Management Evaluation or Quality Control Staff, or other State agency personnel qualified to conduct these reviews. FNS may exempt a State agency from the requirement to conduct post-disaster reviews in a particular area or areas if, due to such factors as the limited volume of disaster issuances in the area, FNS believes that reviews are not warranted.

(3) The State agency shall utilize the case review information to formulate and implement corrective action to improve disaster certification procedures. State agencies shall establish claims in accordance with § 273.18 against any household that received more disaster assistance than it was entitled to receive. The State agency shall restore lost benefits to households which were caused by an error of the State agency as required by § 273.17.

(b) *FNS Responsibility.* The Regional Disaster Task Force shall establish procedures for monitoring and evaluating disaster operations conducted by the State agency. FNS will review on-site operations during the period authorized for processing applications and shall examine the case review information and corrective action formulated by the State agency.

(Catalog of Federal Domestic Assistance Program, No. 10.551 Food Stamps)

Dated: January 9, 1981.

Robert Greenstein,

Administrator.

[FR Doc. 81-2650 Filed 1-26-81; 8:45 am]

BILLING CODE 3410-30-M

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7 CFR Parts 272, 273, and 274

[Amdt. No. 190]

Replacement of Lost or Stolen Food Stamp Authorizations, and Replacement of Nondelivered, Stolen or Destroyed Coupons

AGENCY: Food and Nutrition Service, USDA.

ACTION: Proposed rulemaking.

SUMMARY: This rulemaking establishes procedures under authority of the Food Stamp Act 1977, as amended, (Pub. L. 95-113) which would modify current Food Stamp Program regulations regarding the replacement of lost or stolen food stamp authorizations (ATP's) and nondelivered, stolen, or destroyed food coupons. The proposed amendments also incorporate new provisions allowing the replacement of certain food losses through the issuance of supplemental benefits. These modifications are proposed to reduce losses resulting from fraudulent or erroneous ATP or coupon replacements.

DATE: Comments must be received on or before March 30, 1981, in order to be assured of consideration. After reviewing all comments, the Department will publish final regulations.

ADDRESS: Comments should be submitted to Alberta Frost, Deputy Administrator for Family Nutrition Programs, Food and Nutrition Service, USDA, Washington, D.C., 20250. All written comments will be open to public inspection at the office of the Food and Nutrition Service during regular business hours (8:30 a.m. to 5:00 p.m. Monday through Friday) at 500 12th Street, SW., Washington, D.C. Room 698.

FOR FURTHER INFORMATION CONTACT: Larry R. Carnes, Chief, Regulations and Policy Section, Program Standards Branch, Program Development Division, Family Nutrition Programs, Food and Nutrition Service, USDA, Washington, D.C. 20250; (202) 447-9075.

The Draft Impact Analysis is available on request from the above named individual.

SUPPLEMENTARY INFORMATION: This proposed action has been reviewed under USDA procedure established in Secretary's Executive Order 12044, and has been classified as "not significant".

The proposal has been reviewed with regard to the requirements of Pub. L. 96-354. Robert Greenstein, Administrator of the Food and Nutrition Service, has certified that this proposal does not have a significant economic impact on a substantial number of small entities. The provisions control the issuance of replacement authorization cards and food stamp coupons where authorization cards and food stamps are reported stolen, lost, or destroyed. Requirements are not placed on small businesses or small organizations. There are requirements proposed on State agencies, and to the extent that county governments operate the Food Stamp Program, some requirements would be placed on them. However, the requirements, such as limitations on the numbers of replacements and the circumstances under which replacements can be issued, do not have a significant economic impact on local governments.

Introduction

The Department is concerned with minimizing possibilities for fraud and error in the Food Stamp Program. With this in mind, the Department has re-examined procedures for the replacement of ATP's and coupons which are lost, stolen or destroyed. Given the number and value of replacement issuances, and indications that abuse has occurred in some areas, the Department has decided to propose substantial changes in procedures governing replacements.

The Department proposes to authorize the replacement of lost, stolen, or destroyed ATP's or coupons within limits that restrict opportunities for fraud and abuse. This proposed rulemaking addresses those restrictions by establishing revised policy regarding the conditions under which ATP's and coupons may be replaced.

In developing this proposed rule, the Department focused both on ways in which replacement issuances could be controlled and the development of procedures that are responsive to instances of true participant need and feasible for State agencies.

Replacement of Lost or Stolen Food Stamp Authorizations (ATP's)

Background

As a result of the increased Federal involvement in the issuance process (since 1974 USDA has paid half of the States' issuance costs) the Food and Nutrition Service published Instruction 734-2: Machine Issuance and Authorization to Purchase (ATP) System Procedures and Controls. This instruction included guidelines for State and local agencies to follow when issuing over-the-counter ATP's as replacements for ATP's reported lost, stolen, or undelivered in the mail. The instruction mandated that determinations be made that sufficient time had elapsed for a normal mail delivery to be completed and that the household was certified. A signed affidavit stating that the original ATP would be returned if recovered by the household was also required. Finally, certification workers were warned to be alert for households requesting repeated ATP replacement. Consideration was to be given to other means of coupon delivery after two consecutive reports of nondelivery. Regulations issued pursuant to the Food Stamp Act of 1977 did not drastically alter the provisions of Instruction 734-2. In addition to those noted above, regulations specified that the definition of "sufficient time for ATP delivery" would not exceed 5 days.

In recent years the number of replacement requests has grown in some metropolitan areas. While the intent of the regulations regarding replacements was to permit participants to get prompt assistance, it can be difficult to both guarantee immediate replacement and provide adequate safeguards to prevent duplicate issuance in urban areas with massive caseloads. In order to lessen

the opportunity for fraud and theft in these areas, the Department believes that additional safeguards must be built into the ATP replacement system. Therefore, this proposal would modify the regulations as they relate to ATP replacement in order to reduce the number of stolen and fraudulently redeemed ATP's.

The proposed regulations would establish three limitations on the issuance of replacement ATP's reported as lost or stolen prior to receipt: (1) A specific timeframe for requesting replacements; (2) A specific time period for making replacement issuances; and (3) A limitation on the number of times replacements could be requested by a given household prior to initiation of an alternate issuance system. The proposal also addresses State actions in instances where there is documentation of fraud. Each of these limitations is discussed in greater detail below.

FNS is currently involved in two different alternate ATP issuance projects in New York and Pennsylvania (Philadelphia and Pittsburgh). In New York City, which had a serious ATP replacement problem prior to implementation of the alternative system, a "Rapid Access System" is being tested that provides prompt data for use in determining whether a participant's request for ATP replacement is legitimate. In Pennsylvania, the State and the Department are testing a project involving the direct delivery of ATP's to issuance outlets where they will be picked up and transacted by participants. In the first month of operation, there were no replacements at all issued in the Pennsylvania test districts. In New York City, the number of replacements has dropped sharply and fraudulent duplicate issuance has been severely curtailed. These test projects may suggest additional approaches to handling replacement ATP's.

Timeframe for Claiming Nonreceipt

Limitations established in current regulations provide, among other conditions, that an ATP replacement will only be issued if the original ATP loss is reported in the period for which the ATP was intended to be used.

The Department plans to retain this requirement. Language is being added to clarify that households which are scheduled to receive their ATP's on the 25th of the month or later will have 20 days to request replacements. This 20 day period coincides with the 20 day validity period given to ATP's issued after the 25th and is considered sufficient to allow a participant household to realize the loss and request a replacement.

Timeframe for Replacement Issuance

Current regulations do not specifically mandate a definite timeframe for the replacement of an ATP reported lost or stolen. Aside from the reference to ensuring that sufficient time has elapsed for delivery, no requirement is stipulated. The regulations do state, however, that "sufficient time" shall not exceed 5 days. In some areas, replacement is now granted immediately, and often without investigation as to whether the participant has already transacted the original ATP. This lack of confirmation makes it difficult to detect replacement requests that are fraudulent.

To correct this problem, the Department proposes that State agencies have up to 10 days to issue replacements after a request is made by the household. The 10 day period would allow the participant in need of replacement to receive such replacement without undue delay, while enhancing the ability of States and/or project areas with appropriate systems to detect fraudulent and/or erroneous duplicate issuance of ATP's by ascertaining whether the original ATP has been transacted. Ten days should give many States or project areas without sophisticated systems enough time to check whether the original ATP has been transacted.

