Food and Drugs.

[Docket No. 77N-0150]

[FR Doc. 79-10591 Filed 4-3-79; 3:45 am]

BILLING CODE 4110-03-M

Phenformin Hydrochloride; Withdrawal of Approval of New Drug Application; Final Decision

AGENCY: Food and Drug Administration.
ACTION: Notice.

SUMMARY: The Commissioner of Food and Drugs is publishing his final decision, following a formal evidentiary public hearing, findings of fact, conclusions of law, and final order on the proposal to withdraw approval of the new drug applications (NDA's 11-624 and 12-752, held by Geigy Pharmaceuticals, Division of Ciba-Geigy Corp., Ardsley, New York; NDA's 17-126 and 17-127 held by USV Laboratories, Division of USV Pharmaceutical Corp., Tuckahoe, New York) for phenformin hydrochloride under section 305(e)(2) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e)(2). The Commissioner has determined that

phenformin is not shown to be safe for use under the conditions of use on the basis of which the applications were approved. He has affirmed the Initial Decision of the Administrative Law Judge with modification and supplementation provided in his order. Introduction into interstate commerce of phenformin, except in conformity with an exemption granted pursuant to section 305(i) of the act (21 U.S.C. 355(i)), constitutes a violation of law.

EFFECTIVE DATE: November 15, 1978.

ADDRESS: The transcript of hearing, evidence submitted and all other documents cited in the decision, and the Initial Decision of the Administrative Law Judge, may be seen in the office of the Hearing Clerk (HFA-305), Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Richard A. Anderson, Office of the Associate Commissioner for Health Affairs (HFY-21), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1177.

SUPPLEMENTARY INFORMATION: In the *Federal Register* of November 24, 1978 (43 FR 54995), the Commissioner issued a notice of availability of his final decision in this matter. Because it has been the long-standing policy of the Food and Drug Administration (FDA) to publish all notices of withdrawal of approval of NDA's, and because there has been considerable public interest in the matter, the Commissioner is now publishing the final decision in the *Federal Register*. Further, because the final decision relies very specifically on the Initial Decision of the Administrative Law Judge, the latter is also being published at this time elsewhere in this issue of the *Federal Register*. Also, a denial of petition for reconsideration is published in this issue of the *Federal Register*.

The Commissioner advises that although this document contains minor editorial changes from the final decision, such changes are made only to comply with document drafting guidelines issued by the Office of the Federal Register. There are no substantive differences between the document that follows and the official copy of the Final Decision dated November 15, 1978.

The purpose of this proceeding is to decide whether approval of the new drug applications for phenformin should be withdrawn because phenformin has not been shown to be safe for use under

the conditions of use on the basis of which the applications were approved.

I. Background

Phenformin is an oral hypoglycemic drug used in the treatment of symptomatic adult-onset diabetes. Phenformin was first approved for marketing in the United States in March 1959. Soon thereafter, reports of cases of lactic acidosis associated with the use of phenformin begin to appear in the medical literature. Lactic acidosis is a condition in which abnormal amounts of lactic acid accumulate in the blood. The rate of fatalities in cases of lactic acidosis is about 50 percent. In response to these reports, warning statements and other information were added to phenformin labeling in 1964, 1970, 1974, 1976, and January 1977.

In the *Federal Register* of May 6, 1977 (42 FR 23170), the Director of the Bureau of Drugs, FDA, proposed to withdraw the approval of the new drug applications for phenformin. The proposal stated: "This action is being taken on the basis of the clear association demonstrated between the use of phenformin and the occurrence of lactic acidosis" in diabetic patients. *Id.* "Although the true frequency of the occurrence of lactic acidosis in diabetics using phenformin cannot be determined," the relative frequency among such diabetics "is considerably higher than that being reported for any other form of treatment for diabetes." 42 FR at 23172. "Because lactic acidosis is a frequently fatal complication, because no patient population exists in whom all risk factors for this complication can always be either identified or predicted, and because of the availability of effective alternative orally administered drug products and other drug and nondrug methods for diabetic therapy, the Director [of the Bureau of Drugs] concludes that the risk of phenformin therapy outweighs any possible benefits that can be derived from its use." 42 FR at 23173.

Requests for hearing, together with supportive material, were received from Ciba-Geigy and USV, the two manufacturers of phenformin. In the *Federal Register* of August 12, 1977 (42 FR 40959), FDA announced a formal evidentiary public hearing on factual issues relating to the proposed withdrawal. A prehearing conference was scheduled for August 30, 1977. The Committee for the Care of the Diabetic (CCD) appeared in opposition to the withdrawal as a non-party participant. Prior to the notice announcing the hearing, the Secretary of Health, Education, and Welfare invoked the

imminent hazard clause of section 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e), to suspend immediately approval of the phenformin NDA's (Docket No. 77N-0147). Accordingly, phenformin has not been marketed under the NDA's pending completion of these proceedings on the proposed withdrawal.

At the conclusion of the prehearing conference, the Administrative Law Judge, Daniel J. Davidson, designated the following issues to be addressed at the hearing:

1. Whether, and to what extent, the use to phenformin is beneficial in the treatment of diabetic patients for whom the drug is indicated under the conditions of use prescribed, recommended, or suggested in its labeling.

2. Whether an association has been established between the use of phenformin and the occurrence of lactic acidosis, including fatalities, in patients for whom the drug is indicated under the conditions of use prescribed, recommended, or suggested in its labeling, and what is the incidence of lactic acidosis, including fatalities, in such patients, and in the diabetic population at large.

3. Whether, and to what extent, other therapeutic modalities are appropriate and effective in treating persons for whom phenformin is indicated on the basis of the conditions of use prescribed, recommended or suggested in its labeling.

4. Whether the conditions of use prescribed, recommended or suggested in the labeling for phenformin are adequate to exclude from treatment persons for whom the drug is contraindicated as a result of the presence of factors which predispose to lactic acidosis.

5. Whether, in view of all of the above, the benefits outweigh the risks associated with use of the drug, phenformin.

By Order of August 31, 1977, the Administrative Law Judge also set times for the filing of all documentary material, and he established October 5, 1977 as the date on which the hearing would commence. The hearing began as scheduled and concluded on October 7, 1977.

The Administrative Law Judge issued his Initial Decision on February 6, 1978. He found that (1) phenformin has limited short-term beneficial effects in the treatment of diabetes, (2) a strong association between phenformin and lactic acidosis has been established although its rate of occurrence "is not susceptible of quantification on this

record." (3) the same degree of risk associated with the use of phenformin does not exist with other forms of therapy that are effective for treating diabetes, and (4) the labeling for phenformin is inadequate to exclude from treatment those persons for whom the drug is contraindicated as a result of factors that predispose such persons to lactic acidosis. Initial Decision at 1, 2, 46, 47, 48. Accordingly, the Administrative Law Judge concluded that "the limited benefits of phenformin are insufficient to support a finding of safety in light of the risks attending its general marketing under the approved NDA's. Approval of the NDA's for phenformin should therefore be withdrawn * * *." Initial Decision at 2, 48.

II. Exceptions

On March 3, 1978, CCD filed 18 exceptions to the Initial Decision. Neither Ciba-Geigy nor USV filed exceptions. On March 28, 1978, the Bureau of Drugs submitted its reply to CCD's exceptions. I conclude the CCD's exceptions do not justify reversal of the Initial Decision.

1. Two exceptions question the focus of the Initial Decision on whether phenformin must be withdrawn from the market. CCD argues that the Initial Decision should have considered, and, if necessary required, revision of the labeling for phenformin. CCD contends that there are specific patient populations for whom the benefit of phenformin outweighs its risks, and that those populations can be adequately identified in revised labeling. CCD characterizes the withdrawal issue as a "self-imposed" limitation, which "severely restricted[ed] the scope of the hearing" and resulted in a prejudicial restriction on the evidence presented.

The statute established the standards for approving and withdrawing a new drug application. In either case, the data on safety and effectiveness are measured by the conditions for use prescribed, recommended, or suggested in the drug's labeling. See section 505(d) of the Act. Consistent with section 505(e)(2) of the Act, the notice of opportunity for hearing defined the issue to be decided as whether phenformin is not shown to be safe for use "under the conditions of use upon the basis of which the application were approved,"¹ not whether more restrictive labeling might be drafted and submitted to FDA as a supplement to the NDA.

¹Since the new drug applications include their supplements, the conditions of use against which the Administrative Law Judge evaluated the safety of phenformin are those contained in the revised January 1977 labeling.

