Drug labeler code	Firm name and address
* * *	* * * *
038782	K. C. Pharmacal, Inc., 8345 Melrose Dr., Lenexa, KS 66214
* * *	* * * *

Dated: September 4, 1997.

George A. Mitchell,

Acting Director, Center for Veterinary Medicine.

[FR Doc. 97–24736 Filed 9–17–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 524

Ophthalmic and Topical Dosage Form New Animal Drugs; Cyclosporine

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 a supplemental new animal drug application (NADA) filed by Schering-Plough Animal Health. The supplemental NADA provides for use of cyclosporine ophthalmic ointment on dogs for management of chronic superficial keratitis (CSK) and changing the approved label claim to management of chronic keratoconjunctivitis sicca (KCS).

EFFECTIVE DATE: September 18, 1997.

FOR FURTHER INFORMATION CONTACT: Melanie R. Berson, Center for Veterinary Medicine (HFV–110), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1612.

SUPPLEMENTARY INFORMATION: Schering-Plough Animal Health, Schering-Plough Corp., P.O. Box 529, Kenilworth, NJ 07033, has filed supplemental NADA 141–052 Optimmune® (cyclosporine) ophthalmic ointment that provides for use on dogs for the management of chronic superficial keratitis (CSK) and changing the approved label claim from treatment to management of chronic keratoconjunctivitis sicca (KCS) in dogs. The term management reflects the complexity of the therapy for the diseases. The drug is limited to use by or on the order of a licensed veterinarian. The supplement is approved as of August 26, 1997, and the regulations are revised in 21 CFR 524.575(c)(2) to reflect the approval. The basis of approval is discussed in the freedom of information summary.

In accordance with the freedom of information provisions of 21 CFR part 20 and 514.11(e)(2)(ii), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for use in nonfood-producing animals qualifies for 3 years of marketing exclusivity beginning August 26, 1997, because the supplemental application contains substantial evidence of the effectiveness of the drug involved, studies of animal safety or, in the case of food-producing animals, human food safety studies (other than bioequivalence or residue studies) required for approval of the application and conducted or sponsored by the applicant. The 3 years of marketing exclusivity applies only to the new indication for management of CSK in dogs.

FDA has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. FDA's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above).

List of Subjects in 21 CFR Part 524

Animal drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 524 is amended as follows:

PART 524—OPHTHALMIC AND TOPICAL DOSAGE FORM NEW ANIMAL DRUGS

1. The authority citation for 21 CFR part 524 continues to read as follows:

Authority: Sec. 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b).

2. Section 524.575 is amended by revising paragraph (c)(2) to read as follows:

§ 524.575 Cyclosporine ophthalmic ointment.

* * * * *

(c) * * *

(2) *Indications for use.* For management of chronic keratoconjunctivitis sicca (KCS) and chronic superficial keratitis (CSK) in dogs.

* * * * *

Dated: September 10, 1997.

Michael J. Blackwell,

Deputy Director, Center for Veterinary Medicine.

[FR Doc. 97–24850 Filed 9–17–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 812

[Docket No. 96N–0299]

Investigational Device Exemptions; Treatment Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is establishing procedures to allow for the treatment use of investigational devices. These procedures are intended to facilitate the availability of promising new therapeutic and diagnostic devices to desperately ill patients as early in the device development process as possible, i.e., before general marketing begins, and to obtain additional data on the device's safety and effectiveness. These procedures apply to patients with serious or immediately life-threatening diseases or conditions for which no comparable or satisfactory alternative device, drug, or other therapy exists.

DATES: The regulation is effective January 16, 1998.

FOR FURTHER INFORMATION CONTACT: Joanne R. Less, Office of Device Evaluation (HFZ–403), Center for Devices and Radiological Health (CDRH), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–1190.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of May 22, 1987 (52 FR 19466), FDA published a final rule that codified procedures authorizing the treatment use of investigational new drugs (IND's) (hereinafter referred to as the treatment IND regulation). In publishing the treatment IND regulation, FDA was responding to an increased demand from patients as well as from health professionals to permit broader availability of investigational drugs to treat serious diseases for which there were no satisfactory alternative treatments. For similar reasons, in the **Federal Register** of December 19, 1996 (61 FR 66954), FDA proposed to amend its Investigational Device Exemptions (IDE) regulation (part 812 (21 CFR part 812)) to allow for the treatment use of investigational devices (hereinafter referred to as the treatment IDE regulation). With minor exceptions, the proposal paralleled the treatment IND regulation and extended those provisions to cover the treatment use of investigational devices, including diagnostic devices. The final rule generally codifies the proposal, with some exceptions discussed below. Similar to the proposed rule, this final rule is intended to facilitate the availability of promising new devices to patients as early in the device development process as possible while safeguarding against commercialization of the device and ensuring the integrity of controlled clinical trials.

FDA received six comments on the proposed rule. These comments were from an institutional review board (IRB), a medical device consultant, a medical device manufacturers' association, a medical device manufacturer, an association of surgeons, and a consumer. The comments generally supported the agency's proposal to provide for expanded access to investigational devices under a treatment IDE. A number of comments sought clarification of specific points, or responded to specific questions raised in the preamble to the proposed rule. No comments opposed codification of the treatment procedures. Interested persons were given until March 19, 1997, to comment on the proposed rule.

