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DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 7358; Docket No. FDC-D-520; NDA's
5-795 et al.]

NITROFURAN DRUGS

**Withdrawal of Approval of Certain New
Drug Applications or Pertinent Parts
Thereof**

A notice was published in the FEDERAL REGISTER of March 29, 1973, (38 FR 8186) in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the following new drug applications:

1. NDA 7-358, Furacin Nasal Drops containing nitrofurazone with ephedrine;
2. NDA 12-403, Furacin Otic Drops containing nitrofurazone and nifuroxime with dipiperodon hydrochloride; and
3. That part of NDA 5-795 pertaining to Furacin Ear Solution containing nitrofurazone; all formerly marketed by Norwich Pharmacal Co., Division of Morton-Norwich Products, Inc., 13-27 Eaton Avenue, Norwich, NY 13815.

Other drugs included in the above notice are not affected by this notice and will be handled in separate FEDERAL REGISTER notices.

The bases of the proposed action were that there is a lack of substantial evidence of effectiveness and that the products are not shown to be safe.

On April 30, 1973, in response to the notice, Norwich filed separate requests for a hearing for each of the above new drug applications. On September 5, 1974 and October 4, 1974 Norwich withdraw the requests for hearing for the above products and stated that marketing of these products has been discontinued.

No other person filed a written appearance of election as provided by said notice. The failure to file such an appearance constitutes an election by such persons not to avail themselves of an opportunity for hearing.

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug applications reviewed and are subject to this notice (21 CFR 310.8). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug

Administration, Bureau of Drugs, Office of Compliance (HFD-300), 3600 Fishers Lane, Rockville, MD 20852.

The Director of the Bureau of Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1053, as amended; 21 U.S.C. 355), and under authority delegated to him (21 CFR 2.121), finds that (1) on the basis of new information before him with respect to the drug products, evaluated together with the evidence available to him when the applications were approved, there is a lack of substantial evidence that the drug products will have the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling; and (2) tests by methods not deemed reasonably applicable when such applications were approved, evaluated together with the evidence available when the applications were approved, show that the drugs are not shown to be safe for use under the conditions of use upon the basis of which the applications were approved.

Therefore, pursuant to the foregoing findings, approval of new drug application Nos. 7-358 and 12-403 and approval of those parts of new drug application No. 5-795 pertaining to Furacin Ear Solution and all amendments and supplements applying thereto is withdrawn effective on December 16, 1974.

Shipment in interstate commerce of the above-listed drug products or of any identical, related, or similar product, not the subject of an approved new drug application, will then be unlawful.

Dated: November 25, 1974.

J. RICHARD CROUT,
Director,
Bureau of Drugs.

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FEDERAL REGISTER, VOL. 39, NO. 234—WEDNESDAY, DECEMBER 4, 1974

Page 42018

tion (NDA 5-795) which provides for Furacin Vaginal Suppositories, effective June 9, 1975.

A notice was published in the FEDERAL REGISTER of March 29, 1973 (38 FR 8186), in which the Food and Drug Administration announced an opportunity for hearing on a proposal to withdraw approval of new drug applications or pertinent parts thereof, of the following nitrofurazone drugs: Furacin Nasal Drops (NDA 7-358), Furacin Otic Drops (NDA 12-403), Furacin Vaginal Suppositories (NDA 5-795), Furacin Ear Solution (NDA 5-795), Tricofuron Vaginal Powder and Suppositories (NDA 11-065), Furoxone Tablets (NDA 11-270), and Furoxone Liquid (NDA 11-323), all new drug applications held by Norwich Pharmacal Co., Division of Morton-Norwich Products, Inc., 13-27 Eaton Ave., Norwich, NY 13815 (hereafter Norwich).

The announcement stated that, with the exception of Furacin Ear Solution, Nasal Drops and Otic Drops, the National Academy of Sciences-National Research Council (NAS/NRC), Drug Efficacy Study Group, had reviewed the drug products listed above and classified them as less than effective. The announcement further stated that the Commissioner proposed to initiate action to withdraw approval of these new drug applications on the grounds that (1) new information with respect to the drugs, evaluated together with the evidence available at the time of approval of the applications, shows that there is a lack of substantial evidence that the drugs will have all the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling, and (2) tests by methods not deemed reasonably applicable when such applications were approved, evaluated together with the evidence available when the applications were approved, show that drugs for human use containing nitrofurazone or furazolidone are not shown to be safe for use under the conditions of use upon the basis of which the applications were approved. The Food and Drug Administration also concluded that there was a lack of proof of safety on the grounds, inter alia, that the oral administration of nitrofurazone and furazolidone had been shown to induce mammary neoplasia in rats.

Prior to initiating such action, the Commissioner invited holder(s) of the new drug applications and any other interested persons, including those marketing identical, related, or similar drugs, to submit, by April 30, 1973, a written notice electing whether or not to avail himself of the opportunity for a hearing. Applicants or other persons requesting a hearing were advised to include a well-organized and full factual analysis of the clinical and other investigational data they were prepared to prove in support of the opposition to the proposed withdrawals.

On April 30, 1973 in response to the notice, Norwich filed separate requests for a hearing for each of the six nitro-

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ON APRIL 1, 1975. ETC.

FURACIN VAGINAL SUPPOSITORIES

Denial of Hearing and Withdrawal of
New Drug Application

The Commissioner of Food and Drugs
denies hearing and withdraws approval
for that part of the new drug applica-

four new drug applications listed above. Each request raised a single legal objection, denied the factual findings of the Commissioner, and stated that further supplemental submissions in support of the requests for hearing would be made.