Initiation of an Alternate Issuance System

Some households have reported that they did not receive their ATP several times, requesting replacement ATP's on each occasion. To forestall the possibility of continued loss, whether it stems from repeated theft of the household's ATP or from fraud, the Department is proposing that an alternate ATP delivery system be employed for a particular household after a second replacement request is made within a 6 month period by that household. This would allow participants an opportunity to obtain replacements when the need arises, yet control duplicate issuances through the use of an alternate issuance system such as direct pickup or certified mail. A single loss could result from an isolated incident, but two losses in this 6 month period would indicate the need for an alternate ATP delivery system. The State agency would keep the household on the alternate issuance system for the length of time the State agency determines to be necessary. The State agency could return the household to the regular issuance system when it found that the circumstances leading to the losses had changed and the risk of loss had lessened.

Replacement of ATP's

As noted above it is a goal of this rulemaking to initiate new provisions for building additional safeguards into the ATP replacement system. ATP replacement is addressed in two categories, i.e., ATP replacement for losses occurring prior to receipt and replacement for ATP's which are stolen or destroyed after receipt. The Department recognizes that households have little control over the nondelivery of mail and that nonreceipt of an ATP or coupons creates hardships.

The Department believes losses of ATP's after receipt by the household through theft or destruction are subject to greater control by the household and should be infrequent. Accordinlgy, these rules propose specific limits on the number of times ATP's or coupons may be replaced when they have been stolen or destroyed after receipt. The Department proposes that a household be entitled to receive only one replacement in any 6 month period for either ATP's or coupons destroyed or stolen subsequent to receipt. In this proposal the Department has limited the opportunity for overissuances while providing relief to certain participants who suffer actual losses. The rules also propose that there be no replacement for ATP's or coupons misplaced or lost after receipt. The Department believes it is the responsibility of each household to avoid simply misplacing or losing ATP's or coupons. Current rules are silent on the issue of ATP's misplaced or lost after receipt. The Department is especially interested in comment on this matter.

Action in Instances Where There Is Documentation Indicating Fraud

The Department is proposing new procedures to be used by State agencies in those instances of reported loss where fraud is suspected. The first procedure would require States to withhold a replacement ATP when the State has documentation indicating that the replacement request is invalid. This approach is dependent on a "front end" capability to detect fraud such as the ability to verify that the original ATP has been transacted by the household rather than stolen or lost in the mail. For States without this capability, replacement ATP's would be issued upon request if the household signs a statement attesting to the loss. The statement would warn the household of the legal consequences of intentionally misstating the facts. States would

continue to be required to determine the cause of overissuances and to seek to recoup or otherwise recover losses resulting from fraud on the part of the household. This approach requires reliance on post-issuance activities currently in effect including reconciliation, fraud hearings systems, and claims processing systems.

Replacement of Nondelivered, Stolen or Destroyed Coupons

For purposes of replacement, coupon losses have generally been divided into two categories. The first category covers those coupons which are lost in the mail prior to household receipt. Such coupons have generally been replaced on request, with the household stating that it would return the original issuance should it be received. The regulations implementing the 1977 Act attempted to tighten up this replacement policy by requiring States to use an alternative delivery system for those households reporting two consecutive mail issuance losses.

The second category covers those lost subsequent to household receipt. Prior to the 1977 Act such coupon losses were regarded as an individual disaster or casualty loss. In determining the basis of issuance for the replacement allotment, the previous purchase requirement was considered a hardship or "unusual expense" deduction from household income.

The Department expanded this rule in the Food Stamp Certification Handbook (FNS–732–1) to cover food coupons or foods purchased with coupons which were lost, stolen, or destroyed in an individual disaster. The household could request a second allotment of coupons during the month in which the mishap occurred. After verification of the reported loss, the eligibility worker could process the replacement.

The October 17, 1978, rulemaking (43 FR 47864) which promulgated provisions of the Food Stamp Act of 1977 tightened these procedures by requiring a police report to verify the theft of coupons, by allowing replacement only for stolen or destroyed coupons, by not replacing coupons lost or misplaced by the household, and by removing the provision related to food replacement.

Nevertheless, the Department is concerned over continued coupon losses and believes further restrictions are necessary to reduce mail theft losses and to reduce the potential for fraudulent replacement requests. The proposed rulemaking, therefore, would limit those circumstances and conditions under which replacement coupon issuances can be obtained.

The basic limitations related to the time period for requesting a replacement based on nonreceipt, the timeframe for replacement issuance, and the use of an alternate issuance system which are proposed for ATP replacements are also proposed for coupons lost in the mail prior to receipt. Additionally, this proposed rulemaking contains new safeguards regarding requests for replacement of coupons reported stolen or destroyed subsequent to receipt.

Replacement issuance procedures are proposed to provide some relief regarding personal disasters, such as a fire loss, which eliminate a household's food supply. Each of these provisions is discussed in detail below.

Coupons Lost in the Mail Prior to Receipt

The proposed rules would establish procedures for coupons lost in the mail prior to receipt that parallel those proposed for ATP's lost or stolen prior to receipt. The State agency would have up to 10 days after the report of nonreceipt to replace the coupons, although the State would be required to replace coupons more promptly if it had determined that sufficient time had elapsed for delivery and it had also completed the other required actions to check, to the extent possible, on the validity of the replacement request. In addition, if a household reported nonreceipt twice in a 6 month period, the State agency would be required to institute an alternate issuance system for that household, such as the use of certified mail. Households would be required to report the nonreceipt in the month in which the coupons were intended to be used.

Coupons Stolen or Destroyed After Receipt

The proposed rules contain additional safeguards to protect against households inaccurately reporting that their coupons have been stolen. These safeguards parallel those proposed when households report the theft of an ATP after receipt.

The Department is proposing that replacements of either coupons or ATP's reported as stolen after receipt be made only once during a 6 month period. The Department believes this limitation strikes an equitable balance between attempting to discourage households from making frequent, unwarranted requests for such replacement and the need to serve households experiencing actual losses. Coupons lost or misplaced after delivery would not be replaced as the Department believes it is the responsibility of each household to avoid misplacing coupons and a matter over which the household has complete control. Moreover, the replacement of coupons based solely on a statement by a household that its original allotment has been lost or misplaced leaves the program particularly vulnerable to abuse because no effective method exists to detect whether the household has used the original allotments.

One exception to this policy has been proposed. To compensate households experiencing an individual household disaster (e.g., fire, not theft) which can be verified, additional replacement allotments could be issued. This approach is adopted because the household disasters are capable of verification. Also, the number of instances in which additional replacements are needed for recurrent disasters affecting the same household are expected to be minimal.

Additionally, the proposed rules require that a household requesting a replacement of coupons or of an ATP due to either theft or destruction after receipt must make the request within 10 days after the loss. A household should know immediately that it has suffered such a coupon or ATP loss. This is different from coupons or ATP's lost in the mail prior to receipt. Mail deliveries can be delayed, and a household may not know for some time that its ATP or coupons have been lost or stolen in the mail. The 10 day limit on requests for coupons and ATP's stolen or destroyed after receipt increases the likelihoood that the replacement requests are legitimate.

A final issue concerns the current requirement for verification, prior to issuing a replacement for coupons stolen after receipt, that a police report has been filed by the victim. The Department has learned of instances where the police have refused to release such reports. While the proposed rules do not alter this requirement, the Department solicits comments and recommendations for possible alternate verification criteria of such reported thefts.

Replacement of Food Losses

As discussed briefly above, Federal guidelines under the 1964 Act provided for the replacement of foods which were bought with coupons where the food was lost, stolen or destroyed. This provision was deleted from regulations implementing the 1977 Act to minimize administrative burdens. Since that decision, the Department has received numerous requests from State agencies and individuals to again provide replacement food stamp allotment for lost food. These proposed regulations provide for a limited reinstitution of

such a policy. To reduce the potential for fraud and abuse, the replacement provision is restricted to food losses resulting from a disaster affecting the household.

The Department is proposing that replacement must be requested within 10 days of the disaster, that the State agency have 10 days to make replacement and that the replacement not exceed the household's current monthly allotment. Verification of the disaster must be provided. While no new verification requirements are stated, comments are invited concerning the degree of verification that should be required and specific types of verification which may be of value in such situations.

