IV. Response to Comments

Because of the large number of items of correspondence we normally receive on **Federal Register** documents published for comment, we are not able to acknowledge or respond to them individually. We will consider all comments we receive, and, if we proceed with a subsequent document, we will respond to the major comments in the preamble to that document.

V. Regulatory Impact Statement

This notice does not require an impact analysis because it does not have an economic impact on small entities, small rural hospitals, or State, local, or tribal governments.

In accordance with the provisions of Executive Order 12866, this notice was not reviewed by the Office of Management and Budget.

(Catalog of Federal Domestic Assistance Program No. 93.778, Medical Assistance Program)

(Catalog of Federal Domestic Assistance Program No. 93.773, Medicare—Hospital Insurance; and Program No. 93.774, Medicare—Supplementary Medical Insurance Program)

Dated: September 7, 2001.

Thomas A Scully,

Administrator, Centers for Medicare & Medicaid Services.

[FR Doc. 01–27700 Filed 11–1–01; 8:45 am]

BILLING CODE 4120–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

[Program Announcement No. ACYF–PA–HS–02–01A]

Discretionary Announcement of the Availability of Funds and Request for Applications for Select Service Areas of Early Head Start; Correction

AGENCY: Administration for Children, Youth and Families, ACF, DHHS.

ACTION: Correction.

SUMMARY: This document contains a correction to the Notice that was published in the **Federal Register** on September 20, 2001.

On page 48475, Appendix A, Part II, in the State of Missouri, in the County of St. Charles, in the FY 2002 funding level column, delete ''1,470,549'' and add ''1,497,549''.

On page 48476, Appendix A, Part II, in the State of New York, in the County of Bronx, in the FY 2002 funding level column, delete ''1,334,471'' and add ''1,322,291''. In the State of New York, in the County of Cattaraugus, in the FY 2002 funding level column, delete ''468,962'' and add ''511,079''. In the State of New York, in the County of Cattaraugus, in the FY 2002 funding level column, delete ''450,808'' and add ''568,205''. In the State of New York, in the County of Chenango, in the FY 2002 funding level column, delete ''468,962'' and add ''511,079''. In the State of New York, in the County of Monroe, in the FY 2002 funding level column, delete ''1,995,614'' and add ''2,173,928''. In the State of New York, in the County of Rensselaer, in the FY 2002 funding level column, delete ''670,221'' and add ''732,234''. In the State of New York, in the County of Steuben, in the FY 2002 funding level column, delete ''329,700'' and add ''349,700''. In the State of New York, in the County of Westchester, in the FY 2002 funding level column, delete ''941,224'' and add ''1,033,799''. In the State of New York, in the County of Erie, in the FY 2002 funding level column, delete ''1,277,058'' and add ''1,381,901''. In the State of New York, in the County of Schenectady, in the FY 2002 funding level column, delete ''1,057,663'' and add ''743,672''.

FOR FURTHER INFORMATION CONTACT: The ACYF Operations Center at 1–800–351–2293 or send an e-mail to *ehs@lcgnet.com*. You can also contact Sherri Ash, Early Head Start, Head Start Bureau at (202) 205–8562.

Dated: October 29, 2001.

James A. Harrell,

Acting Commissioner, Administration on Children, Youth and Families.

[FR Doc. 01–27610 Filed 11–1–01; 8:45 am]

BILLING CODE 4184–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01N–0336]

Schering Corp. et al.; Withdrawal of Approval of 51 New Drug Applications and 25 Abbreviated New Drug Applications; Correction

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting a notice that appeared in the **Federal Register** of August 16, 2001 (66 FR 43017). The document announced the withdrawal of approval of 51 new drug applications (NDAs) and 25 abbreviated new drug applications (ANDAs). The document inadvertently withdrew approval of NDA 17–255 for DTPA (chelate) Multidose (kit for the preparation of Tc-99m pentetate injection) held by Nycomed Amersham Imaging, 101 Carnegie Center, Princeton, NJ 08540. FDA confirms that approval of NDA 17–255 is still in effect.

