225.2(g) definition [2] but, in an effort to eliminate any possible confusion, the Commission makes the following correction: In the **Federal Register** published June 10, 1997, on page 31509, in the third column, in paragraph (2), replace ''as currently defined by FRB Rule 225.2(g)'' with ''as defined by FRB Rule 225.2(g) on April 20, 1997.''

Issued in Washington, D.C. on June 20, 1997 by the Commission.

Jean A. Webb,

Secretary of the Commission.

[FR Doc. 97–16625 Filed 6–24–97; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 314, and 600

[Docket No. 96N–0108]

Postmarketing Expedited Adverse Experience Reporting for Human Drug and Licensed Biological Products; Increased Frequency Reports

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations on expedited reporting of postmarketing adverse experiences to revoke the requirement for increased frequency reports as expedited reports for human drug and licensed biological products. This action, which is part of the President's regulatory reinvention initiative, is based on FDA's determination that expedited increased frequency reports have not contributed to the timely identification of safety problems requiring regulatory action and are no longer necessary for FDA surveillance of postmarketing adverse experiences. This action is intended to streamline postmarketing expedited reporting of adverse experiences for human drug and licensed biological products. This action will not affect the requirement for expedited reporting of all serious, unexpected adverse experiences.

EFFECTIVE DATE: July 25, 1997.

FOR FURTHER INFORMATION CONTACT:

For information concerning human drug products: Audrey A. Thomas, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5625.

For information concerning human licensed biological products: Marcel E. Salive, Center for Biologics Evaluation and Research (HFM–220), Food and Drug Administration, 1401 Rockville Pike, suite 200S, Rockville, MD 20852–1448, 301–827–3974.

SUPPLEMENTARY INFORMATION:

I. Background

Under current §§ 310.305(c)(4), 314.80(c)(1)(ii) and (c)(1)(iii), and 600.80(c)(1)(ii) and (c)(1)(iii) (21 CFR 310.305(c)(4), 314.80(c)(1)(ii) and (c)(1)(iii), and 600.80(c)(1)(ii) and (c)(1)(iii)), applicants, manufacturers, packers, and distributors, including licensed manufacturers and other manufacturers of biological products, are required to review periodically the frequency of reports of adverse experiences that are both serious and expected and reports of therapeutic failure (lack of effect), regardless of source, and report any significant increase in frequency as soon as possible but in any case within 15 working days of determining that a significant increase in frequency exists. An increased frequency exists if the adjusted reporting for the reporting interval is at least two times greater than the adjusted reporting for the comparison interval (previous reporting interval). These regulations were issued by FDA to ensure that applicants, manufacturers, packers, and distributors, including licensed manufacturers and other manufacturers of biological products, identify increases in the incidence of serious, labeled adverse experiences that are not anticipated from premarketing clinical trials and that occur with changes in medical practice, such as using a drug or biological product in higher risk populations, at higher dosages, or concomitantly with other drugs or biological products causing interactions.

In the **Federal Register** of October 28, 1996 (61 FR 55602), FDA proposed to amend its postmarketing expedited adverse experience reporting regulations to revoke the requirement for expedited increased frequency reports in §§ 310.305(c)(4), 314.80(c)(1)(ii) and (c)(1)(iii), and 600.80(c)(1)(ii) and (c)(1)(iii), and to revoke the definition of ''increased frequency'' in §§ 310.305(b)(5), 314.80(a), and 600.80(a). As explained in the proposal, FDA determined that increased frequency reports rarely prompted regulatory action during the time that the agency received such reports, and the reports proved to be of little value in identifying increased incidences of serious, labeled experiences. This action does not affect the requirement for expedited reporting of all serious, unexpected adverse experiences. Applicants, manufacturers, packers, and distributors, including licensed manufacturers and other manufacturers of biological products, must continue to submit 15-day Alert reports and followup reports for serious, unexpected events, as required under §§ 310.305(c), 314.80(c), 314.98, and 600.80(c).

II. Rationale

Several factors have contributed to FDA's decision to revoke the requirement for expedited increased frequency reports. Key factors include: (1) Safety problems that have been the subject of these reports could have been detected in other safety reports, (2) the reliability of increased frequency reports is limited, and (3) this action is consistent with recent international efforts to harmonize reporting requirements. These factors are discussed in more detail in the following paragraphs.

Only a small number of drug/biological product safety problems where expedited increased frequency reports played a role in risk assessment have resulted in regulatory action. In each case, the safety problems could have been detected in other safety reports required by FDA such as periodic adverse experience reports, field alert reports, or annual reports. FDA has found that expedited postmarketing adverse experience reporting systems are best used to identify rare, unexpected adverse drug reactions such as aplastic anemia, hepatic necrosis, renal failure, or anaphylaxis that were not detected in preclinical studies or clinical trials during drug development.