The Department believes that there is a need for this type of replacement provision to take into consideration individual household disasters as well as natural disasters affecting more than one household. However, in cases where FNS has issued a disaster declaration and the household is otherwise eligible for emergency food stamp benefits under Part 280 of the regulations, this provision for replacement of food losses would not apply.

Implementation

The Department proposes that State agencies implement the procedures relating to replacement of lost or stolen food stamp authorizations and replacement of nondelivered, stolen or destroyed coupons no later than the first of the month 120 days following the date the final regulations are published. States would be permitted, however, to implement these rules earlier.

Therefore, the Department proposes that 7 CFR Parts 272, 273, and 274 be amended as follows:

PART 272—REQUIREMENTS FOR PARTICIPATING STATE AGENCIES

1. In § 272.1, subparagraph (29) is being added to paragraph (g) in numerical order to read as follows:

§ 272.1 General terms and conditions.

* * * * *

(g) *Implementation* * * *

* * * * *

(29) Amendment *190*. State agencies shall implement these regulations no later than the first of the month 120 days following publication of final regulations.

PART 273—CERTIFICATION OF ELIGIBLE HOUSEHOLDS

2. In § 273.11, paragraph (g)(1) is revised and a new subparagraph (3) is added to (g). The revision and addition read as follows:

§ 273.11 Action on households with special circumstances.

* * * * *

(g) *Households requesting replacement allotments or ATP's—(1) Coupons or ATP's that have been stolen or destroyed after receipt.* A household may request replacement for that portion of its allotment, not to exceed one month's food stamp allotment or for an ATP, which it had received but which was subsequently destroyed in a household disaster such as a fire or flood, or which was subsequently stolen. Replacements of coupons or ATP's lost or stolen in the mail prior to receipt are handled under § 274.2(h) and § 274.3(c).

(i) To qualify for a replacement the household shall report the theft or destruction to the local food stamp office within 10 days of the incident and sign a statement at the food stamp office (a) attesting to the theft or destruction of the household's food stamps or ATP, (B) stating that the original ATP or coupons will be returned to the State agency if recovered by the household, and (C) stating that the household is aware of the penalties for intentional misrepresentation of the facts. The statement shall be retained in the casefile. In the case of theft of coupons, the household shall also report the theft to the local police department and provide to the State agency a copy of the police report or sufficient information to allow the State agency to verify that the theft was reported to the police.

(ii) Upon receiving a request for replacement of coupons or an ATP reported as stolen or destroyed in an individual household disaster, the State agency shall verify the theft or disaster and issue replacement coupons or a replacement ATP, if warranted, within 10 days of receipt of the request. The State agency shall indicate in the casefile that a replacement has been provided. The State agency shall examine the casefile for notation of previous requests by the household for replacement of coupons or an ATP reported stolen subsequent to receipt. Replacement of coupons or an ATP reported as stolen subsequent to receipt shall be made only once in a 6 month period. If, in the previous 5 months, the household has been issued a replacement for either coupons or an ATP reported as stolen subsequent to receipt, than replacement shall be denied. This limit does not apply to replacement issuances of coupons or ATP's when a household has requested replacement of coupons reported as destroyed due to a verified household disaster.

(iii) The State agency shall authorize the issuance of a replacement ATP only if the ATP was valid when issued and if it has been reported lost or stolen in the period of its intended use (for ATP's issued after the 25th of the month, the period intended for their use is 20 days from their issuance). The State agency shall also determine, to the maximum extent practicable, the legitimacy of the request for replacement of the lost or stolen ATP (through such means as determining whether the original ATP has been transacted, and, if so, whether the signature on the original ATP matches that on the request for replacement). The State agency has 10 days to establish these facts, as the replacement, if warranted, must be issued within 10 days.

(iv) In cases in which an ATP replacement is requested, but documentation exists substantiating that the request for replacement is fraudulent, replacement of the ATP shall be denied or delayed. However, in that event the household shall be informed of its right to a fair hearing to contest the denial or delay of the ATP. The denial or delay of the replacement ATP shall remain in effect pending the hearing decision. The State agency may combine the fair hearing with a fraud hearing in accordance with § 273.16(d)(1). To deny or delay a replacement, the State agency must have documentation substantiating fraud, such as a match between the signature on the original ATP that had been transacted and the signature on the replacement request. Fraud could also be indicated where the issuing agent has noted the recipient's correct food stamp identification number (unless the household reports that its ID was stolen) on an original ATP that has been transacted.

(v) Replacement ATP's or replacement coupons which are stolen shall not be replaced.

(vi) The State agency shall not issue a replacement allotment or replacement ATP to a household which reports that its coupons or ATP were lost or misplaced after being received.

(vii) Except as provided for in Part 280, where FNS has issued a disaster declaration and the household is eligible for emergency food stamp benefits, the household shall not receive both the disaster allotment and a replacement allotment under this provision.

* * * * *

(3) *Replacement of food destroyed in a disaster.* In cases in which food purchased with food stamps is destroyed in a disaster affecting a

participating household, that household may be eligible for replacement of the actual value of loss, not to exceed one month's food stamp allotment, if the loss is reported within 10 days and the household can provide verification of the loss. The State agency shall provide an allotment replacement, or an opportunity to obtain an allotment replacement, within 10 days of the reported loss. This provision shall apply in cases of an individual household disaster as well as in natural disasters affecting more than one household. However, in cases where FNS has issued a disaster declaration and the household is otherwise eligible for emergency food stamp benefits under Part 280, the household shall not receive both the disaster allotment and a replacement allotment under this provision.

PART 274—ISSUANCE AND USE OF FOOD COUPONS

3. In § 274.2:

(a) Paragraphs (e)(5) and (g)(1) are revised,

(b) paragraph (g)(3) is removed,

(c) paragraph (g)(4) is redesignated (g)(3), and

(d) paragraph (h) is designated as paragraph (i) and a new paragraph (h) is added. The changes read as follows:

§ 274.2 Issuance systems.

* * * * *

(e) *ATP Issuance* * * *

(5) The State agency shall mail the ATP to the household in a first class nonforwarding envelope, except when the ATP is handled as specified in paragraphs (g) or (h) of this section. The State agency may also use certified mail for ATP delivery, and shall use an alternate method of ATP delivery for households which report two losses of ATP's through the mail within a 6 month period:

* * * * *

(g) *Expedited Service.* (1) The State agency shall manually prepare and issue ATP's at the local level if necessary to provide an opportunity to participate to households certified on an expedited service basis in accordance with § 273.2(i), to comply with the processing standards for initial and recertification and for action on reported changes. To minimize the possibility of misuse of manually prepared ATP's, the State agency shall:

* * * * *

(h) *Replacement of an ATP lost or stolen in the mail prior to receipt.* (1) The State agency shall issue an emergency replacement ATP only if the ATP is reported lost or stolen in the period of its intended use. For ATP's issued after the 25th of the month, the period intended for their use is 20 days from their issuance. Replacements of ATP's stolen or destroyed after receipt are handled under § 273.11(g)(1).

(i) The State agency shall authorize the issuance of a replacement ATP only if the ATP was valid when issued and if it has been reported lost or stolen in the period of its intended use. The State agency shall also determine, to the maximum extent practicable, the legitimacy of the request for replacement of the lost or stolen ATP (through such means as determining whether the original ATP has been transacted, and if so, whether the signature on the original ATP matches that on the replacement). The State agency has 10 days to establish these facts and issue the replacement.

(ii) To obtain a replacement ATP the participant must sign a statement stating that the original ATP will be returned to the State agency if recovered by the household and that the household is aware of the penalties for intentional misrepresentation of the facts. The statement shall be filed in the casefile.

(iii) Replacement ATP's which are stolen shall not be replaced.

(iv) After two requests for replacement of ATP's reported as nondelivered in a 6 month period, the State agency shall issue benefits to that household under an alternate issuance system. The State agency shall keep the household on the alternate issuance system for the length of time the State agency determines to be necessary. The State agency may return the household to the regular issuance system if the State agency finds that the circumstances leading to the loss have changed and the risk of loss has lessened.

(v) On at least a monthly basis the State agency shall provide a list of all ATP's reported as lost or stolen from the mail to the appropriate Postal Inspection Service. The State agency should assist the Postal service during the investigation and shall, upon request, supply the Service with a facsimile of the original and replacement ATP's and a copy of the nonreceipt statement. The State agency shall advise the Service if the original ATP is transacted.