On June 6, 1973, Norwich submitted medical data and proposed revised labeling for Furoxone Tablets and reformulated Furoxone Liquid (NDA 11-270 and NDA 11-323). The original labeling reviewed by the NAS/NRC, Drug Efficacy Study Group, recommended Furoxone for the treatment of bacterial or protozoal diarrhea and enteritis. The proposed revised labeling would limit use of Furoxone solely for typhoid fever, cholera, and *Giardis lamblia*. Since the new labeling is more restrictive than that reviewed by the NAS/NRC, Drug Efficacy Study Group, and since the only data submitted were in support of the safety and efficacy of the revised claims, the request for a hearing on Furoxone Tablets will be the subject of a separate FEDERAL REGISTER notice when review of the data has been completed; a notice covering Furoxone Liquid (old formulations) is published elsewhere in this issue of the FEDERAL REGISTER.¹

On June 21 and November 16, 1973, in an attempt to support the safety and efficacy of Furacin Vaginal Suppositories (NDA 5-795) and Tricofuron Vaginal Powder and Suppositories (NDA 11-065), Norwich submitted additional safety data, marketing data, testimonial letters and affidavits, clinical efficacy studies, and numerous references to the medical literature. In its June 21, 1973 submission, Norwich proposed to relabel Furacin Vaginal Suppositories and requested approval to reformulate and relabel Tricofuron Vaginal Powder and Suppositories. The proposed reformulation of Tricofuron would replace the nifuroxime with nystatin; the proposed relabeling of Tricofuron would restrict the recommended use to treatment of specific mixed infections of the vagina shown to be resistant to other agents. Subsequently, on December 20, 1973, Norwich notified the Food and Drug Administration that the lists of references attached to the affidavits submitted on November 16, 1973, were incorrect. To correct the errors, Norwich submitted new lists of medical references together with copies of the articles referred to therein.

The Tricofuron Vaginal Suppositories and Powder, as presently labeled and formulated, are covered in a separate notice elsewhere in this issue of the FEDERAL REGISTER.² The Director of the Bureau of Drugs will notify Norwich when he decides whether or not to approve the reformulated and relabeled tricofuron products.

On September 5, 1974 and October 4, 1974, Norwich withdrew its requests for a hearing for Furacin Otic Drops (NDA 12-403), Furacin Nasal Drops (NDA 7-358) and Furacin Ear Solution (NDA 5-795). These drugs are the subject of a separate FEDERAL REGISTER notice.

¹ See FR Doc. 14071 *supra*.

² See FR Doc. --

The Commissioner has considered all of the material submitted by Norwich in support of its request for a hearing on the proposed withdrawal of the new drug application for that part of NDA 5-795 covering Furacin Vaginal Suppositories and concludes that there is no genuine issue of material fact requiring a hearing and that the legal objections offered are insubstantial; a full discussion follows:

I. THE DRUG

Furacin Vaginal Suppositories contain 0.3 percent nitrofurazone in a water-miscible base composed of glyceryl monolaurate and polyoxyethylene (4) sorbitan monostearate.

II. RECOMMENDED USES

Furacin Vaginal Suppositories labeling reviewed by the NAS/NRC, Drug Efficacy Study Group, recommends this drug for treatment of bacterial vaginitis and cervicitis and resulting leukorrhea and malodor, prevention of infection before and after cervicovaginal surgery and electrosurgery and before and after radiation therapy of pelvic neoplasms. The proposed labeling included with the June 21, 1973 submission recommends the product for treatment of bacterial vaginitis (due to *Haemophilus vaginalis* and other organisms shown to be unresponsive to different agents) and for use before and following radiation therapy to prevent or treat malodor and discharge caused by bacterial growth in necrotic debris.

III. THE DATA SUBMITTED TO SUPPORT CLAIMS OF EFFECTIVENESS OF FURACIN VAGINAL SUPPOSITORIES

A. *Medical Literature References Submission.* 1. Keith, Louis, Bash, I. M., Dravineks, A., and Krotosyonski, B. K., "Changes of Vaginal Odors of 6 Patients Under Nitrofurazone Treatment," *Journal of Reproductive Medicine*, 4(4): pp. 69-76, April 1970. In this study, six patients with disorders of the genital urinary tract or the vagina and uterus were treated with Furacin Vaginal Suppositories. Two of the six patients were designated as "treatment controls" and were diagnosed as having hematuria, cause unknown, and stress incontinence, respectively. Neither was reported to have malodor. Of the remaining four patients, one was diagnosed as having bacterial vaginitis, and three as having postpartum endometritis. All four were reported to have malodor. A seventh patient, with a urinary tract infection, was designated as a "normal control."

Vaginal vapors were collected before treatment and were compared by using gas chromatographic and odor dilution techniques with vapors collected after treatment. The before and after intervals varied from 4 hours to 24 hours among the various patients.

The study is not an adequate and well-controlled investigation of Furacin Vaginal Suppositories for the labeled indications for the following reasons:

The study subjects included only one with a condition for which the product is, or is proposed to be indicated (bacterial vaginitis with accompanying malodor).

That subject was treated with the drug. It is impossible to have a well-controlled study of a product for its labeled indications when only one subject with such an indication is studied; with, as here, a subject who has the special indication and is not treated with the test drug, it is impossible to determine whether any effect observed in the subject was due to the test drug or other factors, such as the natural history of the condition being treated. Accordingly, the study does not purport to provide for comparison of the results of treatment of the drug for its labeled indications with the results in an appropriate control group, as required by CFR 314.111(a)(5)(ii)(a)(4).

Three out of four of the test subjects with malodor did not have malodor associated with a condition for which the test drug is labeled (they had malodor associated with endometritis, which is mentioned among the drug's indications). No meaningful comparison can be made between results in the treatment group (here, the four subjects with malodor) with the results in an appropriate control (here, the two "treatment controls" and the one "normal control" as required by 21 CFR 314.111(a)(5)(a)(4), because, first, none of the patients designated as "controls" was reported to have malodor, and second, two patients designated as "treatment controls" were themselves treated with the very drug being tested. Effectiveness of a drug for a given condition cannot be demonstrated by observing what happens when the drug is given to patients who lack that condition in the first instance. And effectiveness of a drug for a given condition cannot be demonstrated by administering the drug to two groups of patients, a procedure which results in two uncontrolled tests, not a controlled study.