I find no merit in the CCD contention that the Administrative Law Judge identified "a number of different patient populations for which the benefits of phenformin use outweigh any risks" and that the Initial Decision was able to "specify patient populations which need phenformin." Having discussed the claim by Ciba-Geigy and USV that operators of commercial vehicles in interstate commerce would be precluded from such employment if forced to use insulin therapy rather than phenformin the Administrative Law Judge concluded that "limiting employment possibilities cannot preclude withdrawal of approval of phenformin." Initial Decision at 43. Thereafter, the Administrative Law Judge speculated generally that the "temporary benefits" of phenformin could be of value in a "small number" "unusual cases" and that certain individuals were "possible candidates" if a limited distribution system for phenformin could be established: "the need may exist for a limited distribution of phenformin to special patients under specialized controlled treatment programs." Initial Decision at 44. These remarks do not constitute a "finding" that patient populations exist for whom the benefits of phenformin in general distribution pursuant to current law "outweighs the risks."

AS the Administrative Law Judge went on to point out, such a limited distribution program "cannot be authorized within the parameters of the proceeding which is charged solely with determining the propriety of the proposed withdrawal of approval of the NDA's for general marketing of phenformin." *Id.* FDA does not currently have authority to limit the distribution of drugs through specified channels, except as a consequence of a controlled clinical investigation conducted under an exemption from the new drug application requirements of section 505(i) of the Act. *American Pharmaceutical Association v. Weinberger*, 377 F. Supp. 824 (D. D.C. 1974), *aff'd sub nom. American Pharmaceutical Association v. Mathews*, 530 F.2d 1054 (D.C. Cir. 1977). The authority provided by section 505 cannot be used to limit distribution of drug so long as it is approved under a NDA. Thus, the Administrative Law Judge's discussion of limited distribution referred either to a circumstance in which the NDA for phenformin had already been withdrawn or to an amendment to current law granting FDA authority to limit distribution of approved drugs. In neither case can the discussion be construed as a "finding

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exceptions filed by CCD
the evaluation by the
Administrative Law Judge of the long-
ectiveness of phenformin. CCD
that the question of long-term
effectiveness is improper because the
of secondary failure with
phenformin has been known by FDA
as was not "new evidence" within
the meaning of section 505(e)(2) of the
Act, and because many drugs presently
permitted to be marketed exhibit similar
decreasing effectiveness over time.
CCD's position is that a loss of
effectiveness over time does not render
a drug either legally or medically
ineffective.

I find that the extent of effectiveness
over time is a valid consideration. Adult
onset diabetes is a chronic conditions
with severe complications. Since the
disease requires long-term rather than
intermittent management, it is relevant
to inquire into the duration of the
treatment. The management of a disease
may involve a variety of treatments,
some of which are more useful during a
particular stage. A drug is not unsafe or
ineffective simply because it constitutes
only a portion of the treatment regimen
either in terms of concomitant therapy
or time. Nevertheless, a risk to benefit
evaluation of any treatment must
include an evaluation of the extent of
the benefit.

CCD's assertion that FDA knew of
secondary failure with phenformin
before approval of the NDA's is
incorrect. In fact, significant evidence on
the question of secondary failure
associated with phenformin was
developed only in the context and for
the purposes of the evidentiary hearing.
See CG-81, and Bureau of Drugs Brief,
59-70. In addition, "new evidence"
includes a reevaluation of any evidence
previously submitted. *Beil v. Goddard*,
366 F. 2d 177 (7th Cir. 1966).

3. Three of the CCD exceptions deal
with the University Group Diabetes
Project Study (UGDP), a long-term
prospective clinical trial carried out in
the 1960's. The CCD criticized the
Administrative Law Judge's admission
of the UGDP study results (B-395, B-396)
into evidence without requiring
disclosure of the raw data (individual
reports on all of the individuals who
participated in the study). See Order of
November 11, 1977, denying CCD's
Motion to Strike Or. In The Alternative,
To Produce Evidence. CCD argues that
the failure of the Administrative Law
Judge to require that raw data be filed,
by the Bureau of Drugs pursuant to 21
CFR 12.85 invalidates the hearing

procedure and its results. CCD also
takes exception to the UGDP study
because it believes the study "has been
thoroughly impeached" from an
evidentiary, scientific and medical
veiwpoint. CCD objects to the decision
of the Administrative Law Judge to
permit expert opinion testimony
concerning the safety and effectiveness
of phenformin based upon the UGDP
study. Initial Decision at 7. CCD argues
that reliance upon the UGDP by Bureau
of Drugs witnesses was substantial and
that those experts were biased because
they had been associated with the
study. CCD also alleges that
retrospective studies admitted into
evidence and relied upon by the
Administrative Law Judge followed
upon and were influenced by the results
of the UGDP study. CCD concludes that
by failing to strike the UGDP study or to
consider its impact or other evidence,
the Administrative Law Judge's Initial
Decision is "flawed and not based on
substantial and reliable evidence" and
that his ruling "invalidates the hearing
process."

I affirm the Administrative Law
Judge's ruling on the motion to strike the
UGDP data. The Administrative Law
Judge held that the "lack of availability
of underlying data casts considerable
doubt on the reliability of the UGDP
conclusions from an evidentiary
standpoint. To the extent such data was
not made available, the UGDP
conclusions cannot be considered as
substantiated on the record." *Id.*
Accordingly, in reviewing the Bureau's
evidence on the question of safety, the
Administrative Law Judge referenced
the UGDP study in only one paragraph
of his 8-page summary. Initial Decision,
at 20.

The Administrative Law Judge
concluded that the UGDP study could be
used for two purposes: to raise
questions about the safety of
phenformin and as the basis for expert
opinion. The FDA has long taken the
position that evidence suggestive of a
lack of safety may be considered in
evaluating whether a drug has been
shown to be safe even though the
evidence does not meet the standards
required to establish the safety of the
drug. The Administrative Law Judge's
ruling that the UGDP study might serve
as the basis for expert testimony is
supported by Rule 703 of the Federal
Rules of Evidence, which provides that
even if data are not admissible into
evidence they may nevertheless form
the basis of opinions by experts if they
are the type of data reasonably relied
upon by experts in that particular field.
See *Nanda v. Ford Motor Co.*, 509 F. 2d

213 (7th Cir. 1974); *Jenkins v. United
States*, 307 F. 2d 637 (D.C. Cir. 1962).
Experts routinely keep abreast of the
literature and base their opinions, in
part, on published reports of drug
studies. They rarely see or review the
"raw data." Nor are they required to
base their expert opinions on raw data;
any such conditions would require
expert witnesses to disregard the vast
bulk of their expert knowledge.

The record in this proceeding includes
nearly 400 articles published in the
medical literature. Many of them report
studies on phenformin. None of those
articles is accompanied by the "raw
data" upon which it is based. The
Bureau has relied solely on the
published report of the UGDP study in
the same way that it has relied upon the
other published articles that were
admitted into evidence. 21 CFR 12.85
requires only that the Bureau provide
data upon which it relies; it does not
require the Bureau to submit related
data on which it does not rely.

Because of CCD's emphasis on the
unavailability of the raw data
underlying the UGDP study, I have
reviewed the testimony of the Bureau of
Drugs' expert witnesses and find that
their reliance upon the UGDP study was
not substantial and cannot reasonably
be characterized as pivotal to the
opinions expressed by those witnesses.

I reject the suggestion by CCD that the
witnesses who testified for the Bureau
of Drugs consisted primarily of those
persons whose professional reputations
would be tarnished if the UGDP study
were ever established to have been
faulty. The CCD exception provides no
specific basis upon which to question
the professional integrity of the Bureau's
witnesses. Their curricula vitae strongly
support the Bureau's reliance on their
professional opinions. See B-464, B-466,
B-468, B-470, B-472, B-474, B-476, B-478,
B-480, B-482, B-484, B-486, B-488, B-492,
B-494, B-496, B-498, B-500. Challenges
to scientific integrity of the sort made by
CCD in this case, certainly cannot be
accepted without any support in the
record.

I am aware of the controversy over
the UGDP study. *Bradley v. Weinberger*,
483 F. 2d 410 (1st Cir. 1973). Indeed,
during the course of this proceeding,
FDA participated in an audit of the
UGDP data. Because the audit coincides
with this withdrawal proceeding, and is
not part of this record, I have not
considered the UGDP study in reaching
my final decision. References to the
UGDP study in the substantive portion
of the Initial Decision are not adopted.