(2) In cases in which documentation exists that the request for replacement is fradulent, replacement of the ATP shall be denied or delayed. However, the household shall be informed of its right to a fair hearing to contest the denial or delay of the ATP. The denial or delay of the replacement ATP shall remain in effect pending the hearing decision. The State agency may combine the fair hearing with a fraud hearing, in accordance with § 273.16(d)(1). To deny or delay a replacement, the State agency must have documentation substantiating fraud, such as a match between the signature on the original ATP that has been transacted and the signature on the replacement request, or the notation (by the issuing agent) on an orignial ATP that has been transacted of the recipient's correct food stamp identification number (unless the household reports that its ID was stolen).

* * * * *

4. In § 274.3 paragraphs (c)(1), (c)(2), and (c)(4) are revised to read as follows:

§ 274.3 Issuance of coupons through the mail.

* * * * *

(c) *Coupons lost in the mail prior to receipt.* (1) Coupons are "in the mail" when deposited with the Postal Service. Replacements for coupons stolen or destroyed after receipt are handled under § 273.11(g)(1). When a household reports the nondelivery of an allotment or partial allotment of coupons issued through the mail the State agency shall:

(i) Determine if the coupons were actually mailed or, if a delivery of a partial allotment is reported, determine the value of the coupons not delivered.

(ii) Review the mail issuance log for the return of undelivered coupons.

(iii) Authorize a replacement issuance only if the coupons were validly issued, if they were reported lost or stolen in the period of their intended use, and if sufficient time has elapsed for delivery.

(iv) Provide the replacement in no more than 10 days after the report of nondelivery has been received. The period of intended use of the coupons is the month for which coupons are issued, except that where coupons are issued after the 25th of the month, the nondelivery must be reported within 20 days of the date of expected receipt.

(v) Prepare and have the participant sign a statement that the coupons will be returned to the State agency if recovered by the household and that the household is aware of the penalties for intentially misrepresenting the facts. The statement shall be retained in the casefile.

(vi) Record the report of nondelivery and the date in the issuance log; and

(vii) Report all losses to the postal authorities. State agencies shall, in cooperation with the Postal Service, attempt to determine the cause of each nondelivery and take appropriate corrective action. States shall also report to the postal authorities all patterns of losses in particular project areas or neighborhoods.

(viii) Take other action warranted by the reported nondelivery.

(2) After two reports by a household of nondelivery in a 6 month period the State agency shall utilize other issuance methods for that household. The State agency shall keep the household on the alternate issuance system for the length of time that the State agency determines to be necessary. The State agency may return the household to the regular issuance system if the State agency finds that the circumstances leading to the loss have changed and the risk of loss has lessened. Alternate issuance methods include:

(i) Using certified mail;

(ii) Arranging for the household to pick up its coupon allotment at a specified location; or

(iii) Moving the household from a mail issuance system to a regular over-the-counter system.

* * * * *

(4) Replacement coupons which are stolen shall not be replaced.

* * * * *

91 Stat. 958 (7 U.S.C. 2011–2027)

(Catalog of Federal Domestic Assistance Program No. 10551, Food Stamps)

Dated: January 16, 1981.

Robert Greenstein,

Administrator.

[FR Doc. 81-2651 Filed 1-26-81; 8:45 am]

BILLING CODE 3410-30-M

federal register

Tuesday
January 27, 1981

Part IX

Health and Human Services Department

Food and Drug Administration

Protection of Human Subjects; Informed Consent; Standards for Institutional Review Boards for Clinical Investigations; and Clinical Investigations Which May Be Reviewed Through Expedited Review Procedure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 50, 71, 171, 180, 310, 312, 314, 320, 330, 361, 430, 431, 601, 630, 812, 813, 1003, 1010

[Docket No. 78N-0400]

Protection of Human Subjects; Informed Consent

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing regulations to provide protection for human subjects of clinical investigations conducted pursuant to requirements for prior submission to FDA or conducted in support of applications for permission to conduct further research or to market regulated products. The regulations clarify existing FDA requirements governing informed consent and provide protection of the rights and welfare of human subjects involved in research activities that fall within FDA's jurisdiction.

EFFECTIVE DATE: July 27, 1981.

FOR FURTHER INFORMATION CONTACT: John C. Petricciani, Office of the Commissioner (HFB-4), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301-496-9320.

SUPPLEMENTARY INFORMATION:

In the **Federal Register** of August 14, 1979 (44 FR 47713), the Commissioner of Food and Drugs proposed regulations concerning standards of informed consent. FDA believed that a complete revision of its requirements relating to informed consent is needed because (1) current regulations had not been comprehensively reviewed in 12 years; (2) actions by the Department of Health and Human Services (HHS) and the Congress suggested the need for, and desirability of, strengthening and clarifying informed consent requirements as they apply to research that involves human subjects and is intended for submission to FDA; (3) wherever possible, informed consent requirements adopted by FDA should be identical to, or compatible with, HHS regulations; (4) the General Accounting Office (GAO) has recommended changes in current FDA regulations; (5) Congress, in enacting the Medical Device Amendments of 1976 (Pub. L. 94-295, 90 Stat. 539-583), required that informed consent be obtained before an investigational device is used on a human subject; (6) FDA's Bioresearch Monitoring Program could be conducted more efficiently and effectively with uniform, agency-wide requirements for informed consent; and (7) FDA regulations should take into account the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) regarding institutional review boards (IRB's) and informed consent, published in the **Federal Register** of November 30, 1978 (43 FR 56174).

FDA allowed 90 days for comment on the proposal of August 14, 1979 (44 FR 47713). In addition, FDA held three open hearings to give the public an opportunity to comment on both the informed consent proposal and the IRB proposal that was reproposed in the same issue of the **Federal Register** (44 FR 47699). The hearings were held in Bethesda, MD, on September 18, 1979, San Francisco, CA, on October 2, 1979, and Houston, TX, on October 16, 1979. The comments received at the hearings and the hearing transcripts were made a part of the record of this regulation and are on file in the Dockets Management Branch (formerly the Hearing Clerk's office) along with the written comments received in response to the proposal. Comments were received from clinical investigators, institutional review boards, trade associations, professional societies, drug companies, and private citizens. The substantive comments received and FDA's conclusions about them are discussed below.

General Comments

1. Many comments suggested that FDA's informed consent requirements should be identical to the informed consent requirements adopted by HHS.

FDA agrees that uniformity of requirements is desirable and that uniform requirements would be less confusing to investigators who frequently may conduct both research funded by HHS and research involving FDA-regulated products. The substance of the informed consent requirements of the two regulations, with minor differences, therefore, is identical. The minor differences in wording reflect that (1) Part 50 is an interlocking but separate part of FDA's bioresearch monitoring regulations (2) purely behavioral research is not regulated by FDA, and (3) HHS has promulgated its IRB and informed consent requirements together in one subpart which was published in the January 26, 1981 issue of the **Federal Register**. FDA's bioresearch monitoring regulations when complete will contain separate requirements for and clarify the responsibilities of IRB's, clinical investigators, sponsors and monitors, and nonclinical testing laboratories. FDA does not anticipate that clinical investigators will find the informed consent requirements contained in 21 CFR Part 50 confusing in relationship to the informed consent requirements contained in 45 CFR Part 46.

2. The preamble to the FDA proposal of August 14, 1979 (44 FR 47713) contains an extensive discussion of the history and evolution of the concept of informed consent. FDA pointed out in that discussion that the informed consent provisions for investigational drugs and antibiotics contained in sections 505(i) and 507(d)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i) and 357(d)(3)) (the act) differed from the provisions for investigational devices contained in section 520(g)(3)(D) of the act (21 U.S.C. 360j(g)(3)(D)).