Since the method of selecting subjects did not, on its face, attempt to identify patients with conditions for which Furacin Vaginal Suppositories are intended to treat (only one of six had a condition), the study also lacks the method of selection of subjects which provides any assurance that they are suitable for the purpose of a study aimed at providing evidence of the effectiveness of the drug for its intended uses, as required by 21 CFR 314.111(a)(5)(ii)(2)(i). Further, since subjects were knowingly assigned to groups in such a way that one group contained all patients with malodor and another contained patients lacking malodor, the study, on its face, failed to assure that the groups were comparable with respect to a critical variable, i.e., the condition for which the drug is intended to be treated, as required by 21 CFR 314.111(a)(5)(a)(2)(iii).

With respect to the test results concerning reduction of malodor, results from the one test subject having malodor associated with a condition specified in the drug's labeling (bacterial vaginitis) more than an isolated case report, is unacceptable as the sole basis for the approval of claims of effectiveness (21 CFR 314.111(a)(5)(ii)(c)). Results in

three patients with postpartum endometritis are not pertinent to effectiveness of Furacin Vaginal Suppositories for its labeled indications (current or proposed), which do not include malodor associated with that condition.

The methods used to quantitate "improvement" in malodor are questionable. "Improvement" noted in the two treatment controls was 2 to 20 times greater than that observed in the four subjects with malodor. Since the treatment controls did not have malodor to begin with, it is apparent that the meanings of "improvement," "malodor," or both, employed in the study have no necessary correspondence to the meanings those words have in the clinical context of treating malodor associated with the pathological conditions specified in the labeling for Furacin Vaginal Suppositories. The authors' observations and conclusions respecting "improvement" in any of the conditions involved in the study, thus, do not constitute "quantitative evaluation" within the meaning of 21 CFR 314.111(a) (5)(ii) (a) (4).

2. Gardner, H. L., and Dukes, C. D., "Haemophilus Vaginalis Vaginitis, A Newly Defined Specific Infection Previously Classified, Nonspecific Vaginitis," *American Journal of Obstetrics & Gynecology* Vol. 69:962-976, 1955. This was a study to classify and describe a previously unclassified type of bacterial vaginitis. While the authors mention in passing that the organism under study may be sensitive to certain antibiotics, no effort was made to evaluate the effectiveness of any antibiotic, or of Furacin or any other drug containing nitrofurazone. Hence, the study is not an adequate and well-controlled clinical investigation of the effectiveness of Furacin within the meaning of section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d)) and 21 CFR 314.111(a) (5) (ii).

3. Edmunds, P. N., "Haemophilus Vaginalis, Its Association with Puerperal Pyrexia and Leucorrhoea," *Journal of Obstetrics and Gynaecology British Empire*, 66:917-926, 1959. This study was to describe the diagnosis and incidence of the *H. vaginalis* bacterium in various clinical groups and its relation to other vaginal flora. Like the previous study, the author notes that the organism is sensitive to antibiotics, but no effort was made to evaluate the effectiveness of Furacin Vaginal Suppositories or any other product containing nitrofurazone. Hence, the study is not an adequate and well-controlled clinical investigation of the effectiveness of Furacin within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a) (5) (ii).

4. Gardner, H. L., and Kaufman, R. H., "Benign Diseases of the Vulva and Vagina," C. V. Mosby Co., 1969. The authors treat Furacin only peripherally and the portions of the text relating to Furacin do not purport to describe an adequate and well-controlled clinical investigation of furacin within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a) (5) (ii), since they do no more than state, in three sentences,

that Furacin gives results comparable to the sulfonamides. Absent any details which permit scientific evaluation, it is no more than a testimonial, which is unacceptable as the sole basis for the approval of claims of effectiveness (21 CFR 314.111(a) (5) (ii) (c)).

5. Moore, Richard M., "An Evaluation of Various Methods of Vaginal Asepsis," *American Journal of Obstetrics and Gynecology* 64(2), August 1952. This study was to evaluate the comparative effectiveness of a representative agent of each major family of antibacterials then currently used in the vaginal preparation of the patient for gynecologic surgery. In this study, 325 unselected gynecologic patients were divided into seven groups (six groups of 50, including one "no vaginal medication" group, and one group of 25 who received Furacin Vaginal Suppositories). Vaginal cultures were taken from all patients upon admission for gynecologic surgery before any type of medication was given. All vaginal preparations were administered in the afternoon before surgery and at 5 a.m. on the day of surgery. Patients receiving suppositories were given only one as indicated. Preoperative cultures were obtained just before the patient was sent to the operating room. Postoperative cultures were taken on the fourth day on most, but not all, of the patients.

The results of preoperative preparation were compared with results upon admission in terms of (1) negative cultures, (2) less than admission cultures, and (3) greater than admission cultures. This comparison was made with all groups, including that receiving Furacin Vaginal Suppositories.

The results of postoperative treatment were compared in a similar manner, but were restricted to three groups. The first of these were patients who had received no postoperative medication. The second group included patients who had received penicillin and streptomycin suppositories or penicillin suppositories prior to surgery but who had received no medication postoperatively. The third group included patients who had received postoperative medication of penicillin and streptomycin or penicillin suppositories. There is no group identified in the postoperative culture summary information as having received Furacin Vaginal Suppositories.

The author draws no conclusions regarding the effectiveness of Furacin Vaginal Suppositories in the preoperative vaginal preparation of gynecological patients. The author's conclusions are limited to the penicillin and streptomycin vaginal suppositories and to the penicillin vaginal suppositories, which he claims to be the most effective antibacterial agents used in the study in the preoperative preparation of gynecological patients. With respect to Furacin, the reported results indicate that Furacin is no more effective than a placebo. Thus, of the 50 patients who received "no vaginal medication" prior to surgery, 24 percent were classified by the author as having "less than admission cultures." The response among the 25 patients who received Furacin Vaginal

Suppositories prior to surgery was identical, i.e., 24 percent were classified as having "less than admission cultures." Similarly, these two groups showed almost identical results for the percentages of patients classified by the author as having "greater than admission cultures" (48 and 44 percent, respectively).