II. Highlights of the Final Rule

FDA has retained the basic framework of the proposed rule. Treatment use of an investigational device will be considered when: (1) The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition; (2) there is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population; (3) the device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and (4) the sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

Each application for treatment use shall include, among other things, an explanation of the rationale for the use of the device; the criteria for patient selection; a description of clinical procedures; laboratory tests, or other measures to be used to monitor the effects of the device and to minimize risk; written procedures for monitoring the treatment use; information that is relevant to the safety and effectiveness of the device for the intended treatment use; and a written protocol describing the treatment use.

Treatment use may begin 30 days after FDA receives the treatment IDE submission, unless FDA notifies the sponsor earlier than 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed, approve it with modification, disapprove it, or withdraw approval of the treatment IDE if FDA finds that certain criteria are satisfied.

Safeguards for treatment use of an investigational device include the: Distribution of the device through qualified experts; maintenance of adequate manufacturing facilities; the submission of certain reports; and compliance with the regulations governing informed consent and institutional review boards (IRB's).

The sponsor of a treatment IDE shall submit progress reports to all reviewing IRB's and FDA and shall be responsible for submitting all other reports required under § 812.150.

In response to comments, FDA has made the following changes in the final rule.

FDA has streamlined the reporting requirements in § 812.36(f). First, FDA decreased the frequency with which sponsors must submit progress reports under § 812.36(f). Under the final rule, the sponsor of a treatment IDE is required to submit progress reports on a semi-annual basis, rather than quarterly, to all reviewing IRB's and FDA. Upon filing of a marketing application, the requirement for progress reports is further reduced to annual reporting in accordance with § 812.150. Second, FDA limited the type of information that is to be submitted in a progress report. Under the final rule, these reports are required to include only the number of patients treated with the device under the treatment IDE, the names of the investigators participating in the treatment IDE, and a brief description of the sponsor's efforts to pursue marketing approval/clearance of the device.

FDA has modified the rule with respect to cost recovery by adding new § 812.36(c)(1)(x). In accordance with this provision, if the device is to be sold, the price to be charged is to be based on manufacturing and handling costs only. This decision was based on the fact that under the general IDE, sponsors are permitted to recover, among other costs, research and development costs. Because the research and development expenditures already are being recovered under the general IDE, FDA concluded that cost recovery under the treatment IDE should be limited to that of supplying the device for the treatment use, i.e., manufacturing and handling costs.

FDA is clarifying the final rule to state that treatment use must be for the same use as that studied under an approved IDE. The preamble to the proposed rule addressed this point at 61 FR 66954 at 66955, column 3, and FDA believes it is important to include it in the codified language. See § 812.36(b)(3). This change reflects the fact that it is those indications studied in the controlled clinical trial for which the agency would have the preliminary evidence of safety and effectiveness needed to support the treatment use.

III. Summary and Analysis of Comments and FDA's Responses

A. General Comments

1. One comment stated that the example FDA provided in the preamble to the proposed rule of an approved device that would have met the treatment IDE criteria, i.e., nonthoracotomy (transvenous) defibrillation leads, was inappropriate. According to the comment, unless patients in need of such leads had a complicating disease or condition that prevented surgery, the surgical placement of approved defibrillation leads would have been a satisfactory alternative to the nonthoracotomy (transvenous) defibrillation leads. The

comment stated that placement of the transvenous leads may present less risk to the patient than the surgical placement of defibrillation leads. The comment noted, however, that the regulation does not incorporate risk considerations. If the intent of the regulation is to permit the use of a device based on risk, then the comment suggested that § 812.36(b)(2) be rewritten to include risk-benefit considerations.

FDA agrees that risk/benefit considerations should be part of treatment IDE decisionmaking, but believes that the agency has already addressed this concern adequately in the criteria established under § 812.36(b)(1) and (b)(2), in conjunction with the bases for disapproval or withdrawal of a treatment IDE under § 812.36(d)(2)(iii) and (d)(2)(iv). In the example FDA provided, clinical data from the general IDE showed that nonthoracotomy (transvenous) defibrillation leads addressed an unmet medical need in a defined patient population, i.e., those patients with postradiation mediastinal fibrosis who could not undergo surgical placement of the approved defibrillation leads. FDA's evaluation of a treatment IDE in this context would necessarily include full consideration of the potential risks and benefits of the device, given the clinical and other scientific information known to date, in light of the seriousness of the disease or condition and availability of alternative therapies.

In addition, FDA notes that once a treatment IDE is made available generally, there still remains a risk/benefit consideration for individual patients within the intended patient population. In this situation, the physician and patient would need to decide, based on the available clinical information and the individual patient's condition, whether the treatment use device would expose that patient to an acceptable level of risk. This is a case-by-case decision to be made by the doctor and the patient.

2. A comment stated that the preamble to the proposed rule could be improved by providing fewer ''disease'' examples, and providing more examples of surgical uses, implants, or injury/accident references, where devices might be utilized.

In response to the recommendation, the agency is providing the following examples to better explain when a treatment IDE would be appropriate.

One example of an approved device that would have met the treatment use criteria is an interactive wound and burn dressing indicated for use as a temporary covering for surgically excised full-thickness and deep partial-thickness thermal burns in patients who require such a temporary covering prior to autograft placement. This device would have met the treatment IDE criteria because: (1) The device is intended to treat immediately life-threatening conditions, i.e., full-thickness and deep partial-thickness thermal burns; (2) there were no comparable or satisfactory alternative devices (the only alternative therapy (cadaver skin) is severely limited in supply and has a risk of disease transmission); (3) the device was under investigation in a controlled clinical trial for the same use under an approved IDE; and (4) the sponsor of the controlled clinical trial was pursuing marketing approval of the device with due diligence.