The majority of comments received in response to FDA's proposal to establish uniform requirements patterned upon section 520(g)(3)(d) of the act were in favor of uniformity. In fact, most comments favored uniform requirements not only for FDA-regulated research but for all research subject to the regulations of either FDA or HHS. One comment, however, questioned FDA's legal authority to conform the statutory requirements of sections 505, 507, and 520 of the act, but commended it, stating that the application of a uniform set of standards for informed consent for all clinical investigations would eliminate some of the confusion which has resulted from the promulgation of varying and sometimes inconsistent policies. Another comment stated that absent a single set of regulations, regulatory chaos would result, unintentional noncompliance would be likely, and the aims of subject protection would be defeated. Two comments argued that because the act established standards for investigations involving drugs that differ from the standards established for investigations involving devices, FDA should perpetuate the different standards in its informed consent regulation. Neither of these comments argued that the concept of informed consent had not changed since the Drug Amendments were enacted in 1962, and neither comment offered any particular investigational situation in which they thought an investigator might reasonably determine, as provided in sections 505(i) and 507(d) of the act, that obtaining informed consent would not be "feasible" or "in an investigator's professional judgment, [would be] contrary to [a subject's] best interests."

Only one of the comments objecting to the promulgation of a single standard

offered any extensive rationale for the objection raised. This comment argued that FDA should perpetuate in its informed consent regulation, the "therapeutic privilege" exemption provided by Congress when it enacted the 1962 Drug Amendments. This comment stated that in choosing to disregard the "therapeutic privilege" exemption, FDA was intruding into both the realm of congressional prerogative and the practice of medicine.

According to this comment, the circumstances in which the "therapeutic privilege" ought to apply, were as follows:

> * * * A departure from the absolute requirement of informed consent is necessitated when "patient psychology" is such that a physician must be free to use a new therapeutic measure, without obtaining the patient's informed consent, if in his judgment it offers help of saving life, re-establishing health, or alleviating suffering. When a drug is being used in a clinical investigation *primarily for treatment*, the circumstances call forth the standards pertinent to the traditional physician-patient relationship, instead of those applicable to pure research. (Emphasis added.)

Basically, this comment assumes that a clinical investigation which involves an investigational article used primarily for treatment is not really an "investigation" at all, but is simply "the practice of medicine," and the basic objection expressed seems to be that obtaining informed consent could unjustifiably frighten patients away from participation in an investigational study that might provide significant benefits for that individual and/or society as a whole, while presenting little or no risk to the individual participant.

FDA has considered the objections raised by these comments, has conducted an extensive review of the current legal requirements for informed consent in the treatment as opposed to the investigational/experimental setting, and finds, for the reasons discussed below, that the uniform approach proposed is justified.

The "therapeutic privilege" in the context of experimentation has been subject to increased criticism in recent years. In a paper on the Law of Informed Consent prepared for the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Ref. *1*), the authors concluded that nondisclosure based upon a physician's judgment that it is not in the patient's best interest to know, should never be allowed in the experimental setting.

The authors of this report, who surveyed international, Federal, and local standards of informed consent, concluded that because the purpose of the "therapeutic privilege" doctrine was to make sure that patients get treatment that physicians believe they need, it could have no application to nontherapeutic experimentation where no treatment is involved. The authors also concluded that,

> * * * Because of the great potential for abuse, e.g., the withholding of information for convenience or to assure the patient will not reject the treatment, and because the probability of success with an experimental treatment is either not known or very low, this exception should also not be permitted in the case of therapeutic experimentation. Indeed, as has been noted by a number of commentators, in this situation the physician-experimenter may have much more ability to obtain consent for an experiment than he would have from a normal volunteer who neither has an established dependency relation with him nor expects that the proposed experiment might be personally beneficial to him. As Professor Alexander Capron has observed: The "normal volunteer" solicited for an experiment is in a good position to consider the physical, psychological, and monetary risks and benefits to him when he consents to participate. How much harder that is for the patient to whom an experimental technique is offered during a course of treatment! The man proposing the experiment is one to whom the patient may be deeply indebted for past care (emotionally as well as financially) and on whom he is probably dependent for his future well-being. The procedure may be offered, despite unknown risks, because more conventional methods have proved ineffective. Even when a successful but slow recovery is being made, patients offered new therapy often have eyes only for its novelty and not for the risks.
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> In order to protect self-determination and promote rational decision-making, more, not less, information should probably be required to be disclosed in the experimental therapy situation than in the purely experimental setting with a normal volunteer (Ref. *1*).

FDA agrees with the findings contained in the special report on the Law of Informed Consent. The standard of practice regarding informed consent promulgated by Congress in the Drug Amendments of 1962 was the standard that prevailed at that time. It is not the standard of practice today. FDA is concerned that research subjects be adequately protected from abuses of the kind that have taken place in the past (44 FR 47713–17); and is convinced that one way to protect research subjects against abuse is to ensure that they have the opportunity to be adequately informed before they consent to participate.

FDA does not believe that promulgating a single standard that reflects both current congressional thinking and current standards regarding the practice of medicine represents an unreasonable encroachment upon the prerogatives of either Congress or the medical community. Congress expressly recognized at the time the Medical Device Amendments of 1976 were passed that, in view of changing social policy and advancing biomedical technology, the informed consent provisions of the Medical Device Amendments should be implemented through regulations based upon the recommendations to be made by the National Commission (Ref. *2*). Indeed, the very purpose for which Congress established the National Commission was to assure a thorough review of the basic ethical principles underlying the conduct of biomedical and behavioral research (44 FR 47716).

FDA believes that the regulation does not encroach upon the prerogatives of the medical community because a review of court decisions which have involved informed consent casts doubt on whether the so-called "therapeutic privilege" to dispense with informed consent has any continued viability even in the standard practice of medicine. With increasing frequency, courts have held that when a patient is harmed by a treatment to which he or she might not have consented had he or she been adequately informed of the risks involved in that treatment, the doctor's failure to obtain informed consent may result in a finding of liability for negligence. In *Cobbs* v. *Grant*, 8 Cal. 3d 229, 502 P.2d 1 (1972), the California Supreme Court discussed at length the thesis that medical doctors are invested with discretion to withhold information from their patients and found that discretion to be extremely limited, stating that, "it is the prerogative of the patient, not the physician, to determine for himself the direction in which he believes his interests lie. To enable the patient to chart his course knowledgeably, reasonable familiarity with the therapeutic alternatives and their hazards becomes essential." *Cobbs, supra*, at 242–243. The California Court held that a duty of reasonable disclosure of the available choices with respect to proposed therapy and of the dangers inherently and potentially involved in each choice was an "integral part of the physician's overall obligation to the patient." *Cobbs, supra*, at 243. Under the *Cobbs* rationale, a patient's informed consent is an absolute requirement except in an emergency situation or in a situation in which the patient is a child or incompetent, in which case consent is either implied or sought from a legal

guardian. Thus, in *Cobbs*, the California Court found that consent of the quality required by this regulation should have been obtained from the patient and that it was the patient's prerogative to make the treatment decision based upon adequate information, not the physician's prerogative to limit the patient's choices by limiting the information provided. See generally, *Pharmaceutical Manufacturers* v. *Food Drug Administration*, 484 F. Supp. 1179, 1188 (D. Del. 1980).

The subject of negligence and informed consent is also discussed at length in *Canterbury* v. *Spence*, 464 F.2d 772 (D.C. Cir. 1972), *cert. denied*, 409 U.S. 1064 (1972), an action involving, among other things, the sufficiency of the information provided to a patient. Beginning with the fundamental premise that, "every human being of adult years and sound mind has a right to determine what shall be done with his own body," the *Canterbury* court defines "true consent" as the informed exercise of a choice that, in turn, entails an opportunity to evaluate knowledgeably the options available and the risks attendant upon each. *Canterbury, supra*, at 780. The *Canterbury* court flatly rejected the suggestion that disclosure of risk be discretionary with the physician, stating that any definition of the scope of disclosure purely in terms of a "professional standard" would be "at odds with the patient's prerogative to decide on projected therapy himself." *Canterbury, supra*, at 786. The *Canterbury* court discussed two exceptions to the general rule of disclosure—(1) when the patient is unconscious or otherwise incapable of consenting and (2) when risk-disclosure would be so detrimental as to be unfeasible from a medical point of view. The latter exception, according to the court, must be carefully circumscribed, "for otherwise it might devour the disclosure rule itself. The privilege does not accept the parternalistic notion that the physician may remain silent simply because divulgence might prompt the patient to forego therapy the physician feels the patient really needs." *Canterbury, supra*, at 789. The court did not further elucidate the second exception to disclosure other than to limit it to situations in which the patient's reaction to risk information is "menacing." *Id.* What, precisely, the court meant by "menacing" is not clear. A Massachusetts Court, however, has found that although disclosure of the potential side-effects of a medication might be "frightening" to a mental patient, that fact alone would not justify a failure to inform. See *Rogers* v. *Okin*, 478 F. Supp. 1342, 1387 (D. Mass. 1979).