With respect to postoperative results of the agents tested, the author concluded that the penicillin and streptomycin vaginal suppositories and penicillin vaginal suppositories, administered postoperatively, maintained a relatively sterile field to promote postoperative healing. There is, as mentioned, no indication in the study report that postoperative cultures were obtained and analyzed from the Furacin subjects, and the author makes no conclusion concerning the results of Furacin in the postoperative context.

The author did note that no patient in the Furacin group had a morbid postoperative course in the study. The author states, however, that the size of each of the groups considered was too small for postoperative morbidity to be of any comparative significance. He further states that it was evident that basic surgical technique is of primary importance in the incidence of postoperative morbidity.

The study, therefore, provides no evidence of the effectiveness of Furacin Vaginal Suppositories for the prevention of infection either before or after surgery, or for any other indication.

Further, the study is not adequate and well-controlled within the meaning of 21 CFR 314.111(a) (5) (ii) for the following reasons:

There was no explanation of how the patients were assigned to the test group to assure the comparability in test and control groups of pertinent variables (21 CFR 314.111(a) (5) (ii) (a) (2) (iii)). A signment of patients in a study like this must, in addition to considering the agents being studied, also assure that the surgery employed on each group representative of the surgical procedure which were involved. The author identifies the surgical procedures only as "major cases" and "minor cases." There is thus no assurance of the comparability of test and control groups of pertinent variables, that is, the surgical procedure to which the patients were subjected.

The study does not purport to provide a comparison of the results of postoperative treatment with Furacin with the control or "no vaginal medication" groups in such a fashion as to permit quantitative evaluation (21 CFR 314.111(a) (5) (ii) (a) (4)). There is no record of any postoperative cultures taken from women who had received Furacin Vaginal Suppositories.

Only postoperative morbidity of the Furacin-treated patients was discussed and then only in terms of its incidence in the seven groups (i.e., no scientific comparison is made, and no conclusions are drawn based on the incidences of morbidity). The criteria for defining morbidity and the method or methods of determining morbidity are not explained.

by the author (21 CFR 314.111(a)(5)(ii)(a)(3)). The results with respect to morbidity are thus inconclusive (as stated by the author) and, in any case, Furacin is not indicated for prevention or treatment of that condition.

6. Lang, Warren R., "Experiences in a Vaginitis Clinic," *Journal of the American Medical Association* 174(14):122-125, December 1960 and Lang, Warren, Fritz, Mary Ann, and Menduke, Hyman, "The Bacteriologic Diagnosis of Trichomonal Candidal, and Combined Infections," *Obstetrics and Gynecology* 20(6), December 1962. In the first paper, Dr. Lang summarizes his experiences with vaginitis over a 13-year period; there is no indication that he conducted an adequate and well-controlled clinical investigation, nor does he represent his views to be the product of such an investigation. Although he states, in one sentence, that bacterial vaginitis responds well to Furacin, among other drugs, he presents no data or details to support that conclusion. The reference does not purport to be an adequate and well-controlled clinical investigation of the effectiveness of Furacin within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a)(5)(ii); it is, rather, a testimonial and is unacceptable as the sole basis for a claim of effectiveness (21 CFR 314.111(a)(5)(ii)(c)). The second paper, an extension of the first, is concerned exclusively with the diagnosis and grading of vaginal bacteria and in no way attempts to assess the effectiveness of any drug product. Furacin is nowhere mentioned. It is thus not an adequate and well-controlled clinical investigation of the effectiveness of Furacin within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a)(5)(ii).

7. Capraro, Vincent J., "Pediatric Vulvovaginitis," *Journal Newark City Hospital* 2:15-25, 1965. This paper presents a very general discussion of various aspects of pediatric gynecology, including how to conduct gynecological examinations (without traumatizing younger patients), etiology, experience of the author, and, finally, treatment. Only one sentence in the paper refers to Furacin. It summarily states that Furacin may be used with satisfactory results in some cases of mixed bacterial vulvovaginitis. No data and no report of a controlled study are offered to support the claim. The report does not purport to be an adequate and well-controlled clinical investigation of the effectiveness of Furacin within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a)(5)(ii), but is, rather, a testimonial, and is unacceptable as the sole basis for a claim of effectiveness (21 CFR 314.111(a)(5)(ii)(c)).

8. Robins, Spottswood, "Office Gynecology in Private Practice," *Virginia Medical Monthly* 89:637-641, November 1962. This is another general discussion of office procedure to be followed by practicing gynecologists. Although the author states that Furacin is indicated following electrocauterization, he offers no data or details either to support his

conclusion or to permit scientific evaluation. The report does not purport to be an adequate and well-controlled clinical investigation of the effectiveness of Furacin within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a)(5)(ii); it is, rather, a testimonial and is unacceptable as the sole basis for a claim of effectiveness (21 CFR 314.111(a)(5)(ii)(c)).

9. Grimes, Hugh G., and Geiger, Clyde J., "Furacin (Nitrofurazone) Vaginal Suppositories in Operative Gynecology," *American Journal of Obstetrics and Gynecology* 79(3):441-450, March 1960. This is a study of the effectiveness of Furacin Vaginal Suppositories on postoperative morbidity, healing, vaginal bacterial flora, and pH in 137 patients undergoing gynecologic procedures of varying seriousness. The patients were divided into three major groups: a "control group," an "early treatment group," and a "later treatment group." The "later treatment group" was subdivided into two groups based upon the strength of Furacin Vaginal Suppository used (0.2 percent Furacin or 0.3 percent Furacin). The patients were examined upon admission, preoperatively and postoperatively; the results were then compared. The operative preparation, consisting of a thorough cleansing of the perineum and vagina with soap and water without any specific antiseptic, was the same for all groups. The "early treatment group" (35 patients) received a single Furacin Vaginal Suppository 14 to 16 hours preoperatively, and one suppository per day for 5 days postoperatively beginning on the first postoperative day. The "later treatment group" was subdivided as indicated above. All subjects in this group received a single Furacin suppository preoperatively. Postoperatively, the suppositories were administered twice daily to the respective subgroups beginning on Day 1.