Another example of an approved device that would have met the treatment use criteria is the low density lipoprotein (LDL) apheresis system indicated for use in performing low density lipoprotein cholesterol (LDL–C) apheresis to acutely remove LDL–C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated: functional hypercholesterolemic homozygotes with LDL–C > 500/mg/dl; functional hypercholesterolemic heterozygotes with LDL–C ≥ 300 mg/dl; and functional hypercholesterolemic heterozygotes with LDL–C ≥ 200 mg/dl and documented coronary heart disease. This device would have met the treatment IDE criteria because: (1) The device is intended to treat serious conditions, i.e., functional hypercholesterolemic homozygotes/heterozygotes with certain LDL–C levels; (2) there were no comparable or satisfactory alternative devices (the only alternative therapies available to treat these high risk patients are diet, which can be ineffective, and maximum drug therapy, which can be either ineffective or not tolerated); (3) the device was under investigation in a controlled clinical trial for the same use under an approved IDE; and (4) the sponsor of the controlled clinical trial was pursuing marketing approval of the device with due diligence.

Again, these are illustrative examples only.

3. Two comments requested that FDA discuss the differences and relationships among treatment IDE's, emergency use devices, the Office of Device Evaluation's (ODE) memorandum on ''Continued Access to Investigational Devices During Premarket Approval Application (PMA) Preparation and Review,'' expedited review, and custom devices. One of the comments recommended that CDRH issue separate guidance delineating the differences and relationships among these policies/regulations.

With the exception of custom devices, FDA has issued guidance on all of the topics identified in the previous comments. The agency has provided the following summary of each of these policies and has also identified key similarities and differences between them and the treatment IDE regulation.

1. ''Guidance for the Emergency Use of Unapproved Medical Devices''

Under FDA's ''Guidance for the Emergency Use of Unapproved Medical Devices'' (hereinafter referred to as the Emergency Use Policy), that appeared in the **Federal Register** of October 22, 1985 (50 FR 42866), an unapproved medical device is a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360e) or an approved IDE under section 520(g) of the act (21 U.S.C. 360j(g)). Normally, an unapproved device may be used in human subjects only if it is approved for clinical testing under an IDE. Emergency use of an unapproved device, however, may occur when an IDE for the device does not exist, when a physician wants to use the device in a way not approved under the IDE, or when a physician or institution is not approved under the IDE.

The Emergency Use Policy is different from the treatment IDE regulation in significant ways. First, the Emergency Use Policy is designed for just that—emergencies—and is applied on an individual patient basis. To qualify for emergency use, the treating physician must conclude that: (1) The patient has a life-threatening condition that needs immediate treatment; (2) no generally acceptable alternative treatment for the condition exists; and (3) there is no time to obtain FDA approval due to the immediate need of the patient.

By contrast, treatment use of an investigational device is designed to operate prospectively under a protocol that may cover a large number of patients, so that a treatment IDE application would be submitted to and approved by the agency before patients are treated with the device. Also, the Emergency Use Policy is limited to life-threatening situations, whereas a treatment IDE allows use of the device for serious diseases in addition to those that are immediately life-threatening.

2. ''Continued Access to Investigational Devices During Premarket Approval Application (PMA) Preparation and Review''

Under ODE's policy entitled ''Continued Access to Investigational Devices During PMA Preparation and Review'' (hereinafter referred to as the Continued Access Policy), sponsors of clinical investigations are permitted to continue to enroll subjects while a marketing application is being prepared by the sponsor or reviewed by ODE if there is: (1) A public health need for the device; or (2) preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication. By allowing sponsors to continue to enroll patients while a marketing application is being prepared and/or reviewed, the Continued Access Policy allows increased patient access and the collection of additional safety and effectiveness data to support the marketing application or address new questions regarding the investigational device. The Continued Access Policy may be applied to any clinical investigation that meets the criteria identified above; however, it is intended to be applied late in the device development process, i.e., after the controlled clinical trial has been completed.

There is significant overlap between the treatment IDE regulation and the Continued Access Policy. Both the Continued Access Policy and the treatment IDE regulation are intended to provide additional access to an unapproved device, once preliminary evidence regarding safety and effectiveness is available to FDA. However, because a treatment IDE can be submitted earlier in the IDE process, i.e., once promising evidence of safety and effectiveness has been collected under the IDE but while the clinical study is ongoing, it could provide access to a wider group of patients at an earlier stage in the IDE process. The treatment IDE regulation also has a more narrow application than the Continued Access Policy in that treatment use is intended to address only those patients who have an immediately life-threatening or serious disease or condition whereas the Continued Access Policy, which is applied later in the process, may be considered for any clinical study.