Both *Cobbs* and *Canterbury* were decided in 1972. Since 1972 it has become increasingly clear that a lack of informed consent will result in actionable negligence where injury results, and that the physician's duty to inform includes a duty to impart information sufficient to enable a patient to make an informed decision. The courts recognize that standard of informed consent has evolved and that the standard now requires full disclosure in all but the exceptional case. See *Dessi* v. *United States*, 489 F. Supp. 722 (E.D.Va. 1980); *Rogers* v. *Okin*, 478 F. Supp. 1342 (D. Mass. 1979).

It is not for the medical profession to establish a criterion for the dissemination of information to the patient based upon what doctors feel the patient should be told. See *Lambert* v. *Park*, 597 F.2d 236, 239 n.7 (10th Cir. 1979). According to *Lambert*, a standard that requires all material risks to be divulged,

> * * * Insures the important social policy underlying informed consent, that is, a physician should be required to disclose to his patients all material risks of a proposed procedure *even if other doctors in the community or specialty would not have made so full a disclosure.* This is simply an application of the well-known tort doctrine that proof of compliance with the applicable "industry" standard will not insulate a defendant from liability when the standard itself is inadequate. *Id* at 238–239.

It seems clear that the current standard of care as defined by case law requires disclosure in the ordinary case of exactly the kind required by this regulation. If such full disclosure is required for nonexperimental treatment, it can hardly be argued that it can be dispensed with when the treatment is experimental. See *Ahern* v. *Veterans Administration*, 537 F. 2d 1098 (10th Cir. 1976). The agency, therefore, reaffirms its proposal of a uniform standard governing informed consent.

3. Several comments questioned the applicability of these regulations to studies conducted outside the United States. A few comments stated that standards of protection for human subjects may vary from country to country, and that the United States should not impose its standards on other countries when the human subjects come from those foreign countries in which the studies are being conducted.

FDA agrees with the comments, and notes that its policy regarding investigational studies involving drugs and biological products is set out in § 312.20 *Clinical data generated outside the United States and not subject to a "Notice of Claimed Investigational Exemption for a New Drug"* (21 CFR 312.20). The policy regarding foreign studies and the background to § 312.20 was set out in detail in the preambles to the proposed and final regulation. See 38 FR 24220; September 6, 1973, and 40 FR 16053; April 9, 1975. The agency's policy regarding studies of investigational devices conducted outside the Untied States is similar to that for drugs and biological products and is discussd in the preamble to the recent proposal to establish procedures for the premarket approval of medical devices (PMA), published in the **Federal Register** of December 12, 1980 (45 FR 81769). Proposed § 814.15 of the PMA proposal states the agency policy concerning devices.

The Proposed Regulation

Part 50 will apply to all clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 520(g) of the act, as well as to clinical investigations that support applications for research or marketing permits for products regulated by FDA. These provisions are contained in § 50.1 (21 CFR 50.1) which was promulgated with Subpart C—Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects published in the **Federal Register** of May 30, 1980 (45 FR 36386). When complete, Part 50 will contain all of FDA's regulations concerning the Protection of Human Subjects.

The August 14, 1979 proposal contains all of the definitions applicable to Part 50. The definition of "application for research or marketing permit" (21 CFR 50.3(b)) was made final at the same time as Subpart C—Protections Pertaining to Clinical Investigations Involving Prisoners as Subjects (45 FR 36396), and therefore, is not included here. The definition of that term also may be found as part of Part 56 on Institutional Review Boards (IRB's) which is published elsewhere in this issue of the **Federal Register.** The definitions made final here are congruent with those made final with Part 56, and many of the comments received in response to the IRB proposals were similar to the comments received in response to the Informed Consent proposal. A discussion of the definitions other than "application for research and marketing permit," and comments received in response to this and to the prisoner research proposal follow:

4. Several comments suggested that the proposed definition of clinical investigator in § 50.3(c) was too broad and should be limited through the explicit exclusion of particular kinds of

research such as that involving minimal risk.

FDA disagrees. The National Commission stated that even in no-risk or low-risk studies, respect for the rights and dignity of human subjects would require informed consent before participation in any clinical investigation. Informed consent is, as stated in § 50.20, required in all research subject to these regulations.

5. Two comments suggested that the proposed wording of § 50.3(d) defining "investigator" should be amended to include the primary investigator who might not be the person who actually conducts the investigation or gives immediate direction to those administering or dispensing the test article.

The agency agrees that an investigation may be conducted by several investigators and has modified the language of § 50.3(d) to define the term more broadly. Added to the definition is the language "* * * in the event of an investigation conducted by a team of individuals, is the responsible leader of that team."

6. On its own initiative, FDA has deleted proposed § 50.3(e) defining "person" because the only time that it is used in these regulations is to refer to a living individual. Although additional definitions for the term are applicable to other FDA regulations, they are not applicable to informed consent.

7. One comment stated that proposed § 50.3(h) defining "subject" could be interpreted to deny the administration of a placebo or other control to an unhealthy human.

The agency did not intend the definition of subject to be ambiguous and § 50.3(g) has been slightly modified in this final rule. The definition now clearly states that a subject participates in a clinical investigation either as a recipient of the test article or as a control.

8. Section 50.3(h) defining "institution" replaces § 50.3(i) from the proposed regulations. The revised definition is consistent with the HHS definition and includes any entity including manufacturers, hospitals, and nursing homes.

9. The proposed definition of "institutionalized subject" has been deleted from the final regulations. Because the scope of coverage extends to human subjects, whether or not institutionalized, there is no need for a separate definition for institutionalized subjects at this time.

10. One comment questioned inclusion of cosmetics in proposed § 50.3(k) because cosmetics are not subject to premarket approval and therefore should not be included in the definition of "test article."

The agency agrees and has deleted the term from § 50.3(k) of the final rule, defining "test article." Because cosmetic studies are not submitted to FDA in support of an application for research or marketing permit, they are not subject to Part 50.

11. One comment suggested that FDA adopt the HHS definition of "minimal risk."

FDA agrees with the comment, and has revised the definition in § 50.3(l) accordingly. This definition takes into account the fact that the risks in the daily life of a patient are not the same as those of a healthy individual, and uses the risks in daily life as the standards for minimal risk.

12. Section 50.3(m) defining "legally authorized representative" has been revised slightly from the definition proposed by FDA so that it is identical to the HHS definition.

13. One comment on proposed § 50.20 suggested that incomprehensible consent forms would be useless to human subjects and that FDA should require that information be communicated to subjects in language they can understand.

FDA agrees that information given to human subjects should be in language they can understand, and notes that the National Commission also made this recommendation. Section 50.20 has been reworded to require that information given to the subject or the subject's legally authorized representative be in language that is understandable to the subject or the representative.

14. One comment suggested that all minimal risk studies be exempted from the requirements for informed consent.

The agency does not agree. Both the HHS regulations and the FDA regulations reflect the belief that even minimal risk studies require the informed consent of human subjects before they may participate in a research study. Informed consent is, therefore, a uniform requirement for all investigational studies, no matter how low risk an investigator may believe them to be.

15. One comment suggested that the IRB should determine when informed consent would be necessary. Another comment suggested that low-risk and no-risk studies be exempted from the requirement of informed consent.

FDA disagrees and rejects the comments. Sections 505(i), 507(d) and 520(g) of the act (21 U.S.C. 355(i), 357(d) and 360j(g)) require that FDA promulgate regulations for the exemption of drugs and devices for investigational use. These sections of the act direct FDA to promulgate regulations that will ensure that informed consent will be obtained from each subject or each subject's legally authorized representative as a condition to the issuance of the exemption. The National Commission stated that even in no-risk or low-risk studies, respect for the rights and dignity of human subjects would require informed consent before participation in any clinical investigation. FDA agrees with this position and requires that informed consent be obtained from each subject or representative before a subject may participate in a clinical investigation. The only exception from the requirement which applies to individual situations and not to categories of studies as a whole, is the provision in § 50.23 for emergency use of a test article.

16. One comment stated that FDA lacked the authority to reject a study if the requirement for informed consent were not followed. The comment further stated that in order for FDA to reject a study, the noncompliance with the regulatory requirements must affect the scientific validity of the data generated.