4. CCD takes exception to the ruling of
the Administrative Law Judge admitting

into evidence foreign clinical data submitted by the Bureau of Drugs. CCD contends that the data do not satisfy the requirements of 21 CFR 312.20, and concludes that the Administrative Law Judge applied a double standard for the admission of evidence, whereby controlled clinical studies are required to support an NDA while technically incomplete studies, which would not support a showing of safety or effectiveness, were considered as part of the "overall body of available safety data."

I affirm the decision of the Administrative Law Judge that data that do not meet the requirements of 21 CFR 312.20 nevertheless may be considered in evaluating drug safety. See *Federal Register* of November 19, 1976 (41 FR 51215). The "double standard" complained of by CCD is the standard contemplated by the statute.

I believe, however, that the statement of the Administrative Law Judge that foreign clinical data do not qualify as prima facie evidence of a lack of safety (Initial Decision at 8) should be modified. Although failure of foreign clinical data to meet the requirements of 21 CFR 312.20 may affect their weight in evaluating a drug's safety, this does not mean that they cannot be the basis for a prima facie case that a drug is not safe. I find that a prima facie case for withdrawal or non-approval under section 505 of the Act can be made on the basis of medical facts reported in foreign literature, such as the reports of birth defects resulting from use of thalidomide in Europe. See S. Rept. No. 1744, 87th Cong., 2d Sess., 40 (1962).

5. CCD takes exception to the weight given by the Administrative Law Judge to the testimony of certain diabetologists appearing on behalf of Ciba-Geigy and USV on the question of the safety of phenformin. CCD claims that the Administrative Law Judge disregarded the testimony of these experts because it conflicted with evidence, primarily retrospective studies on cases of lactic acidosis, that CCD believes is not of comparable value. According to CCD, the Administrative Law Judge's evaluation of the testimony of the manufacturers' experts reveals that he had prejudged the case. CCD also takes exception to the Administrative Law Judge's failure to give substantial weight to Ciba-Geigy's nationwide survey of reports of lactic acidosis among patients treated with phenformin.

The Administrative Law Judge found that the Ciba-Geigy data on the rate of incidence of lactic acidosis (CG-26) are deficient due to (1) the recognized

phenomenon of under reporting of adverse effects to drug companies, (2) the tendency of reports in the medical literature to decline once a discovery has been published repeatedly, (3) deficiencies in the criteria used by Ciba-Geigy to screen the data, (4) the inadequacy of the qualifications of the Ciba-Geigy employee who prepared the data, and (5) the absence of a showing by Ciba-Geigy that an effort was made to supplement information that was inadequate and resulted in exclusion from the study of certain reports of lactic acidosis. Initial Decision at 22-26. The Administrative Law Judge "disregarded" the data in that he concluded that they were flawed to such an extent as to preclude their being afforded "any significant evidentiary weight." *Id.* at 26. On the basis of my independent consideration of the record, I affirm the findings of the Administrative Law Judge with respect to the Ciba-Geigy study.

The Administrative Law Judge did not disregard the testimony of the Ciba-Geigy expert diabetologists. Rather, he concluded that their testimony that they had not seen lactic acidosis in their patients was not determinative of the safety of phenformin under general marketing conditions. Several of these experts testified about their knowledge of lactic acidosis in patients other than those under their private care. The majority of diabetics in this country are not treated by expert diabetologists. Initial Decision at 26-28. The Administrative Law Judge concluded, in light of the overall evidence of lactic acidosis associated with phenformin, that the very testimony that phenformin is safe when prescribed by "the most eminent" diabetologists in the United States suggests that patients for whom phenformin is prescribed by general practitioners run "a considerable risk of phenformin-associated lactic acidosis." *Id.* at 28.

6. In a related exception, CCD objects to the Administrative Law Judge's conclusion that proof of the safety of phenformin when administered by specialists is insufficient to justify its continued general marketing. CCD argues that this standard is not sanctioned by law and that the evidence does not support a finding that some physicians with certain training can administer phenformin while others cannot. CCD urges that the Administrative Law Judge cannot base a decision upon factors beyond the scope of FDA's authority.

CCD has misconstrued the statutory requirement of safety and the Administrative Law Judge's reasoning.

Section 505(d)(1) requires that a new drug be "safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof." The statute thus requires general safety for use—that is, safety for use by the general practitioners who do or will use the drug. The Administrative Law Judge found that on the record before him phenformin was not shown to be safe as required by section 505(d)(1). He also noted evidence tending to show that phenformin is safe when prescribed by expert diabetologists. He correctly interpreted section 505(d)(1), however, as requiring a broader showing of safety. In light of the entire record concerning the actual use of phenformin, the evidence tending to show that phenformin may be prescribed safely by expert diabetologists does not establish the general safety required by section 505(d)(1).

CCD's argument would have merit if FDA had authority to leave phenformin on the market by restrict its distribution to the prescription of expert diabetologists or to the prescription of physicians with patients for whom phenformin is appropriate. As Ciba-Geigy and USV recognize, however, FDA does not have such authority. Initial Decision at 28; Ciba-Geigy/USV Brief at 18. Having found that phenformin was not shown to be safe for use by those persons who, pursuant to state law, are licensed to prescribe it and treat diabetic patients, the Administrative Law Judge was required to recommend withdrawal of the NDA's for the general marketing of phenformin.

7. CCD takes exception to the text of a draft *Federal Register* notice of the availability of phenformin pursuant to an investigational new drug exemption (IND), CG-81. (This draft was not admitted into evidence. Initial Decision at 44, n. 5.) CCD alleges that the draft is inconsistent with the position taken by the Bureau of Drugs because the Bureau's notice of opportunity for hearing and its position in this proceeding support the complete withdrawal of phenformin, while the existence of the Bureau-approved IND demonstrated the phenformin can be marketed and distributed under certain controls. CCD concludes that the Bureau's separate actions are conflicting and that the supposed inconsistency "invalidates any results of the administrative proceeding."

This exception is without merit. First, no notice based upon the draft IND document has ever been published in the *Federal Register*. Second, it is not inconsistent for the Bureau to support

withdrawal of approval of phenformin for general marketing while recognizing that an investigational new drug exemption may impose controls that render the use of the drug acceptable and may yield safety data that do not now exist. The Bureau routinely approves IND's for drugs that are not subject to approved NDA's. Thousands of drugs have been so regulated. Indeed, the very purpose of an IND is to authorize a limited investigation of an as yet unapproved use of a drug. There is no legal difference between an IND for a drug that has never been the subject of an approved NDA and an IND for a drug that has.

8. Noting that the Administrative Law Judge held that the rate of occurrence of phenformin-associated lactic acidosis is "not susceptible of quantification on this record," the CCD argues that the Bureau of Drugs has not sustained its burden.

There is an important distinction between a requirement of mathematical quantification of a rate of occurrence of lactic acidosis and the burden to adduce new evidence which, when evaluated together with other data, raises "significant doubts as to the appropriateness of the finding of a prior showing of safety in light of the new evidence." Initial Decision at 5. Although unable to quantify the rate of occurrence of lactic acidosis, the Administrative Law Judge found that lactic acidosis "occurs virtually exclusively among phenformin users," and that the absence of a base rate of lactic acidosis in the diabetic population generally, which is needed to calculate the rate of lactic acidosis among phenformin users, "is typical of many diseases and does not detract from the demonstration of a strong association between phenformin and lactic acidosis." See Initial Decision at 48. On the basis of my independent evaluation of the record, I find that the association between the use of phenformin and the occurrence of lactic acidosis is real and has been substantiated in this proceeding.

9. CCD objects to the ultimate finding of the Administrative Law Judge that other treatment are just as effective as phenformin but do not present the same degree of risk. CCD's objection is on the ground that the testimony of significant side effects associated with the use of insulin was disregarded.

I reject CCD's characterization of the record. The phenformin labeling, B-506(n), states that diet and insulin are the therapies of choice in the control of diabetes. Although there are side effects from treatment with insulin, its overall

effectiveness in treating the chronic complications of diabetes was found to be substantial. Initial Decision at 41. The references in the record to the existence of side effects of insulin therapy were not disregarded by the Administrative Law Judge; on balance, they simply did not outweigh the evidence of its efficacy, or require a conclusion that insulin is less safe than phenformin.