EFFECTIVE DATE: August 16, 2001.

FOR FURTHER INFORMATION CONTACT: Florine P. Purdie, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

In FR Doc. 01–20605 appearing on page 43017 in the **Federal Register** of Thursday, August 16, 2001, the following correction is made: On page 43018, in the table, the entry for NDA 17–255 is removed.

Dated: October 11, 2001.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 01–27520 Filed 11–01–01; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01N–0494]

Prescription Drug Products; Doxycycline and Penicillin G Procaine Administration for Inhalational Anthrax (Post-Exposure)

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is clarifying that the currently approved indications for doxycycline and penicillin G procaine drug products include use in cases of inhalational exposure to *Bacillus anthracis* (the bacterium that causes anthrax). We also are providing dosing regimens that we have determined are appropriate for these products for this use. We encourage the submission of supplemental new drug applications (labeling supplements) to add the dosage information to the labeling of currently marketed drug products.

ADDRESSES: Submit labeling supplements to the Center for Drug Evaluation and Research, Food and Drug Administration, Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Dianne Murphy, Center for Drug Evaluation and Research (HFD–950),

Food and DrugAdministration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2350.

SUPPLEMENTARY INFORMATION:

I. Anthrax

Anthrax is caused by the spore-forming bacterium *Bacillus anthracis*. There are three types of anthrax infection in humans: Cutaneous, gastrointestinal, and inhalational.

Until recently, most human experience with anthrax was associated with exposure to infected animals or animal products. Anthrax is reported annually among livestock. In areas where these animal cases occur, most human cases are the cutaneous form. Such cases occur among workers who have handled infected hoofed animals or products from these animals. Gastrointestinal anthrax has been reported following the ingestion of undercooked or raw meat from infected animals. Inhalational anthrax, resulting from inhalation of aerosolized spores, was associated with industrial processing of infected wool, hair, or hides in the United States in the past. Before October 2001, no case of inhalational anthrax had been reported in the United States since 1978. In 1979, at least 64 people died in Sverdlovsk (currently Ekaterinburg), Russia, of inhalational anthrax after *Bacillus anthracis* spores were accidentally released from a Soviet military laboratory.

Administration of certain anti-microbial agents may prevent or reduce the incidence of disease following inhalational exposure to *Bacillus anthracis*.

II. Approved Drug Products

Drug products containing doxycycline, doxycycline calcium, doxycycline hyclate,[1] and penicillin G procaine are currently approved with indications foranthrax.[2] The approved labeling for the doxycycline products states that the drugs are indicated in infections caused by *Bacillus anthracis*. The approved labeling for penicillin G procaine drug products states that the drugs are indicated for anthrax.

[1] Doxycycline hyclate tablets, equivalent to 20 milligrams (mg) base, and doxycycline hyclate 10 percent for controlled release in subgingival application are not subjects of this notice because they have periodontal indications and do not have indications for anthrax or infections caused by *Bacillus anthracis*.

[2] Other drug products are currently approved with indications for anthrax or infections caused by *Bacillus anthracis*, i.e., minocycline, tetracycline, oxytetracycline, demeclocycline, and penicillin G potassium. We have not completed a review on these other drugs. We will not discuss these other drugs further in this notice.

Presently, the labeling for these drug products does not specify a dosing regimen for inhalational exposure to *Bacillus anthracis*. The indication sections of approved labeling for these drug products does not specify cutaneous, gastrointestinal, or inhalational anthrax. We have determined that the language in the labeling of drug products containing doxycycline, doxycycline calcium, doxycycline hyclate, and penicillin G procaine is intended to, and does, cover all forms of anthrax, including inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

On August 30, 2000, we approved supplements to provide an indication for inhalational anthrax (post-exposure) for ciprofloxacin hydrochloride tablets and ciprofloxacin intravenous (IV) solution, IV in 5 percent dextrose, IV in 0.9 percent saline, and oral suspension. The approved labeling for these ciprofloxacin products provides for a 60-day dosing regimen. Because ciprofloxacin drug products are already specifically indicated for inhalational anthrax (post-exposure) and their approved labeling provides a regimen for inhalational anthrax (post-exposure), we do not discuss ciprofloxacin any further in this notice. It is relevant, however, that the rhesus monkey study supporting the approval of ciprofloxacin for inhalational anthrax also included separate doxycycline and penicillin G procaine treatment arms. Each of these arms showed a survival advantage over placebo.[3] No other antimicrobial drugs were tested in this study.