The reliability of increased frequency reports is limited because of the difficulty in accurately estimating incidence rates. Increased frequency information is derived from incidence rates, which are estimated by dividing

[2] The following were ''institutional customers'' under the FRB rule:

(1) a bank (acting in an individual or fiduciary capacity), savings and loan association, insurance company, investment company registered under the ICA, or corporation, partnership, proprietorship, organization or institutional entity with a net worth exceeding $1,000,000;

(2) an employee benefit plan with assets exceeding $1,000,000, or whose investment decisions are made by a bank, insurance company or investment adviser registered under the Investment Advisers Act of 1940;

(3) a natural person whose net worth (or joint net worth with a spouse) exceeds $1,000,000;

(4) a broker-dealer or option trader registered under the SEA, or other securities, investment or banking professional; or

(5) an entity whose equity owners are institutional customers.

the number of adverse experiences by the number of persons exposed to a drug or biological product. Reporters compare incidence rates estimated for the reporting interval with rates estimated for the previous reporting interval. However, a number of uncertainties contribute to the unreliability of incidence rates. For example, health care providers do not report all adverse experiences or may report them to the sponsor many months after they became aware of them. The number of persons exposed to a drug or biological product during a reporting period is not precisely known; it is only estimated based on sales or production data. The lag time between production or sales by the manufacturer and consumption by patients can vary, adding further distortion to comparisons between reporting periods. Finally, because of incomplete data and the uncertainty caused by the underlying illness, indication, or other drug exposures, adverse experience reports may be attributed to a drug or biological product even though it may not necessarily have caused the adverse experience.

FDA's decision to revoke the requirement for expedited increased frequency reports is also consistent with recent international harmonization initiatives. In the **Federal Register** of October 27, 1994 (59 FR 54046), FDA proposed amending, among other things, its regulations for periodic postmarketing reporting of adverse experiences for human drug and licensed biological products based on recommendations developed by the World Health Organization's Council for International Organizations of Medical Sciences (CIOMS) Working Group II. The revised regulations would include a section for overall safety evaluation that would contain a critical analysis and full discussion of the safety information provided in the periodic report as it pertains to a number of matters, including increased frequencies of known toxicity. Recently, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) developed, based on the CIOMS II proposals, a final guideline for periodic reporting entitled ''Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.'' The guideline, published in the **Federal Register** of May 19, 1997 (62 FR 27470), recommends that the overall safety evaluation section of periodic safety update reports highlight any new information on increased frequencies of known adverse drug reactions, including comments on whether it is believed that these data reflect a meaningful change in adverse drug reaction occurrences. Under this guideline, regulatory authorities will be able to obtain reports of increased frequencies from periodic reports. FDA plans to finalize its proposed amendments to the periodic postmarketing safety reporting regulations in a future issue of the **Federal Register**. These amendments will be based on the CIOMS and ICH recommendations.

III. Comments on the Proposed Rule

The agency received five comments from industry and the public. All of the comments supported FDA's decision to revoke the requirement for expedited increased frequency reports, stating that these reports have not contributed to timely identification of safety problems requiring regulatory action, nor to information for physicians or patient care. All of the comments expressed the belief that because serious and unexpected reports of adverse experiences are investigated and reported under the 15-day Alert report requirement and because overall safety and adverse experience data are summarized in periodic reports, FDA's action to revoke the requirement of increased frequency reports will result in the elimination of resource intensive procedures and provide industry with more time to focus on evaluation of serious and unexpected adverse drug experiences and other important medical product events.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Paperwork Reduction Act of 1995

This final rule does not require information collections and, thus, is not subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (Pub. L. 104–13).

VI. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this final rule will simplify and streamline current requirements, the Commissioner of Food and Drugs certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 310, 314, and 600 are amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.305 is amended by revising paragraph (a), by removing paragraph (b)(5), by removing paragraph (c)(4), by redesignating paragraphs (c)(5) and (c)(6) as paragraphs (c)(4) and (c)(5),

respectively, by revising the first sentence of newly redesignated paragraph (c)(4), and by revising paragraph (f)(1) to read as follows:

§ 310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.

(a) *Scope.* FDA is requiring manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application to establish and maintain records and make reports to FDA of all serious, unexpected adverse drug experiences associated with the use of their drug products.