10. CCD alleges that the Administrative Law Judge "has not properly taken into account the compliance problems inherent in both diet and insulin therapy." CCD claims that these considerations were "frequently stressed in the testimony of CCD and Ciba-Geigy witnesses" and were not given due weight by the Administrative Law Judge.

This assertion is not supported by the record. The Administrative Law Judge found that the "major difficulty encountered in this mode of therapy [diet] has been in effecting compliance with the diet regimen." Initial Decision at 40. Likewise, he recognized the problems with self-administration of insulin. See Initial Decision at 43, 44. The Administrative Law Judge was apparently impressed, however, with the testimony of one witness that " . . . when the advantages of insulin therapy were thoroughly explained to patients for whom diet proved unsuccessful, there was not a single refusal of insulin therapy (Tr. 8)." Initial Decision at 41.

This exception is also rejected because it fails to cite the specific portions of the record on which it relies. Unlike the CCD exception, the Administrative Law Judge cited specific portions of the record in discussing both the problems and successes with diet and insulin regimens. Initial Decision at 40-44. See 21 CFR 12.125(b), which provides that exceptions to the initial decision shall contain "specific reference to those parts of the record upon which the exceptions are based."

11. One CCD exception is based on CCD's view that the Administrative Law Judge "simply restated the contents of these studies [Submitted by the Bureau of Drugs] without critical comment . . . without differentiating what is important and reliable from that which is of minimal reliability." According to CCD, this causes the decision to be arbitrary and capricious and not supported by substantial evidence.

The objection is without merit. In his introductory remarks in that portion of the Initial Decision entitled "Bureau's [safety] Evidence," the Administrative Law Judge reviewed the criteria suggested by Ciba-Geigy for eliminating

bias from study reports, and found that "the [Bureau] studies of Dr. Tranguada, Dr. Fullop and Dr. Brach, et al., do meet this Ciba-Geigy criteria." Initial Decision at 14. The Administrative Law Judge placed primary reliance upon these studies, which he found to be "the best available in the record." Initial Decision at 22.²

12. CCD alleges that the Secretary's Suspension Order and the Administrative Law Judge's Initial Decision are based on entirely different data and that the data relied upon by the Secretary were not given great weight by the Administrative Law Judge. CCD concludes that the differences establish that the data relied upon by the Secretary in the suspension decision are unreliable.

The Secretary's Suspension Order and the Administrative Law Judge's Initial Decision are not based upon "entirely different data." The four specific items referenced in the CCD exception—the UGDP study, the foreign clinical data, the manufacturer's data, and data supplied by Dr. Davidoff—are common to both proceedings. The FDA submissions to the Secretary in the suspension proceeding, however, were stricken from the record in this proceeding. Because the Suspension Order is a separate proceeding, and because of the pending litigation involving the propriety of the Secretary's invocation of the imminent hazard provisions of the Act, *Forsham v. Califano*, 442 F. Supp. 203 (d. D.C. 1977), appeal pending (D.C. Cir.) (No. 77-2072), it would be inappropriate for me to make a detailed comparative analysis of the data presented in these independent proceedings.

I note, however, that the criteria for invoking the imminent hazard provision and those for withdrawing a new drug application are different. Accordingly, it is to be expected that the records of the two proceedings would contain different data.

13. CCD takes exception to the order of the Administrative Law Judge that denied, without prejudice, a motion of CCD pursuant to 21 CFR 12.89(d) to obtain rights additional to those prescribed for non-party participants. See Order of September 26, 1977; see also Initial Decision at 8-9. CCD argues that it represents interests different from

² Although compliance with these criteria could not be determined for other studies, the Administrative Law Judge held that "this does not mean that such studies may not be considered for purposes of raising questions as to the safety of phenformin and as corroboration for similar conclusions reached in the other studies." Initial Decision at 14. The fact that he did not find it necessary to evaluate these other studies critically does not render his decision arbitrary.

those of the Bureau of Drugs and the manufacturers. CCD concludes that the Administrative Law Judge's decision to deny additional rights of participation rests upon "the underlying faulty assumption that basic due process rights may be denied CCD in the discretion of the hearing officer."

Requests for hearing in response to the May 6, 1977 notice were filed by Ciba-Geigy and USV. Accordingly, the NDA holders, together with the Bureau of Drugs, were designated as the parties to the hearing. The CCD did not announce its desire to participate until three days after the expiration of the period for filing notices of non-party participation. Transcript of August 30, 1977 Prehearing Conference at 4, 35-37. CCD was not entitled to greater procedural rights than those accorded it in the proceeding.

Participant rights in formal evidentiary hearings are established by regulation, 21 CFR 12.89(b), and include the right to submit written testimony and documentary evidence, to file briefs, written objections, and other pleadings; and to present oral argument. CCD requested an opportunity to submit written interrogatories and to conduct cross-examination. Due to the expedition with which the hearing was held, in light of the Secretary's suspension order, the use of written interrogatories was not sanctioned for any participant, including the parties. With respect to the request to conduct cross-examination, the Administrative Law Judge's ruling permitted CCD to renew its request on a witness-by-witness basis. See Order of September 26, 1977. Thus, CCD was not prejudiced by its status as a non-party participant.

CCD's allegation that its interest and those of physicians and patients using phenformin were not adequately represented by the manufacturers is not supported by the record. CCD documentary evidence consisted of the affidavits of seven expert witnesses, five of whom also submitted testimony on behalf of Ciba-Geigy. Compare CCD exhibits 1, 3, 4, 5, and 7 with Ciba-Geigy exhibits 2, 3, 5, 9, 14, 16, 17, 42, 61, and 66. In addition, the manufacturer parties vigorously contended that a patient population exists justifying the continued marketing of phenformin under the restrictive January 1977 labeling. This contention appears to be the heart of the CCD position. The argument that CCD has no investment in the existing labeling and "therefore can present a position without a predetermined bias" is not compelling since labeling other than that approved in the new drug applications and their

supplements is not at issue in this withdrawal proceeding.

The granting of additional rights of participation rests within the sound discretion of the Administrative Law Judge and is based upon an evaluation of whether a participant's interest will not be adequately protected otherwise or whether broader participation is required for a full and true disclosure of relevant evidentiary facts. 21 CFR 12.89(d). In view of the breadth of the presentation by Ciba-Geigy and USV, the substantial overlap of their witnesses with those of CCD, the inapplicability of the question of substitute labeling, together with the provision of the Administrative Law Judge's order for request to cross examine specific witnesses, I cannot conclude that the Administrative Law Judge abused his discretion in denying CCD's request. I also note that there is no "right" granted by the statute to a person who is not the holder of an NDA to participate in a withdrawal proceeding in any capacity. Participation status is granted by FDA in the exercise of its discretion any may, therefore, be limited as the agency believes appropriate. The exception is rejected.

III. Review of the Initial Decision

A. Burden of Proof

I adopt the holding of the Administrative Law Judge, Initial Decision at 4-7, that section 505(e)(2) requires the Bureau of Drugs to bear the initial burden of adducing new information that, when evaluated together with the information available when the new drug applications for phenformin were approved, shows that phenformin is not shown to be safe for use under the conditions of use upon the basis of which the applications were approved. To meet that burden, the Bureau "need only raise significant doubts" as to the prior showing of safety. Once this threshold burden is met, the manufacturers are required to prove the safety of phenformin.

I agree with the Administrative Law Judge that the statutory reference to new information "cannot reasonably be construed as only that evidence that came to light subsequent to the date of the approval of the most recent supplemental NDA," so as to preclude the reevaluation of the evidence previously available. In addition to the reasons set forth in the Initial Decision, I find that the application of *Hess & Clark v. FDA*, 495 F.2d 975 (D.C. Cir. 1974), to a withdrawal under the new drug provisions is supported by the

legislative history of the new animal drug provisions of the Act, S. Rep. 1308, 90th Cong., 2d Sess., 5 (1968)³ that the Administrative Law Judge's definition of the Bureau's burden is supported by the legislative history of the 1962 amendments to section 505. See Cong. Rec. 10105-10108 (June 1, 1962); S. Rep. No. 1744, 87th Cong., 1st Sess., 25-26 (1962); Committee on the Judiciary, 37th Cong., 2d Sess., 13, 3 (Committee Print 1962), Cong. Rec. 16302-16304 (Aug. 23, 1962); Section 102(d) of House Bill 11581; H.R. Rep. 2464, 37th Cong., 2d Sess., 1-3, 16 (19 Cong. Rec. 19890-19895 (Sept. 27, 19 H.R. Report No. 2526, 37th Cong., 2d Sess., 19 (1962)). See also *Weinberge Hynson, Westcott & Dunning, Inc.*, 4 U.S. 609 (1973), *North American Pharmacal, Inc. v. Department of Health, Education, and Welfare*, 491 F.2d 546, 551, (8th Cir., 1973), and *Ubiotica Corp. v. FDA*, 427 F.2d 376, (8th Cir., 1970).