III. Doxycycline Drug Products

We have determined that 100 mg of doxycycline, taken orally twice daily for 60 days, is an appropriate dosing regimen for administration to adults who have inhalational exposure to*Bacillus anthracis*. The corresponding oral dosing regimen for children under 100 pounds (lb) is 1 mg per (/) lb of body weight (2.2 mg/kilogram (kg)), given twice daily for 60 days.

We have determined that IV doxycycline can be administered to adults in a 100 mg dose twice daily for inhalational anthrax (post-exposure). The corresponding IV dosing regimen for children under 100 lb is 1 mg /lb of body weight (2.2 mg/kg), twice daily. Intravenous therapy is indicated only when oral therapy is not indicated. Intravenous therapy should not be given over a prolonged period of time. Patients should be switched to oral doxycycline, or another antimicrobial drug product, as soon as possible, to complete a 60-day course of therapy.

[3] Friedlander, A. M. et al., ''Postexposure Prophylaxis Against Experimental Inhalation Anthrax,'' Journal of Infectious Diseases, 167:1239–1243, 1993.

A. Safety

Doxycycline drug products have been used for over 30 years, and the literature on the products is voluminous. We have reviewed the literature dealing with the long-term administration of doxycycline for treatment of diseases other than anthrax. Several articles report the results of studies involving the administration of doxycycline in amounts comparable to the doses recommended in this notice. They also involve administration of doxycycline for 60 days and periods approaching and exceeding 60 days. We have also reviewed data from our Adverse Event Reporting System (AERS). Analysis of these articles and data indicates no pattern of unlabeled adverse events has been associated with the long-term use of doxycycline.

Doxycycline and other members of the tetracycline class of antibiotics are not generally indicated for the treatment of any patients under the age of 8 years. Tetracyclines are known to be associated with teeth discoloration and enamel hypoplasia in children and delays in bone development in premature infants after prolonged use. We have balanced the nature of the effect on teeth and the fact that this delay in bone development is apparently reversible against the lethality of inhalational anthrax, and concluded that doxycycline drug products can be labeled with a pediatric dosing regimen for inhalational anthrax (post-exposure).

We are not recommending that IV doxycycline be administered for prolonged periods because of the possibility of thrombophlebitis and other complications of IV therapy. Thrombophlebitis as a possible adverse reaction is already described in the approved labeling for IV doxycycline drug products. Patients administered IV doxycycline for inhalational anthrax (post-exposure) should be switched to oral doxycycline or another antimicrobial drug product as soon as possible to complete a 60-day course of therapy.

B. Effectiveness

We have reviewed minimal inhibitory concentration (MIC) data for the tetracycline class and *Bacillus anthracis*, pharmacokinetic data, data from the Sverdlovsk incident, and the outcome data from a study of

inhalational exposure to *Bacillus anthracis* in rhesus monkeys.[4] We have concluded that 100 mg of doxycycline, administered twice a day for 60 days, is an effective dosing regimen for adults who have inhalational exposure to *Bacillus anthracis*. The corresponding dosing regimen for children under 100 lb of 1mg/lb of body weight (2.2 mg/kg), given twice daily for 60 days, is also effective.