FDA disagrees with the comment. The Federal Food, Drug, and Cosmetic Act also requires that these regulations have due regard for the interests of patients (21 U.S.C. 355(j)(1) and 21 U.S.C. 357(g)(1)) or be consistent with ethical standards (21 U.S.C. 360j(g)(1)). Therefore, FDA believes it possesses the necessary statutory authority to reject studies where informed consent has not been obtained even though the scientific validity of the data generated may not have been affected, and it reserves the right to do so where circumstances so warrant.

17. Several comments argued that the proposed requirements of § 50.21 concerning the effective date of the regulations were too complicated, too burdensome, and not really necessary for the great number of studies. These comments suggested that the revised informed consent requirements apply only to individuals entering a clinical investigation after the effective date of the regulation.

The agency has considered these comments and agrees that only prospective application of the new uniform informed consent provisions will be required. The requirements of both Part 50 and Part 56 will become effective at the same time, that is, July 27, 1981, and will be applicable only to clinical investigations that begin on or after this date.

In determining that the requirements need apply only prospectively, the agency has taken a number of factors

into account. It has balanced the cost of compliance against the possible added protections to be gained by research subjects, and has determined that the potential cost of imposing the requirements retroactively outweighs the potential gain. The informed consent regulations that will continue to be in effect until the effective date of Part 50 have assured that at least minimum standards of informed consent have been met in studies initiated before the effective date of this regulation. In addition, the agency believes that where an inspection reveals deficiencies in the informed consent obtained in a particular ongoing study, correction can be obtained administratively. Further, at the time an IRB performs its continuing review, the IRB may require correction of deficiencies if, in its judgment, such correction is required. The agency believes, therefore, that prospective application will be sufficient.

18. One comment on proposed § 50.23(a)(2), the exception provided for situations in which communication with the subject is not possible, stated that, as written, the section could apply when a subject spoke only a foreign language.

The agency does not agree. For the exception to apply, all four requirements of the subsection must be met. Inability to communicate in the context of § 50.23(a) clearly means that the subject is in a coma or unconscious. The exception is to be invoked only in emergency situations.

19. One comment stated that the exception requirements of proposed § 50.23 were too restrictive and should be modified to allow an investigator to proceed without consent in a nonlife-threatening but "serious" emergency.

The agency does not agree. The requirements of § 50.23 are based on section 520(g)(3)(D) of the act. Those requirements are quite explicit and allow that consent be dispensed with only if the emergency situation is "life threatening." The comment is rejected.

Elements of Informed Consent

Many comments were received on the eleven basic and five additional items proposed in § 50.25 as the elements of informed consent. Many of these comments suggested that there were too many elements proposed, that they were duplicative, and that they would simply confuse research subjects. Other comments suggested that the elements proposed were too few and suggested the addition of other items of information to the list of elements proposed. The individual comments are discussed below.

20. Several comments said that the statement that an IRB had approved the solicitation of subjects to participate in the research, required by proposed § 50.25(a)(1), could mislead human subjects into thinking that because the study had been approved by an IRB there was no need for them to evaluate for themselves whether or not they should participate in the study.

FDA agrees with these comments and has deleted this requirement from the final regulations. Proposed § 50.25(a)(1) and (2) have been combined.

21. Several comments stated that the proposed requirements contained in § 50.25(a)(2), regarding the scope and aims of the research would require explanations that were both too complex and too lengthy to be meaningful to subjects. Another comment asserted that the word "scope" was so vague as to be meaningless while "aims" was synonymous with "purposes." All of these comments suggested that § 50.25(a)(2) should be simplified so that subjects receive only meaningful information.

The agency agrees with the comments and has rewritten the section for clarity. The requirement now reads: "an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of those procedures which are experimental."

22. Several comments on proposed § 50.25(a)(3) (renumbered as § 50.25(a)(2) in the final rule) objected to including a statement of the likely results if an experimental treatment should prove ineffective. A few comments pointed out that in some studies involving cancer chemotherapies, it would be unkind to include such a statement in the informed consent document because the likely result of ineffective treatment would be death. Other comments pointed out that an explanation of the likely results of an ineffective treatment would not be applicable in a study of normal, healthy volunteers because there would be no difference to them if the treatment failed.

FDA agees with the comments and has deleted the specific language regarding ineffective treatment from the regulation. The agency points out, however, that if an ineffective treatment would result in either a foreseeable risk or discomfort it would have to be described in any case under § 50.25(a)(2).

23. One comment on proposed § 50.25(a)(3), (4), and (5) suggested that investigators should be required, where possible, to give test subjects quantified comparative estimates of risks and benefits of experimental and alternative treatments.

FDA agees that, were it always possible to quantify the risks, benefits, and comparative treatments for purposes of estimation, such quantification would be required. The basis elements represented by § 50.25(a)(2), (3), and (4), do require that human subjects be given a description of any reasonably foreseeable risks or discomforts, benefits, and a disclosure of appropriate alternative procedures or courses of treatment. FDA believes that where such descriptions or disclosures can contain quantified comparative estimates of risks and benefits, they should do so. Where such well-defined estimates are not possible, however, the agency believes that the information required to be disclosed will be sufficient. The agency does not believe that imposing such a strict requirement for every case would be realistic or appropriate.

24. One comment stated that FDA's preliminary assessments of an experimental drug's therapeutic significance should routinely be made available to subjects of drug testing and that this should be included as a basic element of informed consent.

FDA does not agree. FDA's preliminary assessment of the therapeutic significance of an experimental drug or device is based on the same data that are available to an IRB at the time of its initial or continuing review. To the extent that an IRB believes that preliminary data assessment is appropriate to include in a consent form, it may so require.

25. One comment on proposed § 50.25(a)(4) (§ 50.25(a)(3) in the final rule) urged the agency to add a specific requirement that a subject be told if it is reasonably anticipated that the study will neither improve nor relieve his or her condition.

The agency does not agree that such specific language need be added. Adequate disclosure of risks (§ 50.25(a)(2)), benefits (§ 50.25(a)(3)), and appropriate alternative treatments (§ 50.25(a)(4)) will provide sufficient information to a subject to enable the subject to decide whether or not to participate. When use of a test article clearly will not benefit a particular condition, that fact should be made known as a reasonably foreseeable risk.

26. One comment stated that the requirement that benefits be described would be meaningless to normal, healthy volunteers because they would receive no benefit, and therefore, suggested that this requirement be deleted from § 50.25(a) and included in

§ 50.25(b). *Additional elements of informed consent.*

FDA rejects the comment. The agency believes that even if subjects receive no personal benefit from the study, others may receive some benefit, and, where it may reasonably be expected that others may benefit, that information should be disclosed.

27. One comment on proposed § 50.25(a)(5) (§ 50.25(a)(4) in the final rule) stated that a mere disclosure of appropriate alternative treatments would not be sufficient, and suggested that an investigator should have to describe the risks and benefits of such alternatives.

The agency believes that the requirement, as worded, is sufficient. Any explanation of "appropriate alternative treatments" that did not contain some explanation of the risks and benefits of the alternatives would not be a true "disclosure." The agency believes that the full description sought by the comment is required by the element as written.

28. Another comment on proposed § 50.25(a)(5) suggested that the consent form should merely state that alternative treatments are available.

FDA disagrees and rejects the comment because it is important for a human subject to have specific information about alternative treatments in order to evaluate the risks and benefits of experimental treatment. Therefore, except for being renumbered, § 50.25(a)(4) remains unchanged in the final regulation.

29. Several comments on proposed § 50.25(a)(6) suggested that a statement that "new information" developed during the course of the research be provided to the subject, would not be appropriate in every study. In particular, these comments stated that such a statement would be irrelevant to either a single-dose clinical study or a study of extremely short duration.

FDA agrees that the statement should not be required in every case and has, therefore, made this provision an "additional" element to be required when appropriate and is issuing it as § 50.25(b)(5) in the final rule. When appropriate, in this case, will mean in every study of sufficient duration, which the agency believes can be decided by the IRB.

30. Several comments on proposed § 50.25(a)(6) stated that the term "new information" is too all-encompassing and would be extremely difficult to interpret. A few comments suggested that "significant new findings" would be an appropriate substitute for "new information."