The study offers no evidence of the effect of Furacin Vaginal Suppositories on the vaginal bacterial flora when the suppository was given preoperatively. The authors stated that "The suppository given preoperatively did not alter bacterial flora qualitatively or quantitatively in the second preoperative specimen in 84 of 88 patients (95 percent)." The authors concluded that there was no statistically significant difference in postoperative morbidity. Further, the authors pointed out that morbidity is influenced by multiple factors, "including the all-important basic surgical principles," and discussed the test results concerning morbidity only after the qualifying introductory clause, "Presuming these to be constant in our series . . ." The authors noted that early healing was a completely unsatisfactory observation as a basis for comparison of effectiveness of treatment and control groups because all patients had a relatively consistent appearance of the 6-day-old vaginal wound. The study states that late healing was enhanced by Furacin Vaginal Suppositories, and that that observation is statistically significant. Finally, the study states that "Diminu-

tion of the amount and odor of discharge was noted in these patients with satisfactory late healing," but that "This [observation] is certainly subjective nature," and makes no attempt to support the statement by reference to specific data. The study thus purports to provide meaningful information with respect only to Furacin's effect on late healing. Late healing is not an indication for Furacin under either its currently approved or proposed labeling. The study thus provides no information to support the effectiveness of the product for labeled indications.

Further, the study is not an adequate and well-controlled clinical investigation within the meaning of 21 CFR 314.111(a)(5)(ii) for the following reasons: The authors do not describe the method of assigning the subjects to test groups in a way which assures comparability in test and control groups of pertinent variables (21 CFR 314.111(a)(5)(ii)(2)(iii)). Control of variables such as surgical skill, hemostasis, and particular surgical procedure involved, is critical in any study attempting to assess differences in morbidity and wound healing. Also, the authors state that antibiotics were administered on specific indications only, but they do not indicate to which patients or consider whether the administration of antibiotics was comparable in the treatment and control groups (21 CFR 314.111(a)(5)(ii)(a)(2)(iii)).

The authors failed to take steps to minimize observer bias, as required (21 CFR 314.111(a)(5)(ii)(a)(3)). Such steps cannot be omitted when subjective clinical observations such as the rate of postoperative healing or vaginal health are to be assessed. When subjective clinical observations such as postoperative healing or vaginal odor are to be assessed, a placebo suppository should be used (21 CFR 314.111(a)(5)(ii)(a)(4)(ii)).

With respect to diminution of amount and odor of discharge, the authors admittedly made no attempt to subject the condition to rigorous clinical study, i.e., no specific data in connection with, and do not represent that their conclusion, that the amount and odor of discharge were diminished, is other than "subjective" impression, e.g., the methods of observation and recording of the "results" are not stated, as required (21 CFR 314.111(a)(5)(ii)(a)(3)). The study thus does not purport to provide substantial evidence as defined in 21 CFR 314.111(a)(5)(ii), in support of the effectiveness of Furacin in treating odor and discharge from any cause.

10. Schwartz, Jerome, and Nardiell, Vincent, "Furacin Vaginal Suppositories: Their Use With Radiation Therapy for Malignant Pelvic Neoplasms," *American Journal of Obstetrics and Gynecology* 65(5):1069-1072, May 1953. The authors state that previous results with Furacin Vaginal Suppositories in the pre- and post-operative treatment of the cervix and vagina prompted this further study for the drug's use for the post-radiation therapy of the female pelvis. The authors refer to a total of 26 cases in

report, although they indicate that six of those patients had been previously reported in a separate article. In the discussion of the results, however, the authors combine these six and discuss their results in terms of a total of 26 women undergoing X-ray or radium therapy to the pelvis for some type of malignant pelvic neoplasm (i.e., carcinoma of the cervix or vagina) and pelvic recurrences of adenocarcinoma of the ovary.

The authors indicate that at the inception of radiation therapy, or shortly thereafter, all patients were instructed to douche twice daily with vinegar douches and to then insert a Furacin Vaginal Suppository. The authors indicate that some patients were treated with suppositories which contained all of the ingredients except Furacin. After a trial period on the placebo suppositories, these patients were placed on Furacin Vaginal Suppositories. Patients originally receiving Furacin Vaginal Suppositories were thereafter given the placebo suppositories. The effects on the amount and odor of discharge were compared in the patients under both conditions of treatment. The authors state that the control cases treated with the placebo suppositories had minimal diminution in the character, amount, and odor of the vaginal discharge. When these patients were placed on Furacin Vaginal Suppositories, a marked decrease in the amount and odor of the discharge is reported to have occurred. Patients who had begun on the Furacin Vaginal Suppositories and who were subsequently given the control product " . . . invariably commented upon the increase in both the amount and odor of the discharge."

The results of the study are irrelevant to the currently approved labeling indication for Furacin Vaginal Suppositories in the context of radiation therapy because they provide no support for the effectiveness of the product in the treatment and prevention of cervicovaginal infections before and after radiation therapy for cervical and pelvic neoplasms in women. The authors provide no data relating to the presence of identification of microorganisms present before or after radiation. Neither is there any information relating to the effect of Furacin Vaginal Suppositories upon the bacterial flora of the vagina of the patients. The study thus is not, and does not purport to be, an adequate and well-controlled clinical investigation of the effectiveness of the product for its currently approved radiation therapy-related indications (21 CFR 314.111(a)(5)(ii)), nor were the patients selected on the basis of diagnostic criteria designed to assure that they had a condition (cervicovaginal infections before and after radiation therapy) for which the drug is approved, as required by 21 CFR 314.111(a)(5)(ii)(a)(2)(i).