C. Labeling for Oral Doxycyline

We encourage the submission of labeling supplements for orally administered doxycycline, doxycycline calcium, and doxycycline hyclate drug products. The revised labeling should contain a specific indication for inhalational anthrax (post-exposure), the recommended dosing regimen, safety information relevant to use in children, and other information described below. The following specific changes to the current approved labeling are recommended:

- *Indications and Usage*. The indication for anthrax should be revised from ''Anthrax due to *Bacillus anthracis*'' to ''Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.'' This indication should be removed from the paragraph of the ''Indications and Usage'' section that begins ''When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections:'' and inserted at the end of the preceding paragraph that begins ''Doxycycline is indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:.''
- *Warnings*. The last sentence in the first paragraph of the ''Warnings'' section should be revised to read as follows: ''TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.''
- *Dosage and Administration*. The following text should be inserted as the last item of the ''Dosage and Administration'' section:

''Inhalational anthrax (post-exposure):

ADULTS: 100 mg of doxycycline, by mouth, twice a day for 60 days.

CHILDREN: weighing less than 100 lb (45 kg); 1 mg/lb (2.2 mg/kg) of body weight, by mouth, twice a day for 60 days. Children weighing 100 lb or more should receive the adult dose.''

D. Labeling for IV Doxycycline

We encourage the submission of labeling supplements for doxycycline hyclate injectable drug products. The revised labeling should contain a specific indication for inhalational anthrax (post-exposure), the recommended dosing regimen, safety information relevant to use in children and prolonged use, and other information described below. We recommend that labeling supplements for doxycycline hyclate injectable drug products include the following specific changes:

- *Indications*. The indication for anthrax should be revised from''*Bacillus anthracis*'' to ''Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.'' This indication should be removed from the paragraph of the ''Indications'' section that begins ''When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to:'' and inserted at the end of the preceding paragraph that begins ''Doxycycline is indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:.''
- *Warnings*. The last sentence in the first paragraph of the ''Warnings'' section should be revised to read as follows: ''TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.''
- *Dosage and Administration*. The following paragraph should be inserted in the ''Dosage and Administration'' section after the paragraph describing the treatment for syphilis:

''In the treatment of inhalational anthrax (post-exposure) the recommended dose is 100 mg of doxycycline, twice a day. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.''

The following paragraph should be inserted in the ''Dosage and Administration'' section after the paragraph describing the dosages for children above 8 years of age:

''In the treatment of inhalational anthrax (post-exposure) the recommended dose is 1 mg/lb (2.2 mg/kg) of body weight, twice a day in children weighing less than 100 lb (45 kg). Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.''

IV. Penicillin G Procaine Drug Products

We have determined that 1,200,000 units of penicillin G procaine, administered every 12 hours, is an appropriate dosing regimen for adults who have inhalational exposure to *Bacillus anthracis*. The corresponding dosing regimen for children is 25,000 units/kg of body weight (maximum 1,200,000 units) every 12 hours.

A. Safety

Penicillin drug products have been used for over 50 years. The amount of literature on penicillin is correspondingly large. We have reviewed published literature on the safety of penicillin G procaine. We have also reviewed data from AERS. Analysis of these articles and data indicates that no pattern of unexpected adverse events is associated with the use of penicillin G procaine as described in the recommended dosing regimen. All adverse events that we have identified are described in the approved labeling. We note that there may be an increased risk of neutropenia and an increased incidence of serum sickness-like reactions associated with use of penicillin for more than 2 weeks. Because prescribing health care professionals should take those factors into consideration when continuing administration of penicillin G procaine for longer than 2 weeks for inhalational anthrax (post-exposure), we are suggesting that the labeling for the drug products reflect these concerns about neutropenia and serum sickness-like reactions.

B. Effectiveness

We have reviewed MIC data for penicillin G and *Bacillus anthracis*, pharmacokinetic data, data from the Sverdlovsk incident, clinical data regarding the use of penicillins in treatment of primarily cutaneous anthrax, and the outcome data from a study of inhalational exposure to *Bacillus anthracis* in rhesus monkeys.[5] We have concluded that the recommended dosing regimens are effective for adults and children who

[4] Friedlander.

[5] Friedlander.

have inhalational exposure to *Bacillus anthracis*.

