ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that Alcide Corp. has filed a petition proposing that the food additive regulations be amended to provide for the safe use of acidified sodium chlorite solutions for red meat disinfection in processing plants.

DATES: Written comments on the petitioner's environmental assessment by March 7, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Robert L. Martin, Center for Food Safety and Applied Nutrition (HFS–217), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3074.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 7A4532) has been filed by Alcide Corp., 8561 154th Ave. NE., Redmond, WA 98052. The petition proposes to amend part 173 (21 CFR part 173) of the food additive regulations to provide for the safe use of acidified sodium chlorite solutions for red meat disinfection in processing plants.

The potential environmental impact of this action is being reviewed. To encourage public participation consistent with regulations promulgated under the National Environmental Policy Act (40 CFR 1501.4(b)), the agency is placing the environmental assessment submitted with the petition that is the subject of this notice on public display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before March 7, 1997 submit to the Dockets Management Branch (address above) written comments. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the Federal Register. If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the Federal Register in accordance with 21 CFR 25.40(c).

Dated: January 17, 1997.

Alan M. Rulis,

Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 97–2820 Filed 2–4–97; 8:45 am]

BILLING CODE 4160–01–F

Studies of Adverse Effects of Marketed Drugs, Biologics, and Devices; Availability of Grants (Cooperative Agreements); Request for Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA), Center for Drug Evaluation and Research, is announcing the availability of $1.4 million in Fiscal Year 1997 funds for cooperative agreements to study adverse effects of marketed drugs, biologics, and devices. This amount is consistent with the level of funding in the President's budget. FDA expects to make four to six awards in the range of $250,000 to $350,000 for direct and indirect costs. The Government's obligation is contingent upon the availability of appropriated funds from which the cooperative agreements will be funded. The purpose of these agreements is to conduct drug, biologic, and device safety analysis for public health benefit; respond expeditiously to urgent public safety concerns; provide a mechanism for collaborative pharmacoepidemiological research designed to test hypotheses, particularly those arising from suspected adverse reactions reported to FDA; and enable rapid access to multiple data sources to ensure public safety when necessary.

DATES: Application receipt date is March 21, 1997.

ADDRESSES: Application kits are available from, and completed applications should be submitted to: Robert L. Robins, Grants Management Officer, Division of Contracts and Procurement Management (HFA–520), Food and Drug Administration, Park Bldg., rm. 3–40, 5600 Fishers Lane, Rockville, MD 20857, 301–443–6170.

Note: Applications hand-carried or commercially delivered should be addressed to the Park Bldg., rm. 3–40, 12420 Parklawn Dr., Rockville, MD 20857. Please do NOT send applications to the Division of Research Grants, National Institutes of Health (NIH).

FOR FURTHER INFORMATION CONTACT:

Regarding the administrative and financial management aspects of this notice: Robert L. Robins (address above).

Regarding the programmatic aspects of this notice: Charles M. Maynard, Division of Pharmacovigilance and Epidemiology (HFD–733), Food and Drug Administration, 5600 Fishers Lane, rm. 15B–18, Rockville, MD 20857, 301–827–3187.

SUPPLEMENTARY INFORMATION: FDA's authority to fund research projects is set out in section 301 of the Public Health Service Act (the PHS Act) (42 U.S.C. 241). FDA's research program is described in the Catalog of Federal Domestic Assistance, No. 93.103. Applications submitted under this program are not subject to the requirements of Executive Order 12372.

I. Background

New drugs, biologics, and devices are required to undergo extensive testing before marketing. With the submission of adequate data on safety and effectiveness, FDA approves a new drug, biologic, and device application (NDA/PLA/PMA) that permits a manufacturer to market its product in the United States. Although the information provided before marketing is sufficient for approval, it is not adequate to anticipate all effects of a product once it comes into general use.

This request for applications (RFA) is intended to encourage collaboration between FDA and researchers with pharmacoepidemiological data bases to address postmarketing issues confronting the agency. FDA is also interested in the ability to measure and/or estimate incidence rates and test hypotheses based on signals of possible drug, biologic, and device safety problems originating from reports of adverse reactions received by FDA.

II. Program Research Goals

FDA would prefer to fund a variety of data bases representing, without overlap, different patient populations and/or types of patient care settings. The data bases maintained through these agreements must be able to: (1) Provide data on exposure to new chemical entities; (2) perform feasibility studies of multiple drugs and/or multiple outcomes; (3) identify adverse drug, biologic, and device events that occur infrequently; and (4) provide a substantive response within a very short timeframe.