The study does, however, relate to malodor and discharge associated with radiation therapy by reason of bacterial growth in necrotic debris, indications which the NDA-holder proposes for inclusion in new labeling for Furacin Va-

ginal Suppositories. With respect to these indications, the study is not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii) for the following reasons:

The entire substance of the results relating to the effectiveness of the product in controlling malodor and discharge is set forth in a cursory recitation only several lines longer than the brief closing summary. This recitation contains no meaningful attempt to explain the methods of observation and recording of results, as required by 21 CFR 314.111(a)(5)(ii)(a)(3). Specifically, there are no explanations of the following:

a. How the results of the treatment were observed or recorded. The statement is made that there "was a marked diminution in the amount and odor of the vaginal discharge in every patient within 48 to 96 hours." This conclusory statement, as with similar flat assertions in the recitation of results, is unsupported by any description of the manner in which the underlying information was obtained, i.e., by uncritical acceptance of the subjects' impressions, by direct examination performed by the authors, or by combining the subjects' impressions with medical verification by the authors in accordance with objective criteria. Whichever of these methods was employed, the description of the results is further deficient in failing to specify the criteria by which the "results" were identified (i.e., if the subjects' impressions were used, the standards they were given on the basis of which they could reliably report to the investigators that there was in fact a diminution in either malodor or discharge; and if the authors observed the results, or verified the results as reported by the subjects, the criteria they used to measure them). Without explanation of the standards used to gauge the existence or extent of diminution in odor or discharge, the report cannot be considered "adequate" within the meaning of the regulation because it is incapable of scientific evaluation.

b. The method of quantitation, if any, employed in the study. The only terms in the recitation of results which imply magnitude are "marked diminution," "minimal diminution," "marked decrease," and "the increase." Without knowing with some precision what these terms mean, or how they were understood by those reporting and/or observing the results, there is no way of either independently evaluating the results or of verifying the validity of the authors' evaluation of them.

c. The manner in which the investigators assessed the subjects' responses. As mentioned, it is possible that the subjects' responses were assessed solely on the basis of the subjects' own interpretation of events, which could constitute a critical defect in the study rendering it less than adequate and well-controlled. This possibility is a real one, given use in the report of phrases like "the patient at no time noted," "the individuals so treated reported," and "[t]hese patients invariably commented upon." It is not possible to determine whether a study is

in fact "adequate and well-controlled" unless the basis for assessing the subjects' responses is stated in, or is reasonably apparent from, the text of the study report. Here, it is not.

d. The steps taken to minimize bias the part of the subject and observer. The significant variables in this study concern the degree of diminution of amount and amount of discharge. There is indication that changes in these variables were measured against objective criteria, and the text of the study strongly implies that, on the contrary, they were based solely on gross sensory impressions thus raising the problem of possible bias. It is, therefore, important to know what steps were taken to minimize subject and observer bias as a basis for determining whether the study was adequate and well-controlled. The report of the study is completely silent in this respect. There is indication in the report that the subjects (who were also, apparently, observers of their own conditions) were not told whether they were receiving the active treatment or the placebo, or whether the investigators (assuming, since the report does not say, that they made independent observations) knew when they interviewed or examined the subjects whether the subjects had been given the product under study or the placebo. The study does not explain how, or whether, the potentialities for bias were minimized.

For the reasons above, this study is not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii)(3). Even if submitted as a corroborative study under 21 CFR 314.111(a)(5)(c), this study would not be considered for it lacks the details which permit scientific evaluation.

11. McClanahan, H. L., and Woodworth, H. B., Jr., "The Postpartum Cervix," *Obstetrics and Gynecology*, 14(5), 1 November 1959. In this study, 400 recent delivered women were divided into two equal groups. Two hundred were instructed to insert Furacin Vaginal Suppositories every night for 18 days beginning on the seventh postpartum day; the remaining 200 were not given any medication. All 400 were told to refrain from sexual activity and douches. Evaluation of effect was made at the sixth postpartum week by tabulating the incidence of cervical diseases in the 400 women.

The study is not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii) for the following reasons:

It fails to set forth what steps, if any, were taken to minimize observer and patient bias, as required by 21 CFR 314.111(a)(5)(ii)(a)(3). In particular, the study does not state whether the investigators were aware at the time of interviewing and/or examining the subjects whether the subjects were in the treatment or control group. Presence or absence of such knowledge is a significant factor in determining whether a study is "adequate and well-controlled" in view of the possibility of bias on the part of an observer called upon, as here, to diagnose the existence of conditions on

basis of medical judgment, rather than of objective laboratory measurements.

The study report indicates that test subjects were selected solely on the basis of having been recently delivered. Thus, the study does not include a method of selection which assures that the patients were suitable for the purposes of the study, as required by 21 CFR 314.111(a)(5)(ii)(a)(2)(i). The report includes several statements to the effect that pathological conditions of the cervix are so common among recently delivered women that it can be assumed that all such women have such conditions. No basis for this assumption is stated other than the authors' clinical impressions. Unsubstantiated assertions that all women who have recently delivered babies also have pathological conditions of the cervix cannot substitute for clinical diagnosis that the test subjects do in fact have such conditions. Further, Furacin Vaginal Suppositories is not indicated for use in all pathological conditions of the cervix from which recently delivered women might suffer. Thus, even if the authors of this study provided a basis for the initial assumption that all such women have pathological cervical conditions, the study nevertheless fails to provide a method for selecting test subjects suitable for a study of the effectiveness of the conditions for which Furacin is indicated in its labeling.

The authors state that some of the patients resumed sexual relations (with possible reinfection resulting), and that 85 percent had resumed douching before the evaluation was made. Thus the study, on its face, did not employ a method to assure that the test and control groups were comparable with respect to pertinent variables, as required by 21 CFR 314.111(a)(5)(ii)(a)(2)(iii). It is thus impossible to compare the results of therapy with results in an appropriate control (21 CFR 314.111(a)(5)(ii)(a)(4)).