C. Labeling

We encourage the submission of labeling supplements for penicillin G procaine injectable drug products. The revised labeling should contain a specific indication for inhalational anthrax (post-exposure), the recommended dosing regimen, safety information relevant to prolonged use and use in children, and other information described below. The following specific changes to the current approved labeling are recommended:

- *Indications.* In the ''Indications'' section, the indication for anthrax should be revised from ''Anthrax'' to ''Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of the disease following exposure to aerosolized *Bacillus anthracis*.''
- *Precautions*. In the ''Precautions'' section, at the end of the paragraph that begins ''In prolonged therapy with penicillin, and particularly with high-dosage schedules, periodic evaluation of the renal and hematopoietic systems is recommended,'' the following text should be added: ''In such situations, use of penicillin for more than 2 weeks may be associated with an increased risk of neutropenia and an increased incidence of serum sickness-like reactions.''
- *Dosage and Administration*. In the ''Dosage and Administration'' section, immediately following ''Anthrax—cutaneous: 600,000 to 1,000,000 units/day.'' the following text should be inserted:

''Anthrax—inhalational (post-exposure): 1,200,000 units every 12 hours in adults, 25,000 units per kilogram of body weight (maximum 1,200,000 unit) every 12 hours in children. The available safety data for penicillin G procaine at this dose would best support a duration of therapy of 2 weeks or less. Treatment for inhalational anthrax (post-exposure) must be continued for a total of 60 days. Physicians must consider the risks and benefits of continuing administration of penicillin G procaine for more than 2 weeks or switching to an effective alternative treatment.''

V. Conclusions

Drug products containing the following active ingredients are currently approved for administration in cases of inhalational anthrax:

- Doxycycline
- Doxycycline calcium
- Doxycycline hyclate
- Penicillin G procaine

We encourage the submission of labeling supplements for these drug products. The revised labeling should specifically mention inhalational anthrax (post-exposure), the recommended dosing regimen, safety information relevant to prolonged exposure (60 days or longer), and other information described in this notice. The requirement for data to support these labeling changes may be met by citing the published literature we relied on in publishing this notice. A list of the published literature and reprints of the reports will be available forpublic inspection in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. It is unnecessary to submit copies and reprints of the reports from the listed published literature. We invite applicants to submit any other pertinent studies and literature of which they are aware.

VI. Published Literature

The published literature we have relied on in making our recommendations will be placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. A list of this published literature will be on display in the Dockets Management Branch and on the Internet at www.fda.gov/cder/drug/infopage/penG_doxy/bibliolist.htm.

Dated: October 26, 2001.

Bernard A. Schwetz,

Acting Principal Deputy Commissioner.

[FR Doc. 01–27493 Filed 10–29–01; 4:35 pm]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Meeting

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the Advisory Committee to the Director, National Cancer Institute.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

Name of Committee: Advisory Committee to the Director, National Cancer Institute.

Date: November 20, 2001.

Time: 11 am to 1 pm.

Agenda: The purpose of the meeting will be to discuss the Gynecologic Cancers Progress Review, Group Report.

Place: National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Building 31, Room 11A03, Bethesda, MD 20892 (Telephone Conference Call).

Contact Person: Chitra Mohla, Executive Secretary, Office of Scientific Opportunities, National Cancer Institute, National Institutes of Health, Bldg. 31, Rm. 11A03, Bethesda, MD 20892, (301) 496–1458.

This notice is being published less than 15 days prior to the meeting due to scheduling conflicts.

Any interested person may file written comments with the committee by forwarding the statement to the Contact Person listed on this notice. The statement should include the name, address, telephone number and when applicable, the business or professional affiliation of the interested person.

Information is also available on the Institute's/Center's homepage: *deainfo.nci.nih.gov/advisory/joint/htm,* where an agenda and any additional information for the meeting will be posted when available.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research; 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)

Dated: October 26, 2001.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 01–27505 Filed 11–1–01; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Meeting

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the National Cancer Institute Director's Consumer Liaison Group.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

Name of Committee: National Cancer Institute Director's Consumer Liaison Group.

Date: November 8, 2001.

Time: 2 pm to 4 pm.