The goal for these cooperative agreements is to investigate suspected associations between specific drug and

possible biologic and device exposures and specific adverse events and to quantitate such risk. The specific objectives are to: (1) Provide immediate access to existing data sources with the capability of providing assessments of study feasibility; (2) respond to particular drug, biologic, and device safety questions within a few weeks; and (3) provide a substantive response to those questions deemed feasible within a few months.

Data base characteristics should include the ability to:

(1) Estimate adverse event rates or relative risks for specific event.

(2) Estimate the contribution of various risk factors associated with the occurrence of adverse events (e.g., age, sex, dose, coexisting disease, disease severity, concomitant medication).

(3) Determine adverse event rates for generic entities as well as for classes of drugs.

(4) Determine rate and depth of usage of new drugs into the formulary.

(5) Obtain data from laboratory results.

(6) Link to state vital statistics, if possible.

(7) Link to cancer registry.

(8) Determine inpatient exposure.

(9) Long term followup of exposure and outcomes.

(10) Determine adverse events related to vaccines.

(11) Ability to follow cohort (retrospectively or prospectively) based on device exposure or clinical diagnosis for case-control or cohort studies.

(12) Ability to study all medical devices, especially newer technologies approved by FDA since 1990.

In addition, FDA is interested in data bases capable of innovatively applying the objectives stated above to specifically defined populations including but not limited to children, pregnant women, and the elderly.

The ideal data source would capture all drug exposures linked longitudinally to each patient regardless of health care delivery setting. Because the outcomes of interest could be either acute or chronic effects, all health provider encounters, i.e., medical records, would be captured whether in the ambulatory, emergency, chronic care, or acute care setting. The ideal data source would have the statistical power to identify rare adverse events in the population of interest. The ideal data base would also be automated with a computerized system available for linking each patient to all relevant medical care data including drugs, biologics, and device exposure data, coded medical outcomes, vital records, cancer registries, and birth defect registries. Additional points would be awarded for linkage of data bases to laboratory values and easy accessibility of records. The location and accessibility of the medical records are very important concerns to FDA. For rare events, the capability of performing case-control studies is valuable.

Submitted applications must include an indepth description of the data base and provide descriptive and quantitative information on diagnoses of drug, biologic, and device exposures in the population. The quality and validity of the data should be described in detail.

III. Reporting Requirements

Program progress reports will be required quarterly. These reports must be submitted within 30 days after the last day of each quarter based on the budget period of the cooperative agreement. Financial Status Reports (SF–269) will be required annually. These reports must be submitted within 90 days after the last day of the budget period of the cooperative agreement. Failure to file the Financial Status Report (SF–269) in a timely fashion will be grounds for suspension or termination of the grant.

Program monitoring of the grantees will be conducted on an ongoing basis and written reports will be prepared by the project officer. The monitoring may be in the form of telephone conversations between the project officer and/or grants management specialist and the principal investigator. Periodic site visits with appropriate officials of the grantee organization may also be conducted. The results of these reports will be recorded in the official grant file and may be available to the grantee upon request consistent with FDA disclosure regulations.

A final program progress report, Financial Status Report (SF–269), and Invention Statement must be submitted within 90 days after the expiration of the project period as noted on the Notice of Grant Award.

Up to two representatives from each cooperative agreement may be required, if requested by the Project Officer, to travel to FDA up to twice a year for no more than 2 days at a time. These meetings will include, but are not limited to, presentations on study design and findings and discussions with the FDA staff involved in the collaborative research. At least one FDA employee may visit the cooperative agreement site at least once a year for collaboration and information exchange.

IV. Mechanism of Support

A. Award Instrument

Support of this program will be in the form of cooperative agreements. All awards will be subject to all policies and requirements that govern the research grant programs of the Public Health Service (PHS), including the provisions of 42 CFR part 52, 45 CFR parts 74 and 92, and PHS Grants Policy Statement.

B. Eligibility

These cooperative agreements are available to any public or private nonprofit organization (including State, local, and foreign units of government) and any for-profit organization. For profit organizations must exclude fees or profit from their requests for support. Organizations described in section 501(c)4 of the Internal Revenue Code of 1968 that engage in lobbying are not eligible to receive grant/cooperative agreement awards.

C. Length of Support

The length of support will depend upon the nature of the study and may extend beyond 1 year, but may not exceed 3 years. The first year will be competitive and the remaining 2 years will be noncompetitive. Future support will be contingent upon: (1) Performance during the preceding year, and (2) the availability of Federal fiscal year appropriations.