12. Schwartz, Jerome. "Furacin Vaginal Suppositories in Pre- and Postoperative Treatment of Cervix and Vagina," *American Journal of Obstetrics and Gynecology*, 63(2):579-582, March 1952. This report assesses the effects of Furacin on wound healing, infection, and amount and odor of vaginal discharge in the post operative cervix of 90 patients. Both Furacin and vinegar douches were administered to all patients. The report concludes that Furacin promoted healing, reduced infection and malodorous discharge, and had other favorable results in all pathological contexts included in the study, i.e., post-electrosurgical treatment of the cervix, vaginal operations, total abdominal hysterectomy, and postradiation treatment of carcinoma of the cervix.

The study is not an adequate and well-controlled clinical investigation within the meaning of 21 CFR 314.111(a)(5)(ii) for the following reasons:

The method of assignment of the subjects for inclusion into the test group or control group is not specified (21 CFR 314.111(a)(5)(ii)(a)(2)). Thus, there is no way to determine how the subjects

were assigned to the groups, or whether there was assurance of the comparability of test and control groups.

The author does not explain the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subject's response, and steps taken to minimize bias on the part of the subject and observer (21 CFR 314.111(a)(5)(ii)(a)(3)). Illustrative of this defect is the fact that no explanation is given of the standards employed by the investigators to gauge the extent of the results of treatment with Furacin Vaginal Suppositories. Thus, the conclusion is offered in connection with use of Furacin in post-radiation situations that "there was a remarkable reduction in the amount of vaginal discharge which was practically odorless." Nothing in the report gives content to the term "remarkable reduction." Nothing in the report defines "odorless." Another example of failure to comply with this provision of the regulations is that there is no indication that any measures were taken to minimize subject and observer bias. The study deals with clinical effects (e.g., rate of healing, amount and odor of discharge) which depend on the exercise of medical judgment for their identification and assessment, and so the possibility of bias on the part of the observer must be taken into account in some way to make the study scientifically meaningful. The study report is silent on this point.

Although a table in the study report refers to "control group," the text nowhere discusses or even mentions the existence of such controls, and there is no explanation of what that term means in this study, nor of the results observed in the controls. The only results which are discussed are those observed in subjects who received Furacin Vaginal Suppositories. Statements such as "healing time was accelerated," and "decreased postoperative infection" are made without reference to any discernible objective standard, much less to the results in an appropriate control. Thus, on its face, the study contains no comparison of the results in treated subjects with the results in a control group, as required by 21 CFR 314.111(a)(5)(ii)(a)(4).

Interpretation of results is obscured by the vinegar douches used by all patients. There is no way to tell whether the observed effects were due to Furacin or to the vinegar douches, and thus even if the study utilized an untreated control group, the study would not provide a comparison of the results of Furacin-treated patients with the results in a control group, as required by 21 CFR 314.111(a)(5)(ii)(a)(4), because no patients received only Furacin.

13. Kanter, A. E. "Infection Following Gynecological Surgery," *Clinical Obstetrics and Gynecology*, 2:564-581, June 1959. This paper discusses complications following pelvic surgery. It makes no attempt to study the efficacy of any drug product. Furacin is mentioned in a single sentence along with other vaginal suppositories. The paper does not purport to

describe an adequate and well-controlled clinical investigation of the effectiveness of furacin within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a)(5)(ii). It is at best a testimonial, which is unacceptable as the sole basis for a claim of effectiveness (21 CFR 314.111(a)(5)(ii)(c)).

B. *Affidavits, Testimonial Letters and Marketing Data.* The affidavits and testimonial letters from practicing physicians and marketing data submitted by Norwich do not provide substantial evidence of the effectiveness of furacin. *Weinberger v. Hyson, Westcott and Dunning, Inc.*, 412 U.S. 609 (1973); *Weinberger v. Bentez Pharmaceuticals, Inc.*, 412 U.S. 645 (1973); *Upjohn Co. v. Finch*, 422 F.2d 944, 951-954 (C.A. 6, 1970); *PMA v. Richardson*, 318 F. Supp. 301, 309-310 (D. Del., 1970). Such material, which lacks details which permit scientific evaluation, is not considered in evaluating whether substantial evidence exists supporting the effectiveness of a drug (21 CFR 314.111(a)(5)(ii)(c)).

C. *Proposed Revised Labeling of Furacin Vaginal Suppositories.* As part of its submission in response to the Notice of Opportunity for Hearing, Norwich, on June 21, 1973, proposed new labeling for Furacin Vaginal Suppositories. The data submitted by Norwich in support of its request for hearing have been specifically reviewed with respect to currently approved labeling. Necessarily, the analysis of the studies, in relation to the criteria for adequate and well-controlled investigations, also applies to the proposed relabeling described in the June 1973 supplement, and this has been so indicated where relevant. It has been determined that the cited studies are not adequate and well-controlled. Results of these studies, therefore, do not provide substantial evidence in support of the effectiveness of Furacin Vaginal Suppositories for currently approved indications. The question of whether the evidence submitted supports the effectiveness of the product for proposed labeling obviously has no bearing on whether a hearing is justified in relation to evidence submitted to support currently approved labeling. In view of his analysis, the Commissioner does not believe that a hearing could be justified in connection with the proposed new labeling on the basis of the data cited by the applicant. In any event, for those indications proposed in the June 21, 1973 submission, the Commissioner concludes that the applicant must submit a new drug application establishing the safety of Furacin Vaginal Suppositories and containing substantial evidence of its effectiveness under those conditions of use for which Norwich wishes to market the product.