* * * * *

(c) * * *

(4) To avoid unnecessary duplication in the submission of, and followup to, reports required in this section, a packer's or distributor's obligations may be met by submission of all reports of serious adverse drug experiences to the manufacturer of the drug product. * * *

* * * * *

(f) *Recordkeeping.* (1) Each manufacturer, packer, and distributor shall maintain for a period of 10 years records of all adverse drug experiences required under this section to be reported, including raw data and any correspondence relating to the adverse drug experiences, and the records required to be maintained under paragraph (c)(4) of this section.

* * * * *

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

3. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

4. Section 314.80 is amended by removing the definition for *Increased frequency* in paragraph (a), by removing paragraph (c)(1)(ii), by redesignating paragraphs (c)(1)(iii) and (c)(1)(iv) as paragraphs (c)(1)(ii) and (c)(1)(iii), respectively, by revising the first two sentences in the introductory text of newly redesignated paragraph (c)(1)(ii), by removing the last sentence in paragraph (d)(1), by revising paragraph (f)(1), and by revising the last sentence in paragraph (l) to read as follows:

§ 314.80 Postmarketing reporting of adverse drug experiences.

* * * * *

(c) * * *

(1) * * *

(ii) The requirements of paragraph (c)(1)(i) of this section, concerning the submission of 15-day Alert reports, shall also apply to any person (other than the applicant) whose name appears on the label of an approved drug product as a manufacturer, packer, or distributor. However, to avoid unnecessary duplication in the submission to FDA of, and followup to, reports required by paragraph (c)(1)(i) of this section, obligations of a nonapplicant may be met by submission of all reports of serious adverse drug experiences to the applicant. * * *

* * * * *

(f) *Reporting Form FDA–1639.* (1) Except as provided in paragraph (f)(3) of this section, the applicant shall complete a Form FDA–1639 (Adverse Reaction Report) for each report of an adverse drug experience.

* * * * *

(l) * * * For purposes of this provision, the term ''applicant'' also includes any person reporting under paragraph (c)(1)(ii) of this section.

* * * * *

PART 600—BIOLOGICAL PRODUCTS: GENERAL

5. The authority citation for 21 CFR part 600 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 519, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374); secs. 215, 351, 352, 353, 361, 2125 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25).

6. Section 600.80 is amended by removing the definition for *Increased frequency* in paragraph (a), by removing paragraph (c)(1)(ii), by redesignating paragraphs (c)(1)(iii) and (c)(1)(iv) as paragraphs (c)(1)(ii) and (c)(1)(iii), respectively, by revising the first sentence in the introductory text of newly redesignated paragraph (c)(1)(ii), by removing the last sentence in paragraph (d)(1), by revising paragraph (f)(1), and by revising the last sentence in paragraph (m) to read as follows:

§ 600.80 Postmarketing reporting of adverse experiences.

* * * * *

(c) * * *

(1) * * *

(ii) The requirements of paragraph (c)(1)(i) of this section, concerning the submission of 15-day Alert reports, shall also apply to any person other than the licensed manufacturer of the final product whose name appears on the label of a licensed biological product as a manufacturer, packer, distributor, shared manufacturer, joint manufacturer, or any other participant involved in divided manufacturing.

* * *

* * * * *

(f) *Reporting forms.* (1) Except as provided in paragraph (f)(3) of this section, the licensed manufacturer shall complete the reporting form designated by FDA (FDA–3500A, or, for vaccines, a VAERS form) for each report of an adverse experience.

* * * * *

(m) * * * For purposes of this provision, this paragraph also includes any person reporting under paragraph (c)(1)(ii) of this section.

Dated: June 19, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–16684 Filed 6–20–97; 3:54 pm]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 520

Oral Dosage Form New Animal Drugs; Gentamicin Sulfate Oral Solution

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of an abbreviated new animal drug application (ANADA) filed by Med-Pharmex, Inc. The ANADA provides for the use of gentamicin sulfate oral solution for the control and treatment of colibacillosis in weanling swine and for the control and treatment of swine dysentery caused by *Treponema hyodysenteriae*.

EFFECTIVE DATE: June 25, 1997.

FOR FURTHER INFORMATION CONTACT: Lonnie W. Luther, Center for Veterinary Medicine (HFV–102), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–0209.

SUPPLEMENTARY INFORMATION: Med-Pharmex, Inc., 2727 Thompson Creek Rd., Pomona, CA 91767, has filed ANADA 200–190, which provides for the control and treatment of colibacillosis in weanling swine caused by strains of *Escherichia coli* sensitive to gentamicin, and for the control and treatment of swine dysentery associated with *T. hyodysenteriae*.