D. Funding Plan

The number of cooperative agreements funded will depend on the quality of the applications received and the availability of Federal funds to support the projects. $1.4 million is budgeted for this program. It is anticipated that four to six awards will be made for approximately $250,000 to $350,000 total direct and indirect cost. Federal funds for this program are limited. Therefore, should FDA approve two or more applications that propose duplicative or very similar data resources, FDA will support only the source with the best score.

V. Delineation of Substantive Involvement

Program support will be offered through cooperative agreements because FDA will have a substantive involvement in the programmatic activities of all the projects funded under this RFA. Involvement may be modified to fit the unique characteristics of each application. Substantive involvement includes, but is not limited to the following:

1. FDA staff will participate in the selection and approval of the drug, biologic, and device exposures and medical events to be studied predicated upon public health needs. The drug exposure and medical events to be studied will be jointly agreed upon by the extramural investigator and the FDA staff.

2. FDA scientists will collaborate with awardees in study design and data analysis. Collaboration may include sharing of the analysis data set, interpretation of findings, review of manuscripts, and where appropriate, coauthorship of publications.

VI. Review Procedure and Criteria

A. Review Procedure

All applications submitted must be responsive to the RFA. Those applications found to be nonresponsive will not be considered for funding under this RFA and will be returned to the applicant.

Responsive applications will undergo dual peer review. An external review panel of experts in the fields of epidemiology, statistics, and data base management will review and evaluate each application based on its scientific merit. Responsive applications will also be subject to a second level review by the National Advisory Environmental Health Science Council for concurrence with the recommendations made by the first level reviewers, and funding decisions will be made by the Commissioner of Food and Drugs.

B. Review Criteria

Applications will be reviewed according to the following criteria with each criteria being of equal weight. All applications will be scored with a maximum of 100 points allowable.

1. Size and Characteristics of the Data Base (67 points). The size and characteristics of the data base should include the following:

a. A large population size of individuals for whom drug, device, and biologic exposure and medical outcome data are available. Our goal will be to award data bases with a population of at least 2,000,000 current enrollees. No points will be awarded for data bases with a population size of less than 250,000. Data bases comprised of only one of the special populations for which data are desired (i.e., children, pregnant women, and the elderly) may be awarded full points for smaller population sizes. Investigators who mainly use a case-control design, should be able to provide information on at least 500 cases of a specific disease or disorder and exposure primarily to new molecular entities.

b. Ability to assemble and follow (retrospectively or prospectively) well defined cohorts based on drug, device, and biologic exposure or clinical diagnosis for the purpose of performing case-control or cohort studies.

c. Ability to access and to link to the patient all health provider encounters and drug, biologic, and device exposure information regardless of patient care setting. Full points will be awarded to data bases that capture full drug, device, and biologic exposure and in-patient outcome data from hospital, ambulatory care and long-term care settings.

d. Ability to detect rare adverse drug, biologic, or device events in one or more specific target populations of interest (i.e., children, pregnant women, and the elderly).

e. Ability to study all drug products especially new molecular entities (NME's) approved by FDA since 1991 and newly approved medical devices and biologics.

f. Ability to ascertain patient enrollment and turnover rates as demonstrated by descriptions of the entry and dropout rates and the average length of enrollment. For investigators primarily employing the case control design, ability to attain complete and unbiased ascertainment of cases and controls.

g. A standard set of drug and disease classification systems.

h. Ability to successfully retrieve a high proportion of medical records (sufficient to address the issue presented) in a timely fashion. Documentation of a large proportion of medical records retrieved in a specified time period should be included.

i. Ability to link to cancer registry and to state vital statistics.

j. Ability to identify risk factors for drug-associated outcomes and assess potential confounders.

k. Ability to assess drug interactions.

l. A long calendar time period for which data are available and longitudinally linkable. No points will be awarded to data bases with less than 2 years of history.

m. A short lag time (< 6 months) between patient events (hospitalization, etc.) and availability of clean data.

2. Information Systems and Software Capabilities (12 points). Information systems and software capabilities should include the following:

a. A well defined and acceptable description of computer resources and the extent of automation and software capabilities.

b. Availability of computerized data elements (in patient drugs and diagnoses, outpatient drugs and diagnostic procedures, medical records) or progress towards automation of those data elements not yet available.

c. Existing software to calculate person time at risk and time of event occurrence.

d. Ability to complete routine searches of the data base within a short time period of about 15 working days.

e. Ability to generate customized SAS, ASCII, or other appropriate data sets to facilitate data transfer and research collaboration.