The Administrative Law Judge measured the cut-off period for new evidence by the January 1977 labeling. See Initial Decision at 4, 5. However, Ciba-Geigy and USV state that the approval of a supplement to the new drug applications was granted in June 1976, in conjunction with the June 1976 labeling. Ciba-Geigy/USV Brief at 63. If one takes the manufacturers' date, it becomes even clearer that there is no evidence, not previously available, upon which it can be found that phenformin no longer shown to be safe. For example, due to a time lag in reporting some of the reports of lactic acidosis in 1975 and 1976 (CG-26) were unavailable in June 1976 but were available by January 1977.

B. Position of Participants

The Administrative Law Judge's preliminary summary of the position of the parties accurately reflects the evidence and arguments presented by them at the proceeding.

With respect to the position of CCD adopt the summary in the Initial Decision at 8-9, as modified by my response to the CCD exception, para. at 26-29, *supra*.

C. Basic Mechanisms of Phenformin Activity

In response to the position taken by Ciba-Geigy and USV, the Administrative Law Judge found that section 505(e)(2) does not require that the Bureau establish "a plausible biomedical

³The withdrawal provision for new animal drug was derived from and is nearly identical to the corresponding provision for new drugs. See *Agri-Tech, Inc. v. Richardson*, 482 F.2d 1148, 1150 (8th Cir. 1973).

explanation as to why such elevations [of blood lactate levels] occur" before phenformin may be shown not to be safe. Initial Decision at 9. The Administrative Law Judge reasoned that since establishment of clearly defined mechanisms of action is not required to prove the effectiveness of a drug, its absence does not preclude consideration of a lack of safety. Mechanisms of action have not been identified for certain drugs marketed subject to approved new drug applications. This, of course, is not a desirable situation but reflects certain limits, both technical and ethical, on the extent to which biomedical research may establish pharmacological modes of activity in human subjects. As a result of these constraints, there are many drugs where the precise mechanism of action is unknown.

I affirm the Administrative Law Judge's statement of the law.

I affirm with the Administrative Law Judge's finding that "there is substantial evidence relating to mechanisms of action of phenformin" and that although scientific research "is not totally definitive, it does provide a probable explanation for the occurrence of lactic acidosis" associated with phenformin. Initial Decision at 9, 12.

D. Safety Evidence

The Administrative Law Judge summarized the manufacturers' position as follows:

Ciba-Geigy claims that no scientifically valid conclusions concerning an association between phenformin and lactic acidosis can be drawn by simply aggregating cases of lactic acidosis during phenformin therapy, without reference to (a) existing label restrictions, (b) the background occurrence of lactic acidosis in the patient population in question, or (c) the various bias factors typically accompanying retrospective (or even prospective) searches for an adverse reaction. Initial Decision at 13.

The Administrative Law Judge gave careful consideration to the factors identified by Ciba-Geigy, although he disagreed with the company's proposed conclusion that the Bureau's evidence does not establish an association between phenformin and lactic acidosis. He found however, that the rate of occurrence of lactic acidosis associated with the use of phenformin "is not susceptible of quantification on this record." Initial Decision at 1, 47. The Administrative Law Judge recognized the shortcomings in gathering adverse reaction reports, and he gave greater weight to those reports that met the guidelines suggested by Ciba-Geigy. See Initial Decision at 14, 22-25.

The approval or withdrawal of a new drug application is made with reference to the conditions of use prescribed, recommended or suggested in the drug's labeling. However, section 505(e)(2) specifically provides that the evidence of a lack of safety must be "evaluated together with the evidence available . . . when the application was approved." Thus, experience with a drug prior to its current labeling is relevant to a withdrawal proceeding under this section of the Act. One of the issues established for resolution in this proceeding was:

(4) Whether the conditions of use prescribed, recommended, or suggested in the labeling of phenformin are adequate to exclude from treatment persons for whom the drug is contraindicated as a result of the presence of factors which predispose to lactic acidosis.

The Administrative Law Judge found that the January 1977 labeling, particularly the contraindications designed to prevent the use of phenformin by diabetics with conditions that predispose them to develop lactic acidosis, was inadequate because a reasonable expectation does not exist that the labeling could and would be followed. The Administrative Law Judge also found that lactic acidosis occurred even among those patients taking phenformin at the daily dose established in the January 1977 labeling and for whom predisposing or contraindicated conditions do not exist.

Upon review of the entire administrative record, I find that the Bureau met its burden of establishing that phenformin is no longer shown to be safe. Initial Decision at 15-22. I agree with the Administrative Law Judge that "there can be no doubt an association exists between phenformin and lactic acidosis" (Initial Decision at 22) and that the association exists even in cases of compliance with the January 1977 labeling (Initial Decision at 18, 22, 32-33).

The Ciba-Geigy data offered to establish the safety of phenformin consisted primarily of a review of cases of lactic acidosis associated with phenformin reported in the United States literature or directly reported to the manufacturer and the testimony of expert diabetologists "which shows that within the group of patients under their care, there is virtually no incidence of lactic acidosis associated with phenformin therapy." See Initial Decision at 22-29. See also CG-1-22, CG-25, CG-51, B-59.

The Ciba-Geigy study of adverse reactions (CG-26) was found by the Administrative Law Judge to "suffer

from several defects." For this reason, he concluded that the study "cannot qualify as a reasonable determination of the total number of phenformin-associated lactic acidosis cases occurring in the United States. A fair view of this study demonstrates it to be flawed to such an extent as to preclude its being afforded any significant evidentiary weight . . ." Initial Decision at 26. For the reasons stated by the Administrative Law Judge, as supplemented by my Findings of Fact, para. 27, I agree with this conclusion.

Ciba-Geigy submitted into evidence the testimony of diabetologists who have had "extraordinary success" (22) in administering phenformin without observing lactic acidosis. These witnesses have "never seen a case of phenformin-associated lactic acidosis in patients under their care." The Administrative Law Judge found that "considering the large number of patients treated by these diabetologists without any incidence of lactic acidosis, the rate of occurrence in this population is extremely small." *Id.* However, the Administrative Law Judge concluded (Initial Decision at 29):

Nevertheless, proof of the safety of phenformin when administered by specialists is insufficient to justify continued approval of phenformin because the majority of diabetics are treated by their primary physicians rather than specialists (Tr. 116-117). If phenformin is to enjoy continued marketing, it will be available to all physicians without regard to their expertise or experience. If doctors are unable to prescribe phenformin without endangering the lives of their patients, the low risk of danger of this drug when in the hands of an expert does not *a priori* justify its continued marketing. The FDA is, as stated by Ciba-Geigy and USV, powerless to limit approval of a drug only to administration by specialists. Therefore, if phenformin is unsafe when administered by generalists because its risk to the American public at large is greater than its benefit, its approval must be withdrawn.

The expert testimony submitted by Ciba-Geigy does not establish the safety of phenformin for general continued marketing under an NDA. See my response to CCD exceptions, paras. 5 and 6 at 16-20, *supra*. I adopt the Administrative Law Judge's finding as supplemented by my Findings of Fact, para. 30.

E. Detection of Predisposing Factors/Inability to Comply With Label Requirements

In considering the adequacy of the phenformin labeling, the Administrative Law Judge summarized the contention of the manufacturers and then stated his view of the proper test of compliance:

Ciba-Geigy and USV suggest that the adverse effects of phenformin therapy occur only when patients have some deficiency which predisposes them to lactic acidosis. They view these adverse effects as avoidable by testing the patient for these factors prior to administration of the drug (Ciba-Geigy-USV Brief at 55). To substantiate this argument, it must be shown that the preexisting condition would have been diagnosed at the time the drug was prescribed using methods that are likely to be part of the usual practice of medical community. Furthermore, it must be shown that any development of these predisposing factors after treatment would be identified and would result in the withdrawal of the medication before the onset of lactic acidosis. Initial Decision at 29.