3.''PMA/510(k) Expedited Review''

According to ODE's ''PMA/510(k) Expedited Review'' policy (hereinafter referred to as the Expedited Review Policy), expedited review of a marketing application may be considered for a device intended for or meeting at least one of the following criteria: (1) Life-threatening or irreversibly debilitating condition with no alternative modality. The condition or potential condition/disease is serious or life-threatening or presents a risk of serious morbidity and no alternative legally marketed diagnostic/therapeutic modality exists; (2) life-threatening or irreversibly debilitating condition with approved alternatives, but where the new device provides for clinically important earlier diagnosis or significant advances in safety and/or effectiveness over the existing alternatives; (3) a revolutionary (breakthrough) device, i.e., the device represents a clear clinically meaningful advantage over existing technology defined as having a major increase in effectiveness or reduced risk compared to existing technology; and (4) a specific public health benefit, i.e., the availability of the device is otherwise in the best interest of the public health.

Under the Expedited Review Policy, granting expedited review ensures that the marketing application will receive priority review, i.e., review before other pending PMA's or 510(k)s. Therefore, the Expedited Review Policy differs from the treatment IDE regulation in that expedited review pertains to the review priority given to marketing applications, whereas treatment use pertains to expanding access to patients of a device during the course of the clinical investigation.

As stated previously, FDA intends to interpret the criteria for treatment IDE's in the same way CDRH applies the criteria for expedited review of marketing applications. FDA anticipates that most requests for treatment use would involve devices that meet the criteria for expedited review, i.e., the device: (1) Is intended for a life-threatening or irreversibly debilitating condition for which there is no alternative therapy or for which the device provides a significant advance in safety and effectiveness over the existing alternatives; or (2) meets a specific public health need. These criteria are similar because the same public health considerations that justify expanding access to an investigational product also justify giving a marketing application for that device top priority. In both cases, the likely patient benefit warrants special policies.

4. Custom Devices

FDA has not issued a guidance document concerning custom devices, but a custom device is defined in § 12.3(b). A custom device is one that:

(1) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist; (2) is not generally available to, or generally used by, other physicians or dentists; (3) is not generally available in finished form for purchase or for dispensing upon prescription; (4) is not offered for commercial distribution through labeling or advertising; and (5) is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.

Because all the preceding criteria must be met for a device to qualify as a custom device and because the use of a custom device is exempt from the IDE regulation (§ 812.2(c)(7)), the provision usually covers only a single device and is not frequently applicable.

FDA believes that the existing guidance documents on these topics, together with the preceding discussion, satisfies the concern raised in the comment.

4. One comment suggested that FDA add a reference to the Emergency Use Policy to permit shipment of devices in emergency situations such as those in 21 CFR 312.36. The same comment asked FDA to clarify that IRB review is not necessary in the case of emergency use for a single patient.

Emergency use for a single patient is governed by FDA's Emergency Use Policy. As noted previously in the Emergency Use Policy, an unapproved device may be shipped without FDA approval to a physician who is faced with an emergency situation that meets the outlined criteria.

The comment's request for clarification regarding IRB review in the case of an emergency use for a single patient is also addressed in the Emergency Use Policy. Under this guidance, in the event that a device is needed to treat a life-threatening disease or condition, FDA would expect the physician to follow as many patient protection procedures as possible. These include, among other things, obtaining the IRB chairperson's concurrence and complying with the institution's requirements regarding such use. Therefore, IRB approval for emergency use would only be required if such review were necessary under the procedures of that particular institution.

5. One comment raised a concern that the treatment IDE review procedures and reporting requirements will create additional work that will delay FDA's review of PMA's.

FDA disagrees. As stated in the preamble to the proposed, FDA anticipates a limited number of treatment IDE's and has estimated it is

likely to receive six annually. (See 61 FR 66954 at 66959.) Although these treatment IDE's will create additional work for the agency, such a limited number will not cause delays in FDA's review of PMA's. Moreover, in the 10 years since the treatment IND rule was issued, the agency has not experienced delays in the review of new drug applications due to the additional work created by the treatment IND review procedures and reporting requirements.

B. Specific Comments

1. A comment noted that § 812.36(a) defines an ''immediately life-threatening disease or condition,'' but does not define a ''serious disease or condition.'' The comment asserted that the term ''serious'' disease or condition should either be defined in or omitted from the regulation because it is likely to be a ''gray area'' with regard to interpretation of the regulation. The comment preferred that the term ''serious'' be omitted because the diseases intended to be included under this definition, i.e., early stages of breast cancer, proliferative vitreoretinopathy, and advanced Parkinson's disease, would meet the definition of an ''immediately life-threatening disease or condition.''

FDA does not intend to add a definition of ''serious disease or condition'' to the final rule. The agency has concluded that defining the term ''serious disease or condition'' could be unduly restrictive and limit the agency's discretion when determining whether certain stages of a disease or condition are ''serious.'' In addition, the agency's experience under the treatment IND regulation demonstrates that a definition is unnecessary; the agency has been successful in identifying the serious diseases or conditions appropriate to treatment IND even though the term is undefined in that regulation. If a sponsor is not sure of whether a particular stage of a disease or condition would be considered ''serious,'' the sponsor should contact the appropriate review division in ODE for clarification.

FDA did not omit the term ''serious disease or condition'' from the regulation because, contrary to the comment's assertion, the diseases or conditions intended to be included under the serious disease or condition definition would not meet the definition of immediately life-threatening disease or condition in all circumstances. For example, advanced Parkinson's disease would normally be considered a serious disease or condition rather than an immediately life-threatening disease state, i.e., there is not a reasonable likelihood that death will occur within a matter of months nor is premature death likely without early treatment.