3. Personnel (15 points). Personnel should have the following qualifications:

a. Extensive research experience, training, and competence with a demonstrated ability to draw on consultative expertise in the areas of postmarketing surveillance and epidemiology.

b. Information systems expertise with previous experience in the organization and manipulation of large data sets, and specific experience in data bases under agreement.

c. Investigators should demonstrate a willingness to collaborate with FDA scientists as well as with other investigators funded by this cooperative agreement program. Such demonstration may include suggestions for design of the study, analysis of data sets, and publication of results among FDA and Cooperative Agreement investigators.

4. Budget (3 points). Reasonableness of the proposed budget. Special consideration will be given to methodology which is cost effective (e.g., well-structured medical records and/or record linkage) if otherwise scientifically acceptable.

5. Demonstrated ability to initiate, conduct, complete, and publish epidemiology studies in a timely manner (1 point).

6. Plans for complying with regulations for protection of human subjects as applicable to the proposed study project (1 point).

7. Research experience, training, and competence of the principal investigator and the support staff and the resources available to them. Special consideration will be given to investigators with knowledge and previous experience in postmarketing surveillance and drug epidemiology, but applicants with strong acute and chronic disease epidemiology background are encouraged to apply (1 point).

VII. Submission Requirements

The original and five copies of the completed Grant Application Form PHS 398 (Rev. 5/95) or the original and two copies of Form 5161 (Rev. 7/92) for applications from State and local governments, with sufficient copies of

the appendix for each application, should be delivered to Robert L. Robins (address above). No supplemental material will be accepted after the closing date. FDA's authority to fund research projects is under section 301 of the PHS Act. FDA's research program is described in the Catalog of Federal Domestic Assistance, No. 93.103. Applications submitted under this program must comply with 45 CFR part 46—Protection of Human Subjects where applicable and requirements of the Office of Protection from Research Risks. The outside of the mailing package and item 2 of the application face page should be labeled ''Response to RFA–FDA–CDER–97–1''.

VIII. Method of Application

A. Submission Instructions

Applications will be accepted during normal working hours, 8 a.m. to 4:30 p.m., Monday through Friday, on or before the March 14, 1997, deadline.

Applications will be considered received on time if sent or mailed on or before the receipt dates as evidenced by a legible U.S. Postal Service dated postmark or a legible date receipt from a commercial carrier, unless they arrive too late for orderly processing. Private metered postmarks shall not be acceptable as proof of timely mailing. Applications not received on time will not be considered for review and will be returned to the applicant.

Note: (Applicants should note that the U.S. Postal Service does not uniformly provide dated postmarks. Before relying on this method, applicants should check with their local post office.)

B. Format for Application

Applications must be submitted on Grant Application Form PHS 398 (Rev. 5/95). All ''General Instructions'' and ''Specific Instructions'' in the application kit should be followed with the exception of the receipt dates and the mailing label address. Do not send applications to the Division of Research Grants, NIH. This information collection is approved under OMB No. 00925–0001. Applications from State and local governments may be submitted on Form PHS 5161 (Rev. 7/92) or PHS 398 (Rev. 5/95). The face page of the application must reflect the request for applications number RFA–FDA–CDER–97–1. This information collection is approved under OMB control number 0937–0189.

C. Legend

Unless disclosure is required by the Freedom of Information Act as amended (5 U.S.C. 552) as determined by the freedom of information officials of the Department of Health and Human Services or by a court, data contained in the portions of an application that have been specifically identified by page number, paragraph, etc., by the applicant as containing confidential commercial information or other information that is exempt from public disclosure will not be used or disclosed except for evaluation purposes.

Dated: January 30, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–2870 Filed 2–4–97; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 96E–0362]

Determination of Regulatory Review Period for Purposes of Patent Extension; DIFFERIN Topical Gel

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for DIFFERIN Topical Gel and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Commissioner of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Written comments and petitions should be directed to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Brian J. Malkin, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Commissioner of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product DIFFERIN Topical Gel (adapalene). DIFFERIN Topical Gel is indicated for the topical treatment of acne vulgaris. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for DIFFERIN Topical Gel (U.S. Patent No. Re. 34,440) from Centre International de Recherches Dermatologiques (CIRD), and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated October 24, 1996, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of DIFFERIN Topical Gel represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for DIFFERIN Topical Gel is 2,447 days. Of this time, 1,401 days occurred during the testing phase of the regulatory review period, while 1,046 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) became effective*: September 20, 1989. FDA has verified the applicant's claim that the date that the investigational new drug application became effective was on September 20, 1989.

2. *The date the application was initially submitted with respect to the human drug product under section 505(b) of the Federal Food, Drug, and*