I adopt this statement of the test of compliance with phenformin labeling. The Administrative Law Judge noted that there are differences of opinion among experts as to the methods adequate for identifying those persons who are predisposed to develop lactic acidosis and who, therefore, are contraindicated for its use under the January 1977 labeling. However, he found the evidence adduced by the Bureau of Drugs to be more persuasive. With respect to screening for impaired renal function, the Administrative Law Judge concluded that "compliance with the label requirements at the primary physician level or with the consistency in the practice of specialists is unlikely to prevent the occurrence of lactic acidosis." Initial Decision at 31. With respect to liver disease, another contraindication for phenformin therapy, he found that "time and cost considerations cause primary physicians to do a less than thorough workup for liver disease prior to prescribing phenformin * * *. Therefore, severe but chronic liver damage is likely to remain undetected." *Id.* I also find, on the basis of the record developed in this proceeding, that screening practices routinely performed on diabetic patients will not assure detection of patients for whom phenformin is contraindicated. See Initial Decision at 29-32.

The manufacturers asserted that phenformin's effects should be considered only with regard to those patients meeting the present label requirements. While acknowledging that section 305(e) measures safety in terms of conditions of use prescribed in a drug's labeling, not under actual conditions of use, the Administrative Law Judge also found substantial evidence of noncompliance with prior labeling restrictions. He reasoned:

The principal difficulty is that the general practitioners who care for the majority of adult-onset diabetics would be unable in their normal practice to discover the

existence of all predisposing factors of lactic acidosis and would therefore be unable to comply with the conditions of use prescribed, recommended, or suggested in the [current] labeling.

* * * Available tests are generally unable to rule out renal and hepatic insufficiency.*

* * * [The phenformin labeling cannot] reasonably be expected to result in the desired limitation of the population to which it will be administered.

Although the prescription of a drug outside of its package recommendation would not, *per se*, be considered as *prima facie* evidence as to its lack of safety for the purpose of withdrawal of approval of an NDA, the widespread use of a drug contrary to the label requirements should not be ignored. This is particularly true when the prescription practices outside of label requirements are widespread, predictable and substantiated by epidemiological trends in evidence.

* * * The majority of lactic acidosis cases associated with phenformin therapy reported to Ciba-Geigy were eliminated from consideration in the Ciba-Geigy study on the basis that the administration of the drug was not within the confines of the label requirements. It therefore appears that there are many cases of the American medical community not complying with the label requirements when prescribing phenformin. Initial Decision, 34-37.

The question of physician compliance with labeling restrictions has been of great concern to FDA and the entire medical community. See Initial Decision at 36-37. Additional doubts arise when labeling is new, prescribing patterns under it are not known, and previous label restrictions have not enjoyed a uniformly high degree of compliance. The manufacturers, however, bear the ultimate burden of proving safety under current labeling. The Administrative Law Judge found that the conditions of use prescribed in January 1977 labeling are "inadequate to preclude from treatment [with phenformin] those persons for whom the drug is contraindicated." Initial Decision at 1, 47.

There have been numerous changes in phenformin labeling in recent years. See B-506 and CG-25. The 1970 labeling contained a lactic acidosis warning and reference to related contraindications, including the major predisposing factors listed in the current labeling. Ex. E to CG-25. The 1974 and 1976 modifications were even more severe in warning of lactic acidosis and designating conditions predisposing to lactic acidosis. See Exs. P and N to CG-25. The 1970-1976 labeling has been

inadequate to prevent misprescription demonstrated by evidence of the phenformin in contraindicated patients. Much of the evidence of this contraindicated use comes from Ciba-Geigy's own data (CG-26). Due to time lag in reporting known cases of lactic acidosis and underreporting generally, this evidence applies primarily to practices under pre-1977 labeling.

However, the Administrative Law Judge concluded that the January 1977 labeling is, as a practical matter, susceptible to a high degree of compliance and cannot reasonably be expected to be closely followed by physicians" (Initial Decision at 37). Although experience with the new labeling has not been extensive. For physicians to be able to follow the January 1977 labeling, they would have to be able to identify those patients for whom phenformin is contraindicated. Most physicians who prescribe phenformin cannot do that. Due to inadequate screening, those persons most at risk cannot be identified. Due to the appearance of lactic acidosis among patients with no predisposing conditions, even properly screened patients are at risk. Consequently, current labeling has not been proven to be adequate. Therefore, I adopt the Administrative Law Judge's discussion (Initial Decision at 34-37).*

F. Risk/Benefit.

I adopt the Initial Decision (37-42). I find also that the evidence of the effectiveness of phenformin must be considered together with the inability of physicians to routinely demonstrate which portion of concomitant therapy is responsible for a perceived beneficial effect, and the infrequency of periodic testing to determine whether the effect is sustained for as long as it appears to be.

The benefit/risk assessment should include a ruling on the assertion by Ciba-Geigy and USV that phenformin is particularly useful for those diabetics with an excess of insulin and for whom additional insulin is therefore not an appropriate treatment. I find this claim to be unsupported on the record in this proceeding. See Findings of Fact, para 32.

*The Administrative Law Judge suggests that phenformin labeling is so "vague" (Initial Decision at 35) as to preclude a reasonable expectation of compliance. If he was taking exception to the phraseology used to describe the contraindications, I disagree, and do not adopt this particular finding. The Administrative Law Judge also suggested that prescription practices outside of phenformin labeling have been "predictable." *Id.* I agree to the extent that persons predisposed to lactic acidosis cannot be predicted under the current labeling.

*ents for Whom Benefit of
ormin Therapy May Outweigh*

purpose of this proceeding is to determine whether phenformin is shown safe for general marketing under conditions prescribed.

recommended, or suggested in its labeling. See my response to CCD exception, para. 1 at 7-10, *supra*. The presence of a more limited patient population for whom the benefits of phenformin therapy may outweigh the risks is not at issue. *Id.* The question of a voluntary, limited distribution program raised in the Secretary's suspension order is also not part of this proceeding.

For these reasons and in view of pending litigation concerning the propriety of the Secretary's invocation of the imminent hazard provisions, I do not adopt this section of the Initial Decision (at 42-44) but rather find as follows: The effect of withdrawal of phenformin on certain employment opportunities of diabetics does not preclude a decision that phenformin has no longer been shown to be safe. Limitations on occupational options because of health problems are not unique. Because phenformin is not currently labeled for use in only those patients who are allergic to insulin or unresponsive to desensitization, such use for that population is not an issue in this proceeding; and even a finding of safety for such use would not constitute a finding of general safety for use under phenformin's labeling and would not be sufficient to avoid withdrawal.

H. CCD Witnesses.

I adopt the Administrative Law Judge's summary of the CCD data submitted in this proceeding. See my response to CCD exception, para. 13 at 26-29, *supra*.

I. Discussion and Conclusions/Ultimate Findings and Order.

Having made reference to the administrative record throughout his opinion, the Administrative Law Judge summarized the evidence, without citation, and stated his conclusions and findings with respect to the issues designated at the August 30 prehearing conference. See Initial Decision at 45-48. I am issuing Findings of Fact, Conclusions of Law, and a Final Order. In most instances, these will supplement the discussion, conclusions, and findings of the Initial Decision. However, to the extent that my findings are inconsistent with those of the Administrative Law Judge, the Initial Decision is superseded. As modified by my Findings of Fact,

responses to CCD exceptions and comments on the Initial Decision, contained in this order, the Initial Decision is adopted and made a part of the final order.

IV. Findings of Fact and Conclusions of Law.

A. Findings of Fact.

1. Phenformin hydrochloride (phenformin) is a new drug within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(p), which has been shipped in interstate commerce pursuant to new drug applications filed by Geigy Pharmaceuticals, Division of Ciba-Geigy Corporation (NDA's 11-624 and 12-752), and USV Laboratories, Division of USV Pharmaceutical Corporation (NDA's 17-126 and 17-127) and approved by the United States Food and Drug Administration.

2. Phenformin is indicated only for symptomatic, adult onset, nonketotic diabetes mellitus (diabetes) (B-306(n)). According to its labeling, phenformin lowers elevated blood glucose levels in diabetics.

3. Phenformin is recommended for use only if diet and weight reduction have first been tried and have failed and only when insulin cannot be used and the sulfonylurea drugs do not achieve adequate control. *Id.*

4. Diabetes is a chronic metabolic disorder in which there is an inadequate secretion or utilization of insulin for normal metabolism (B-497 at 1, B-487 at 12-14, Tr. 92). Diabetes is characterized by an abnormal elevation in blood sugar, which has been used as a principal benchmark in its diagnosis and treatment (B-497 at 2, 8-9, Tr. 87-88, 294).