2. One comment stated that the definition of ''immediately life-threatening disease or condition'' is severe in its limitations. As a result, the comment suggested that FDA adopt the definition used for expedited review, i.e., a condition or disease that is irreversibly debilitating with no alternative treatment modalities or meets a specific public health need. The comment believed that this would cover serious disease states but not restrict those diseases to those likely to result in imminent death. The comment stated that this definition is appropriate because FDA intends to interpret the criteria for treatment use IDE's in the same way FDA applies the criteria for expedited review of PMA's.

FDA disagrees with the recommendation to modify the definition of ''immediately life-threatening disease or condition.'' As stated in the preamble to the proposed rule, with minor exceptions, the treatment IDE regulation parallels the treatment IND regulation and extends those provisions to cover treatment use of investigational devices. FDA does not believe that this definition will be problematic in light of the fact that FDA is adopting the same definition in the treatment IDE regulation that is used in the treatment IND regulation. Since the implementation of the treatment IND regulation in 1987, FDA has not had any experience that would indicate that the definition is severe in its limitations. The agency also believes that adopting the same definition of immediately life-threatening disease or condition in both treatment regulations will promote consistency.

3. One comment recommended that FDA expand the definition of an ''immediately life-threatening disease or condition'' to include diseases or conditions that threaten the integrity of the nervous system. According to the comment, an investigational device might prevent devastating neurological illness even though death is not imminent.

FDA disagrees with expanding the definition of immediately life-threatening disease or condition to include neurological illnesses not resulting in imminent death because the agency intended that such illnesses be included under the definition of a serious disease or condition. For example, as stated in the proposed rule, advanced Parkinson's disease, which causes severe neurological impairment, would be considered a serious disease or condition appropriate for a treatment IDE. (See 61 FR 66954 at 66955.) Likewise, advanced multiple sclerosis would also be considered a serious disease or condition because, although it does not result in imminent death, it causes severe neurological impairment.

4. A comment requested that § 812.36(b)(3) be clarified to read that patients who were in the ''parent'' controlled clinical trial under the approved IDE be allowed to continue under the treatment IDE, after the parent controlled clinical trial has been completed, but before FDA approval is received. The comment referred to the July 15, 1996, memorandum entitled, ''Continued Access to Investigational Devices During Premarket Approval Application (PMA) Preparation and Review.''

FDA agrees that patients who were originally enrolled in the ''parent'' controlled clinical trial, which is now complete, could qualify for continued access to the device under the Continued Access Policy described in section III.A.2 of this document. The agency does not believe a change to the regulation is needed to accommodate this situation.

5. In the preamble to the proposed rule in § 812.36(e), FDA solicited comments on the appropriate approach to take with respect to charging for devices under treatment IDE's. (See 61 FR 66954 at 66958.) Specifically, FDA posed the following questions in connection with § 812.36(e):

1. Do the IDE and Treatment IDE Regulations Provide Sufficient Protection Against Commercialization?

FDA received one comment, which stated that the IDE regulation, the proposed rule on treatment IDE's, market forces, and expedited review procedures, where appropriate, protect against commercialization of devices distributed under IDE's or treatment IDE's. First, according to the comment, §§ 812.40 and 812.43 and proposed § 812.36(e) limit distribution of investigational devices by ensuring that only qualified investigators receive the device. Failure of the manufacturer to control distribution often draws attention from competitors who report such violations to FDA, thus adding an additional commercialization control element. Secondly, the comment pointed out that § 812.7(c) and proposed § 812.36(e) prohibit sponsors from unduly prolonging an investigation. Thirdly, according to the comment, proposed § 812.36(f) adds another layer of control over commercialization of treatment investigational devices by requiring sponsors to provide a description of their efforts to pursue marketing approval/clearance of the device in the progress reports which are

to be submitted to both FDA and the IRB's. Finally, the comment noted that if a device meets the criteria for a treatment IDE, it will also meet the criteria for expedited review of PMA's. Accordingly, the comment suggested that in cases where a treatment IDE is approved, expedited review of the PMA should be automatically granted. Expedited reviews should add another layer of control against clinical trial prolongation once the trial has been completed and the PMA is pending because it is anticipated that the PMA would be reviewed more quickly.

FDA agrees that the IDE and treatment IDE regulations should provide sufficient protection against commercialization of the investigational device. In the general IDE regulation, § 812.7(c) prohibits sponsors from unduly prolonging an investigation, § 812.43(b) limits distribution of the investigational device to qualified investigators, and § 812.150(b)(5) requires the submission of progress reports to FDA and the IRB's. Under § 812.36(e), sponsors of treatment IDE's are subject to all of the requirements of the general IDE regulation. Sponsors of treatment IDE's are also subject to § 812.36(f), which requires sponsors to describe their efforts to pursue marketing approval/clearance of the device in their progress reports.

2. Is It Appropriate for Sponsors to Recover Research and Development Costs in Addition to the Costs of Manufacturing and Handling of an Investigational Device?

One comment stated that it is not appropriate for sponsors to recover research and development costs when charging for devices under a treatment IDE because the assignment of such costs to the limited number of devices under the treatment IDE will result in the device being extremely costly and, therefore, not used. The comment also stated that delaying recovery of the research and development costs until device approval will provide an incentive for the sponsor to obtain such approval.