IV. THE DATA SUBMITTED TO SUPPORT CLAIMS OF SAFETY

Norwich has submitted a number of animal studies to establish the safety of the products under consideration here and in support of certain animal drugs which also contain nitrofurazone. The Commissioner has not yet completed his

NOTICES

review of this material. However, since the Commissioner has concluded that Norwich has failed to support the claimed efficacy of these drugs with evidence meeting the statutory standard of "adequate and well-controlled clinical investigations," under section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a) (5) (ii), it is not necessary to await the Commissioner's evaluation of the safety data. The lack of substantial evidence of effectiveness requires denial of a hearing for these products (21 U.S.C. 355(c); 21 CFR 314.115; *E. R. Squibb & Sons, Inc. v. Weinberger*, 483 F. 2d 1382, 1386 (C.A. 3, 1973)).

V. LEGAL ARGUMENTS

In its hearing request for the product above, Norwich states that the new drug issue cannot be decided in an administrative proceeding to withdraw approval of a new drug application. After submission of the request, the Supreme Court held that the Food and Drug Administration has jurisdiction in an administrative proceeding to determine whether a drug product is a "new drug" within the meaning of the Federal Food, Drug, and Cosmetic Act. *Weinberger v. Hynson, Wescott & Dunning, supra*; *Weinberger v. Bentez Pharmaceuticals, Inc., supra*; *CIBA Corp. v. Weinberger*, 412 U.S. 640 (1973).

Norwich also states that its November 16, 1973 submission, consisting of affidavits from three experts, establishes a genuine issue of fact which requires a hearing. However, each of Norwich's affidants bases his opinion on the studies previously submitted by Norwich, his own personal experience, and "pertinent reports included on the list of references" attached to each of their affidavits, none of which, as shown above, constitutes substantial evidence within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a) (5) (ii). Norwich's affidavits are testimonials and do not raise an issue of fact requiring a hearing.

VI. FINDINGS

On review of the documentation and legal arguments offered to support the claims of effectiveness for Furacin Vaginal Suppositories and the necessity for an evidentiary hearing, the Commissioner finds that Norwich has failed to set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing, that the legal arguments offered are insufficient to justify an evidentiary hearing, and that there is a lack of substantial evidence that this drug has the effects it is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1052, as

amended (21 U.S.C. 355(e))) and under authority delegated to the Commissioner (21 CFR 2.120), the hearing is denied and the approval for that part of the new drug application (NDA 5-795) providing for Furacin Vaginal Suppositories, and all amendments and supplements thereto, is hereby withdrawn, effective June 10, 1975.

Dated: May 15, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.
[FR Doc. 75-14070 Filed 5-29-75; 8:45 am]

CARDIOVASCULAR AND RENAL
ADVISORY COMMITTEE

Notice of Meeting

Pursuant to the Federal Advisory Committee Act of October 6, 1972 (Pub. 92-463, 86 Stat. 770-776 (5 U.S.C. A D)), the Food and Drug Administration announces the following public advisory committee meeting and other requirements in accordance with provisions set forth in section 10(a) (1) (2) of the act:

| Committee name | Date, time, place | Type of meeting and contact person |
|--|--|---|
| Cardiovascular and Renal Advisory Committee. | June 10, 9 a.m. Conference Room L. Parklawn Bldg., 5600 Fishers Lane, Rockville, Md. | Open—Joan C. Standaert (HFD-110), Fishers Lane, Rockville, Md. 20852, 443-4730. |

Purpose. Reviews and evaluates all available data concerning the safety and effectiveness of presently marketed and new prescription drug products proposed for marketing for use in the treatment of cardiovascular and renal disorders.

Agenda. Discussion of NDA 12-151 Spironolactone (Aldactone) and NDA 12-616 Spironolactone Hydrochlorothiazide (Aldactazide). Following routine committee business, a discussion relative to the toxicity of Spironolactone will ensue. A recent study of 78 weeks in the rat revealed a dose related increase in tumors of the thyroid and testes. Earlier studies of 52 weeks in monkeys and 104 weeks in rats utilizing lower doses will be reviewed in light of the new data. There will, in addition, be a discussion of possible liver involvement.

The Committee will review these findings and deliberate upon their relevance to the continued marketing and/or labeling of Spironolactone and Spironolactone/Hydrochlorothiazide and their indications for use.

Agenda items are subject to change as priorities dictate.

Dated: May 22, 1975.

SAM D. FINE,
Associate Commissioner for Compliance.
[FR Doc. 75-13908 Filed 5-29-75; 8:45 am]

Public Health Service
HEALTH SERVICES ADMINISTRATION
Delegation of Authority

On May 1, 1975 the Assistant Secretary for Health made the following delegations of authority to the Executive Officer, Public Health Service, and to the Administrator, Health Services Administration:

Under the authority delegated to me by the Secretary on July 29, 1974, I hereby delegate to the Executive Officer, Public Health Service, the authority to perform all functions of the Secretary in connection with the bringing of civil

actions under section 1312, Public Health Service Act (42 U.S.C. 300e-1X), and authority to direct and supervise the implementation of section 1312. These authorities may not be further redelegated.

I hereby delegate to the Administrator, Health Services Administration, the authority to monitor and investigate compliance of entities with applicable requirements of Title XIII, PHS Act, regulations issued thereunder, and assurances which they provided thereunder, and as may be necessary for proper implementation of section 1312 of the Act, and the authority to pursue remedies as may be available with respect to such entities, other than the authority to bring civil actions under section 1312, Public Health Service Act. These authorities may be redelegated.

In addition, I hereby delegate to the Administrator, Health Services Administration, the authority to perform functions of the Secretary, under section 1310, Public Health Service Act (42 U.S.C. 300e-9). This authority may be redelegated.

These delegations are effective immediately.

R. MOURE,
Executive Officer
Public Health Service

MAY 2, 1975.

[FR Doc. 75-14172 Filed 5-29-75; 8:45 am]

Office of the Secretary
NATIONAL COMMISSION FOR THE
SECTION OF HUMAN SUBJECT
BIOMEDICAL AND BEHAVIORAL
SEARCH
Meeting

Notice is hereby given that the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research will meet on May 2 and 21, 1975, in Conference Room B Wing, Building 31, National Institute of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. The meeting will convene at 9 a.m. each day and will