5. Diabetes is frequently accompanied by severe complications, most particularly cardiovascular and kidney diseases (Tr. 106-107, 295, B-497 at 9-10, CG-43 at 7). Diabetes is the fifth leading cause of death in the United States (CG-43 at 7).

6. There are approximately 5 million diagnosed diabetics in the United States today, most of whom are under treatment (CG-43). About 3 to 12% of these persons were taking phenformin during 1975-1976 (CG-43, CG-20 at 2, CG-11 at 2). The number of persons being treated with phenformin declined from 481,000 in 1974 to approximately 337,000 in 1977 (CG-43, CG-30).

7. The great majority (80-90%) of adult-onset diabetics are overweight (Tr. 406, CG-9 at 2, CG-11 at 2).

8. Dietary control is the most preferred and most effective means for

treating adult onset diabetes (B-506(n), B-469 at 3, B-473 at 5, B-499 at 19-20, B-495 at 7, CG-2 at 2, CG-11 at 3). Dietary regulation is the treatment of choice because, when a diabetic's caloric intake is decreased, there is less stress on the available insulin supply, insulin sensitivity is improved (Tr. 11, 94), and the ability to utilize naturally produced insulin is enhanced (B-495 at 10, B-487 at 14-15).

9. The use of exogenous (not produced naturally in the body) insulin is effective in the treatment of adult-onset diabetes by rectifying the insulin deficiency. (B-479 at 17, B-475 at 7). There is evidence that the administration of exogenous insulin also retards the vascular complications of diabetes (Tr. 24, 292-296, B-487 at 12).

10. Phenformin is effective in lowering blood sugar, but this effect is frequently limited to two years or less (Tr. 200-201, 296-297, 303-310, B-475 at 8-9, B-473 at 6, B-489 at 26, B-469 at 9, 13-14, 31). Moreover, the apparent effectiveness is difficult to measure and verify because phenformin is often used in combination with diet and/or sulfonylurea drugs (Tr. 167, 408, 426, 479-483, 523, B-499 at 4, CG-61, CG-20 at 2, CG-15 at 1-2).

11. Phenformin does not stimulate insulin production (B-306(n)). Phenformin does not promote the use of naturally produced insulin (B-495 at 10, Tr. 278-280). Phenformin does not aid or correct the metabolic abnormalities of diabetes (Tr. 295-297, B-497 at 4-5, B-487 at 12-14, B-499 at 20-21). Phenformin does not correct the complications of diabetes (Tr. 443-451, B-344 at 1060). Phenformin does not promote weight reduction (Tr. 450-451, B-509 at 4, 11, B-503 at 6-7, B-475 at 13, B-487 at 16-19, B-72 at 642, B-396 at 105, B-497 at 4).

12. There are essentially no adverse effects involved in the treatment of diabetes by diet and weight reduction. The adverse effects of insulin are far outweighed by its beneficial effects (Tr. 20-21, 198-199, 292-293, 410-411, B-177 at 1, B-475 at 7).

13. Some diabetologists experience difficulty in achieving patient compliance with diet and/or insulin therapies. These problems can be and usually are overcome by diabetologists (Tr. 20-21, 199-200, CG-2 at 2, B-465 at 2-3, 13, B-469 at 3-4, B-503 at 4, B-497 at 24-25).

14. Lactic acidosis is a disorder of intermediary metabolism, in which there is an abnormal accumulation of lactic acid in the blood and tissues (B-469 at 5, B-412 at 40, Tr. 261-262).

15. The fatality rate among persons who suffer from lactic acidosis is

approximately 50% (CG-26, Tables 4 and 5, B-94).

16. Diabetes does not itself cause lactic acidosis (Tr. 262-263, 270, B-499 at 6-10, 17-20, B-475 at 15-17, B-184, B-412 at 50, B-467 at 7-10).

17. A biochemical basis supports the relationship between phenformin and the under utilization and over production of lactate, and the evidence of the modes of phenformin activity provides a probable explanation for this relationship (Tr. 266, 269-277, 461-462, 633-636, B-274, B-88 at 186, B-501 at 2-6, CG-24 at 12, 23, B-487 at 10-11, 16-19, B-497 at 18-23, B-499 at 10-15). The relationship is also supported by the frequently short time between the ingestion of phenformin and the onset of lactic acidosis (B-63 at 44, B-479 at 12-14, B-272 at 70-72, B-467 at 10-11, B-412 at 180).

18. There is a disproportionate incidence of lactic acidosis among diabetics taking phenformin (Tr. 47, 276, B-465 at 11-12, B-473 at 6-9, B-475 at 11-12, 15-17, B-499 at 5-10, 17-18, B-467 at 7-10, B-503 at 10, B-509 at 3, B-479 at 6-10, B-485 at 10, B-64, B-471 at 2, 7-9, CG-20 at 4).

19. Reports in the published medical literature and in retrospective studies constitutes substantial and convincing evidence of the association between lactic acidosis and phenformin, when used alone or in combination with the sulfonylurea drugs (B-64, B-65, B-471, B-290, B-94, B-493 at 3-10, B-92, B-93, B-235, B-236, B-338, B-390, B-33, B-42, B-15, B-96, B-272, B-473 at 6-9, B-475 at 15-18, B-467 at 8-13, B-479 at 3-11, Tr. 634).

20. The association between phenformin and lactic acidosis appears to be dose-related (B-509 at 2-4, B-59, CG-26, Tables 6 and 7, B-481 at 29-30, B-495 at 5, B-64, B-471 at 12-17, B-479 at 11-13, B-63). The association is also supported by evidence involving suicide attempts by use of phenformin (B-479 at 11-14, B-63 at 43-44).

21. An association between phenformin and lactic acidosis need not be based upon quantification of the background incidence of lactic acidosis among the population at large or among the diabetic population not taking phenformin. The background occurrence or incidence is unknown for the vast majority of nonreportable diseases (Tr. 218-219, 363-366, 493-494).

22. A precautionary warning about the possible association between lactic acidosis and phenformin was added by USV to the phenformin labeling in 1964 (CG-25 at 1-2, B-506(e)). A strengthened lactic acidosis warning and statement of contraindications, designed to screen

diabetic patients predisposed to lactic acidosis, were added to the labeling in 1970 (CG-25 at 3). In 1974, the lactic acidosis warning was strengthened and a more detailed description of medical conditions predisposing patients to lactic acidosis was included (CG-25 at 7, B-506(k)). A black box warning concerning lactic acidosis was included in phenformin labeling approved June 1976 (CG-25 at 7-8, B-506(m)).

23. The 1970-1976 labeling did not result in limiting the use of phenformin to those patients for whom it was not contraindicated (CG-26, CG-25 at paras. 24, 25, 28 and Exs. 2 and AA, CCD-5, CG-31, CG-63 at 19-20, CG-20 at 2-4, Tr. 348, 357, 383, compare Tr. 355-360 with B-24 at 102 and B-23 at 339, CG-49 at 3).

24. The current (January 1977) labeling for phenformin (B-506(n), Ex. V to CG-25) is designed to restrict its use to only those patients with none of the lactic acidosis predisposing risk factors.

25. The current labeling cannot reasonably be expected to result in the detection of those persons for whom phenformin is contraindicated:

a. With respect to screening for predisposing renal dysfunction, the recommended tests are inadequate and are frequently not performed by general practitioners (B-503 at 12-13, B-495 at 4, B-497 at 4-5, B-487 at 20-22, B-483 at 7-10, B-467 at 11-13, B-489 at 11-14, Tr. 112-116, 592-594).

b. With respect to screening for predisposing liver disease, routine workup is inadequate (Tr. 29-32, 112-121). Thus, compliance with the labeling requirements by general practitioners is unlikely to prevent the occurrence of lactic acidosis (B-471 at 29-30, B-467 at 8-11, 17-18).

26. Lactic acidosis is associated with the use of phenformin even in compliance with the January 1977 labeling, that is, at or below 100 mgs. daily dose and without predisposing risk factors (CG-26, Table 6, B-59 at 4-8, 14-15, and Table 3, B-481 at 29-30, B-495 at 4, B-412 at 180-185, B-272 at 70-72, B-96 at 974-975, B-471 at 2-7, 13-14, 20-31, B-467 at 4-13, 18-19, B-236, B-94, B-493 at 4-13, B-64, Tr. 359-360).