Three other comments stated that sponsors should be able to recover research and development costs as well as manufacturing and handling costs, as is the case with IDE's in general. According to two of the comments, not allowing sponsors to recover these costs will result in a reduction of the number of IDE's and treatment IDE's. One of the comments noted that charging a lower price for a device under a treatment IDE than under the IDE in general could dissuade sponsors from submitting treatment IDE applications. According to the second comment, the majority of devices that would be under treatment IDE's are breakthrough technologies developed by small start-up and medium sized companies, which often depend upon venture capital to develop new devices. The comment further asserted that these companies cannot afford the costs of a clinical trial unless they are compensated. Alternatively, the comment noted that larger companies may opt not to apply for an IDE or treatment IDE if the costs of research, development, manufacturing, and handling as well as the expense of the trial itself cannot be adequately recovered by postapproval sales.

Upon consideration of the comments, FDA has decided that it is not appropriate for sponsors to recover research and development costs under treatment IDE's. FDA acknowledges that the investment cost of developing a device may be high and that the actual cost recovered by the sponsor may be a factor in proceeding with development of the device. (See 43 FR 20726 at 20742.) Nevertheless, it is a well-established principle, that no profit should be made on experimental devices. (See 45 FR 3732 at 3741, January 18, 1980; Medical Devices; Procedures for IDE's; Final rule.) Based on this principle, and on the fact that research and development expenditures may be recovered under the general IDE, FDA has concluded that cost recovery during a treatment IDE should be limited to those direct costs of supplying the device for the treatment use, i.e., manufacturing and handling costs. In this way, manufacturers would not incur additional costs as a result of participating in a treatment IDE. FDA recognizes, however, that manufacturing and handling costs per unit may be higher during production of a limited number of units than during full commercial distribution.

3. Should Prior FDA Approval for Charging Be Required?

One comment stated that § 812.20(b)(8), which requires a sponsor to justify why the price charged for the device does not exceed research, development, manufacturing, and handling costs, should also be part of the treatment IDE application. Another comment believed that sponsors should inform FDA in the treatment IDE application if and how much they intend to charge for the device. The comment stated that the sponsor should provide a justification for the charge based on actual manufacturing and handling costs only, and FDA approval of the charge would be implied when FDA approves the treatment IDE application. Another comment stated that prior FDA approval of costs is not appropriate because such approval would result in a longer treatment IDE approval process.

FDA agrees that, as with IDE's in general, prior approval for charging for the treatment use device should be required. Therefore, FDA has added § 812.36(c)(1)(x), which states that if the device is to be sold, the treatment IDE sponsor is required to submit the price charged for the treatment use device and a statement indicating that the price is based on manufacturing and handling costs only.

FDA disagrees that prior approval of costs will result in a longer approval process for treatment IDE applications. Under § 812.30(a) of the general IDE regulation, FDA is required to notify a sponsor in writing of its decision to approve the investigation as proposed, approve it with modifications, or disapprove it within 30 days of receipt of the application. That review includes a review of the sponsor's decision to charge for the device. Under § 812.36(d)(1), FDA is also required to review treatment IDE applications within the 30-day timeframe; there is no reason to assume the approval process for treatment IDE's will be protracted.

6. According to one comment on § 812.36(f), quarterly reports to the IRB's and FDA should be subject to restrictions intended to protect confidential information.

FDA agrees that treatment IDE progress reports ordinarily should be kept confidential. As provided for under § 812.38(a) of the IDE regulation in general, FDA will not disclose the existence of an IDE until FDA approves a marketing application for the device unless its existence has previously been publicly disclosed or acknowledged. Even if the existence of an IDE has been disclosed or acknowledged by the sponsor, as is likely with respect to treatment IDE's, the information contained in an IDE or treatment IDE, including progress reports submitted under § 812.36, is generally protected from disclosure.

A second comment on proposed § 812.36(f) alleged that quarterly reporting is an unnecessary burden on sponsors. The comment noted that the parallel IND regulation does not require additional quarterly reporting. The comment also alleged that this requirement conflicts with the Paperwork Reduction Act, in that it adds a layer of paperwork never before required for IDE's. According to the comment, the adverse reporting procedures for IDE's would provide enough safeguards for treatment IDE's without adding a new layer of paperwork.

FDA agrees in part with the comment. Upon reconsideration, FDA has concluded that such frequent reporting, in addition to the annual reporting requirement under the regular IDE, is not necessary. Therefore, FDA has revised the reporting requirements to include those elements needed to monitor the size and scope of the treatment IDE, and to assess the sponsor's due diligence in seeking marketing approval. Under final § 812.36(f), the sponsor of a treatment IDE is required to submit progress reports on a semi-annual basis to all reviewing IRB's and FDA until the filing of a marketing application. These reports shall be based on the period of time since initial approval of the treatment IDE and shall include only three items: (1) The number of patients treated with the device under the treatment IDE; (2) the names of the investigators participating in the treatment IDE; and (3) a brief description of the sponsor's efforts to pursue marketing approval/clearance of the device. Upon filing of a marketing application, progress reports will be required to be submitted annually in accordance with § 812.150(b)(5). At the sponsor's option, the annual report for the treatment IDE may be combined with the annual report for the general IDE or may be submitted separately.

FDA disagrees that the submission of progress reports conflicts with the Paperwork Reduction Act. In accordance with § 812.150(b)(4), the sponsor of an IDE is required to submit to FDA, at 6-month intervals, a current list of all investigators participating in the investigation. Furthermore, under § 812.150(b)(5), at regular intervals and at least yearly, the sponsor of an IDE is required to submit progress reports to all reviewing IRB's and FDA. Under final § 812.36(f), the sponsor of a treatment IDE will be required to submit reports on the treatment use at 6 month intervals, the same frequency required for updating information about investigators of controlled clinical trials. Although the content of the semi-annual report differs, the information required is minimal, but nevertheless necessary, to maintain control over the treatment use. Therefore, FDA believes that semi-annual reporting for treatment IDE's is consistent with the reporting requirements for IDE's in general and does not conflict with the Paperwork Reduction Act.

Finally, FDA agrees that the adverse event reporting requirements for IDE's in general should provide adequate patient protection for treatment IDE's. (See § 812.150(b)(1).) Under final § 812.36(f), semi-annual progress reports for treatment IDE's are no longer required to include a summary of anticipated and unanticipated adverse device effects because this information will be captured in the annual progress reports of § 812.150(b)(5) and by the 10-day reporting requirements of § 812.150(b)(1).

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this final rule 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. 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) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Pub. L. 104–121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). 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 relevant information should already be available to FDA in the sponsor's IDE, limited additional information relative to the safety and effectiveness of the device for treatment use would be required in the treatment IDE application. In fact, applications for treatment use may be submitted as supplements to the IDE for the controlled clinical trial in order to eliminate additional burden that could result if sponsors were required to submit new applications. As a result, this final rule will not impose significant economic impact on any small entities. The Commissioner, therefore, certifies that the final rule will not have a significant economic impact on a substantial number of small entities. In addition, this final rule will not impose costs of $100 million or more on either the private sector or State, local, and tribal governments in the aggregate, and therefore a summary statement of analysis pursuant to section 202(a) of the Unfunded Mandates Reform Act of 1995 is not required.

VI. Paperwork Reduction Act of 1995

This final rule contains information collections requirements that are subject to review by the OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection requirements are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Investigational Device Exemptions; Treatment Use.

Description: This regulation establishes the procedures for the treatment use of investigational devices. The purpose of this regulation is to permit broader availability of investigational devices to treat serious or immediately life-threatening diseases or conditions for which there are no satisfactory alternative treatments. Under the final rule, treatment use of an investigational device would only be considered when the following criteria are satisfied: (1) The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition; (2) there is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population; (3) the device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and (4) the sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

The burdens connected with the requirements for applications for treatment use are limited, but consistent with protecting patient safety and monitoring proper use. Each application would include, among other things, an explanation of the rationale for the use of the device; the criteria for patient selection; a description of clinical procedures, laboratory tests, or other measures to be used to monitor the effects of the device and to minimize risk; written procedures for monitoring the treatment use; information that is

relevant to the safety and effectiveness of the device for the intended treatment use; and a written protocol describing the treatment use. Sponsors of an approved treatment IDE would be required to submit semi-annual progress reports until a marketing application is filed, and annual reports thereafter.

Description of Respondents: Businesses or other for profit organizations.

ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
812.36(c)	6	1	6	120	720
812.36(c)	6	2	12	20	240
Total					960

There are no operating and maintenance costs or capital costs associated with this information collection.

Based on its experience with the treatment use of drugs and FDA's knowledge of the types of devices that may meet the treatment use criteria, FDA estimates that an average of six applications will be submitted each year. Based upon FDA's knowledge of the preparation of IDE's, FDA estimates that it will take approximately 120 hours to prepare a treatment use IDE. Thus, the total annual burden for preparing applications will be 720 hours.

Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection requirements in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

List of Subjects in 21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 812 is amended as follows:

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

1. The authority citation for 21 CFR part 812 continues to read as follows:

Authority: Secs. 301, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701, 702, 704, 721, 801, 802, 803 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381, 382, 383); secs. 215, 301,351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b–263n).

2. New § 812.36 is added to subpart B to read as follows:

§ 812.36 Treatment use of an investigational device.

(a) *General.* A device that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of a treatment investigational device exemption (IDE). The purpose of this section is to facilitate the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness. In the case of a serious disease, a device ordinarily may be made available for treatment use under this section after all clinical trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use under this section prior to the completion of all clinical trials. For the purpose of this section, an ''immediately life-threatening'' disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For purposes of this section, ''treatment use''of a device includes the use of a device for diagnostic purposes.

(b) *Criteria.* FDA shall consider the use of an investigational device under a treatment IDE if:

(1) The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;

(2) There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;

(3) The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and

(4) The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

(c) *Applications for treatment use.* (1) A treatment IDE application shall include, in the following order:

(i) The name, address, and telephone number of the sponsor of the treatment IDE;

(ii) The intended use of the device, the criteria for patient selection, and a written protocol describing the treatment use;

(iii) An explanation of the rationale for use of the device, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments;

(iv) A description of clinical procedures, laboratory tests, or other measures that will be used to evaluate the effects of the device and to minimize risk;

(v) Written procedures for monitoring the treatment use and the name and address of the monitor;

(vi) Instructions for use for the device and all other labeling as required under § 812.5(a) and (b);

(vii) Information that is relevant to the safety and effectiveness of the device for the intended treatment use. Information from other IDE's may be incorporated by reference to support the treatment use;

(viii) A statement of the sponsor's commitment to meet all applicable responsibilities under this part and part 56 of this chapter and to ensure compliance of all participating investigators with the informed consent requirements of part 50 of this chapter;

(ix) An example of the agreement to be signed by all investigators participating in the treatment IDE and

certification that no investigator will be added to the treatment IDE before the agreement is signed; and

(x) If the device is to be sold, the price to be charged and a statement indicating that the price is based on manufacturing and handling costs only.