27. The Ciba-Geigy study of the cases of confirmed lactic acidosis associated with phenformin (CG-26) is deficient, and the incidence of lactic acidosis suggested by the data in that study is unreliably low.

a. The study included only those reports in the United States medical literature, whereas several of the retrospective studies are reported in the foreign medical literature (e.g., B-63, B-275, B-276, B-412). Moreover,

occurrences of lactic acidosis are likely to be underreported due to a loss of interest in the medical community or a significant number of such reports have been published (B-475 at 12).

b. Physicians are under no legal obligation to report adverse reaction drug firms. Voluntary reporting, upon which the study is based, significantly understates the true number of adverse reactions (B-479 at 11, B-481 at 8-11, CG-1 at 6, Tr. 43, 336-339, 342-345, 4505). In measuring adverse reactions retrospective and prospective patient record reviews, while not ideal, are entitled to greater weight than voluntary reporting to manufacturers (B-481 at 14, Tr. 342-345; compare B-479 at 2- with Tr. 564-566).

c. The study excluded those cases where there were data indicating impaired renal function. Although impaired renal function is a predisposing factor, those responsible for the study did not determine whether the impaired renal function preexist use of phenformin or appeared as a consequence of the phenformin-associated lactic acidosis. Thus, exclusion of these data was unjustified (Tr. 552, 568, 592-594, CG-26 at 5-6, 475 at 14-15, B-483 at 10-12, B-467 at 13, B-493 at 4-8, B-471 at 21-32).

d. The study excluded cases where the data were inadequate to determine the presence of predisposing factors; attempt to obtain such information documented in the record (CG-26 at 5).

e. The criteria used in the study to determine the presence of lactic acidosis were more conservative than those used by most investigators (CG-49 at 3, B-471 at 1-5).

28. The reported decrease in the incidence of phenformin-associated lactic acidosis during 1974-1977 was discounted due to underreporting, a corresponding decrease in the number of diabetics taking phenformin from 481,000 in 1974 to 337,000 in 1977, and reporting lag time of approximately months (printout attached to CG-26 Ciba-Geigy/USV Proposed Finding Fact, para. 22b; Tr. 623-625).

29. Most diabetics in this country are treated for diabetes by a physician, not treated by a diabetologist (B-471 at 10, B-471 at 23, B-499 at 18-20, Tr. 116-117).

30. The evidence strongly suggests that the incidence of lactic acidosis is greater among patients of general practitioners than among patients of diabetologists (B-477 at 5, B-493 at CG-2 at 4, CG-12 at 9, CG-14 at 2, 10 at 3, B-471 at 23, B-499 at 18-20, 116-119, 347-348, 383, 425-430, 516-

31. The testimony of diabetologists about the absence of lactic acidosis among their patients is evidence that the great majority of phenformin-associated lactic acidosis occurs among patients of those physicians with the least special training in screening and testing patients for use of phenformin and in recognizing the consequent lactic acidosis. *Id.* In addition, a significant number of cases of lactic acidosis could exist among the patients treated by diabetologists and general practitioners in the course of their individual practice and be undetected due to their relative infrequency. See Tr. 298-300; *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973).

32. Phenformin has not been shown to be uniquely useful in treating the obese adult-onset diabetic who is "hyperinsulinemic" (B-497 at 5-13 and 25-26, B-309 at 10-11, B-362 at 363-367, B-475 at 18-19, B-503 at 3-4, and B-495 at 9-10, B-469 at 11-13).

33. The removal of phenformin from the market will not seriously disrupt treatment of diabetic patients (CG-10 at 4, B-309 at 3-4, B-467 at 19, B-465 at 4-5, 9-10, B-469 at 8-9, B-479 at 17-19, B-495 at 6-7, B-503 at 7, 14, B-499 at 18-20, B-471 at 22-23, 32, Tr. 298-300).

B. Conclusions of Law.

1. The Bureau of Drugs has sustained its burden of showing, based on new evidence of clinical experience, evaluated together with the data available when the NDA's for phenformin were approved, that phenformin is not shown to be safe for use under the conditions approved in its new drug applications.

2. The Bureau of Drugs has established an association between lactic acidosis and phenformin. Although this relationship has not been conclusively shown to be causal, there is a substantially disproportionate incidence of lactic acidosis among diabetics treated with phenformin.

3. Lactic acidosis is associated with phenformin at dosage levels at or below those prescribed in the January 1977 labeling. Lactic acidosis is associated with phenformin absent the "predisposing factors" for which phenformin is contraindicated.

4. It has not been shown that the current labeling contraindications will reduce the incidence of phenformin-associated lactic acidosis so as to render phenformin safe for use.

5. The risks of the use of phenformin outweigh its benefits.

V. Final Order

Therefore, on the basis of the foregoing Findings of Fact and Conclusions of Law, the Initial Decision of the Administrative Law Judge, as modified by this order, and the record of the proceedings, and under the Federal Food, Drug, and Cosmetic Act (sec. 505(e)(2), 52 Stat. 1052 as amended (21 U.S.C. 355(e)(2))) and the authority delegated to the Commissioner (21 CFR 5.1), the new drug applications for phenformin, and all the amendments and supplements thereto, are hereby withdrawn, effective November 15, 1978. The introduction or delivery for introduction into interstate commerce of phenformin, except pursuant to an exemption granted under section 505(i) of the act, is prohibited. 21 U.S.C. 331(d).

Dated: November 15, 1978.

Donald Kennedy,
Commissioner of Food and Drugs.

[Docket No. 77N-0150]

[FR Doc. 79-10593 Filed 4-5-79; 3:45 am]

BILLING CODE 4110-03-M

Phenformin Hydrochloride; Proposal to Withdraw Approval of New Drug Applications; Initial Decision

AGENCY: Food and Drug Administration.
ACTION: Notice.

SUMMARY: The agency is issuing the Administrative Law Judge's Initial Decision on the proposal to withdraw approval of new drug applications for phenformin hydrochloride.

ADDRESS: The Initial Decision may be seen in the office of the Hearing Clerk (HFA-305), Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Richard A. Anderson, Office of the Associate Commissioner for Health Affairs (HYF-21), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1170.

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the Federal Register, the agency is publishing the Commissioner's final decision on withdrawal of approval of new drug applications for phenformin hydrochloride and his denial of a petition for reconsideration. The Administrative Law Judge's Initial Decision on phenformin hydrochloride is set forth below:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE Food and Drug Administration Initial Decision¹

[Docket No. 77N-0150]

Proposal to Withdraw Approval of the New Drug Applications for Phenformin Hydrochloride

1. Phenformin found to have limited short-term beneficial effects in the treatment of diabetics under the conditions of use prescribed, recommended or suggested in its labeling.

2. The conditions of use prescribed, recommended or suggested in the labeling for phenformin found inadequate to exclude from treatment those persons for whom the drug is contraindicated as a result of factors which predispose patients to lactic acidosis.

3. The occurrence of lactic acidosis found associated with the use of phenformin in patients for whom the drug is indicated under its current labeling and the incidence of such occurrences as compared to the diabetic population at large is not susceptible of quantification on this record.

4. Therapeutic modalities other than phenformin found shown to be effective for treating patients for whom phenformin is indicated in its labeling without the same degree of risk associated with the use of phenformin.

5. The limited benefits of phenformin found insufficient to support a finding of safety in light of the risks attending its general marketing under the approved NDA's. Approval of the NDA's for phenformin ordered withdrawn pursuant to § 505(e) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e).

William Bickerstaff, George Doherty, Richard Morey, Richard Nolan, Richard Serbin, Alfred Schretter, Nicholas Weiskopf for the manufacturing parties.

Neil Chayer, Michael Morrell, Anthony Roccogranti, and Daniel Shaw for the Committee for the Care of the Diabetic.

Arnold Friede, Frederick Degnan, for the Bureau of Drugs, Food and Drug Administration.

By DANIEL J. DAVIDSON, Administrative Law Judge

By notice published in the Federal Register of August 12, 1977 (42 FR 40959), this matter was assigned for formal evidentiary public hearing by

¹Pursuant to § 12.125(a) (21 CFR 12.125(a)), exceptions to this initial decision must be received by the Hearing Clerk not more than 30 days after the date hereof. Replies to exceptions must be received by the Hearing Clerk not more than 20 days thereafter.