(2) A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an ''investigator'' under the IDE and is responsible for meeting all applicable investigator responsibilities under this part and parts 50 and 56 of this chapter.

(d) *FDA action on treatment IDE applications.* (1) *Approval of treatment IDE's.* Treatment use may begin 30 days after FDA receives the treatment IDE submission at the address specified in § 812.19, unless FDA notifies the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed or approve it with modifications.

(2) *Disapproval or withdrawal of approval of treatment IDE's.* FDA may disapprove or withdraw approval of a treatment IDE if:

(i) The criteria specified in § 812.36(b) are not met or the treatment IDE does not contain the information required in § 812.36(c);

(ii) FDA determines that any of the grounds for disapproval or withdrawal of approval listed in § 812.30(b)(1) through (b)(5) apply;

(iii) The device is intended for a serious disease or condition and there is insufficient evidence of safety and effectiveness to support such use;

(iv) The device is intended for an immediately life-threatening disease or condition and the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the device:

(A) May be effective for its intended use in its intended population; or

(B) Would not expose the patients to whom the device is to be administered to an unreasonable and significant additional risk of illness or injury;

(v) There is reasonable evidence that the treatment use is impeding enrollment in, or otherwise interfering with the conduct or completion of, a controlled investigation of the same or another investigational device;

(vi) The device has received marketing approval/clearance or a comparable device or therapy becomes available to treat or diagnose the same indication in the same patient population for which the investigational device is being used;

(vii) The sponsor of the controlled clinical trial is not pursuing marketing approval/clearance with due diligence;

(viii) Approval of the IDE for the controlled clinical investigation of the device has been withdrawn; or

(ix) The clinical investigator(s) named in the treatment IDE are not qualified by reason of their scientific training and/or experience to use the investigational device for the intended treatment use.

(3) *Notice of disapproval or withdrawal.* If FDA disapproves or proposes to withdraw approval of a treatment IDE, FDA will follow the procedures set forth in § 812.30(c).

(e) *Safeguards.* Treatment use of an investigational device is conditioned upon the sponsor and investigators complying with the safeguards of the IDE process and the regulations governing informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter).

(f) *Reporting requirements.* The sponsor of a treatment IDE shall submit progress reports on a semi-annual basis to all reviewing IRB's and FDA until the filing of a marketing application. These reports shall be based on the period of time since initial approval of the treatment IDE and shall include the number of patients treated with the device under the treatment IDE, the names of the investigators participating in the treatment IDE, and a brief description of the sponsor's efforts to pursue marketing approval/clearance of the device. Upon filing of a marketing application, progress reports shall be submitted annually in accordance with § 812.150(b)(5). The sponsor of a treatment IDE is responsible for submitting all other reports required under § 812.150.

3. Section 812.150 is amended by revising paragraph (b)(5) to read as follows:

§ 812.150 Reports.

* * * * *

(b) * * *

(5) *Progress reports.* At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with § 812.36(f) and annual reports in accordance with this section.

* * * * *

Dated: August 20, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97–24735 Filed 9–17–97; 8:45 am]

BILLING CODE 4160–01–F

FEDERAL MEDIATION AND CONCILIATION SERVICE

29 CFR Part 1404

Expedited Arbitration

AGENCY: Federal Mediation and Conciliation Service.

ACTION: Final rule.

SUMMARY: This addition to the arbitration regulations is intended to create a new service know as ''expedited arbitration.'' This service will provide a streamlined arbitration process for non-precedential and non-complex grievance arbitration cases while encouraging the parties to select new arbitrators in order to enhance their career development. This new service is the result of specific recommendations of the Arbitration Focus Group by FMCS on March 27, 1997.

EFFECTIVE DATE: This regulation is effective October 1, 1997.

FOR FURTHER INFORMATION CONTACT: Peter Regner, 202–606–8181.

SUPPLEMENTARY INFORMATION: The Federal Mediation and Conciliation Service, in an effort to receive public input on its proposed new service of expedited arbitration, published the draft version of its proposed rule in the June 30, 1997 issue of the **Federal Register** (62 FR 35112). Nine arbitrators responded in writing to the proposed rule. In general, all individuals supported the new service. Almost all of them, however, objected to limiting eligibility to deliver this service to those arbitrators listed on the FMCS Roster of Arbitrators for five (5) years or less. More specific information about the public response is contained in the following section-by-section analysis.

Subpart D—Expedited Arbitration

Section 1404.17 Policy

The first section was further clarified by adding the ''unique'' issues would also be inappropriate for expedited arbitration, as would complex or precedential issues.

Section 1404.18 Procedures for Requesting Expedited Panels

Subsection (d). The procedures for requesting expedited arbitrators were modified slightly by allowing the parties to select a second arbitrator from the panel submitted to them in the event their first choice was not available to serve. This was in response to one comment opposing a direct appointment by FMCS in the event the original arbitrator selected by the parties was not able to serve. The parties now have an additional option.