FDA agrees with the comments and has substituted "significant new findings" for "new information." Thus, only relevant substantive information that might affect a subject's willingness to continue participation in the study need be communicated.

31. One comment stated that proposed § 50.25(a)(6) was unnecessary because it is implicit in every clinical investigation that an ethical and conscientious researcher would inform subjects if new risks or side effects were noted. One comment suggested that the requirement was unnecessary because other regulations require prompt notification and withdrawal of treatment following the occurrence of serious adverse reactions.

FDA disagrees with these comments. FDA believes that an investigator should be required to advise subjects of new risks or adverse reactions that may affect the subject's willing and continued participation in the study. Therefore, even though an ethical investigator would notify subjects of newly determined risks or adverse reactions, and other regulations require prompt reporting to the IRB and FDA of these findings, FDA believes that the investigator should be explicitly required to tell subjects of significant new findings, when necessary and appropriate. The comments are rejected.

32. A number of comments objected to the requirement, contained in proposed § 50.25(a)(7) (§ 50.25(a)(5) in the final rule), that research subjects be informed in advance of their participation in an investigation that FDA may inspect the subject's records. Several of these comments asserted that if subjects were so informed they would refuse to participate in FDA-related investigations.

The agency does not believe that telling subjects that their records might be inspected by FDA will be a serious deterrent to subject participation. Medical records are frequently subject to third party review (e.g., insurance companies) and, although it may be true that informing potential subjects that study records may be inspected by FDA may deter some subjects from participation, that fact can scarcely be cited as a reason not to inform. Indeed, it is particularly important that any subject who feels strongly that his or her study records ought not be seen by anyone other than the clinical investigator be told ahead of time that an expectation of total privacy is not realistic in the context of clinical research being conducted for submission to FDA.

As discussed in the preamble to the proposal, FDA believes in the protection of subject privacy, and FDA does not routinely inspect subject records. However, the agency must inspect such records when it has reason to believe that the consent of the subjects was not obtained or when there is reason to believe that the study records do not represent actual studies or do not represent actual results obtained. Where an individually identifiable medical record is copied and reviewed by the agency, the record is properly safeguarded within FDA and is used or disseminated under conditions that protect the privacy of the individual to the fullest possible extent consistent with laws relating to public disclosure of information (e.g., Freedom of Information Act and Privacy Act) and the law enforcement responsibilities of the agency. Clinical studies are submitted to FDA to obtain an approval to market a regulated product, and the agency must be able to verify the basis for an approval whenever either a question of validity of results or subject rights arises. Moreover, not all raw data produced in the course of a clinical investigation involves "patient records" of the kind envisioned by many of the comments. Many clinical investigations are short-term and involve subjects who may or may not be patients. There may or may not be a doctor-patient relationship between the clinical investigator and the subject and there may or may not be an expectation on the part of the subject that the records of his or her participation in the investigation will be treated as confidential. Subjects who participate in clinical investigations are frequently paid to participate, and, in such cases, the relationship between the investigator and the subject will be a contractual one. For example, in those cases in which a sponsor or monitor will review the subjects' records, the subjects should be so informed. It is particularly important that any subject who has an expectation of privacy regarding the subject's records of participation in FDA-regulated research be informed about the extent to which these records will be kept confidential so that any subject who feels strongly about the records may refuse to participate. The agency believes that providing this information to a subject is both fair and necessary. The motivation of subjects who participate in clinical research varies widely, and the agency does not believe that providing this information will prevent vast numbers of subjects from agreeing to participate. The comments do not require any change in § 50.25(a)(5).

33. Several of the comments on proposed § 50.25(a)(7) objected that the requirement of a notice in the consent document that FDA might inspect subject records constituted a request that subjects waive their legal rights to privacy as a condition to giving their informed consent. One comment stated that proposed § 50.20 prohibits inclusion in informed consent documents of exculpatory language that waives or appears to waive a subject's legal rights. As an alternative to proposed § 50.25(a)(7), several comments suggested that the regulation be revised to provide that FDA would seek permission from individual patients to inspect or copy their records if the need arose.

The agency rejects all of these comments. The basis of FDA's right to inspect subject records was discussed both in the preamble to the proposal (44 FR 47721) and in the response to comment 32 in this preamble. The agency is not requiring any subject to "waive" a legal right. Rather, the agency is requiring that subjects be informed that the "legal right" to privacy that they might expect in other contexts does not apply in the context of regulated research. FDA need not "seek permission" when the need to inspect such records arises because to do so would, in essence, delegate improperly an authority vested in the agency by Congress.

34. Two comments noted that because FDA states in the preamble to the proposal that it has the right to copy medical records containing the names of research subjects when there is reason to believe that consent was not obtained, or there is doubt that the records represent actual studies or actual results obtained, proposed § 50.25(a)(7) should provide that the consent form also inform the research subject that identifying information may be inspected and copied by FDA.

FDA believes that the required statement, as phrased, is sufficient. The language, therefore, as issued in § 50.25(a)(5) of this final rule is unchanged.

35. One comment stated that many institutions would not wish to include the notice required by § 50.25(a)(5) on all their consent forms. Therefore, there would have to be a separate consent form for FDA-regulated research. This comment suggested that this requirement be deleted.

FDA rejects the suggestion. While it may be true that some institutions do not wish to have the notice of possible FDA inspection of subject records on all of their consent forms, the agency believes it is important that human subjects included in FDA-regulated research be aware that FDA might need to see their records. FDA believes that consent forms should be individualized for each study in any case, because standardized consent forms could not possibly take into account all the elements necessary to obtain adequate informed consent for every clinical investigation.

36. Several comments on proposed § 50.25(a)(9) (§ 50.25(a)(6) in the final rule) stated that because of the possibility of unanticipated injuries, it would be impossible to describe in advance the nature of any compensation and medical treatment for injury that might occur as a result of the study. Several comments stated that it would be difficult, if not impossible, to distinguish between those injuries that are compensable and those that are not.

These comments misunderstand the requirement. All that is required is a statement that compensation or medical treatment are or are not available if unanticipated injuries occur and of what they consist. Such a statement will be adequate if it merely states that medical care will or will not be provided in the event of injury and describes the extent of available compensation, if any. Compensation for injury may vary with the extent of the injury or may be limited. A description so stating will be adequate.

37. One comment suggested that because proposed § 50.25(a)(10) was merely an extension of § 50.25(a)(8), they should be combined.

The agency agrees. Proposed § 50.25(a)(8) required an offer to answer any questions the subject or the subject's representative might have about the research, the subject's rights, or related matters. Proposed § 50.25(a)(10) required that the subject be told whom he or she should contact if harm occurred or if there were questions. These two requirements have been combined and published in this final rule as § 50.25(a)(7). This provision requires that subjects be given an explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.

38. One comment on proposed § 50.25(a)(8) stated that although the clinical investigator could respond to questions concerning the research, the clinical investigator was not necessarily the appropriate person to answer questions about the subject's rights.

While the comment may be true, the final regulation issued as § 50.25(a)(7) does not require that one particular person answer all questions raised by the subject. Rather, the regulation requires that a subject be told whom to contact regarding particular problems. Where one person cannot respond to all the questions, more may and should be designated. The agency believes that the final regulation clarifies this provision.

39. One comment suggested that the information regarding whom to contact was merely a procedural item and that it should, therefore, not be a "basic" element of § 50.25(a) but should be made an "additional" element of proposed § 50.25(b).

FDA disagrees. The items of information required to be disclosed under "additional elements," § 50.25(b)(1) through (6), are those items that are either irrelevant to some categories of research (i.e., single-dose studies) or items that are discretionary and that may be required by the IRB. The information regarding whom to contact is equally important in all studies, should be required to be provided in every case, and therefore is retained in § 50.25(a)(7) of this final rule.

40. Two comments suggested that proposed § 50.25(a)(11) (§ 50.25(a)(8) in the final rule), as worded, might be interpreted to mean that a subject who was being paid to participate in a clinical investigation could receive full payment even if he or she dropped out. These comments suggested that the provision be revised to state that a subject could discontinue participation "without loss of already earned benefit."

The agency does not agree that the provision should be revised. In any study in which a subject is paid, the contractual agreement may specify the basis of compensation and, therefore, the degree of "entitlement." If, in such a case, full payment requires completion of the study, and a subject fails to complete the study, he or she will not be "entitled" to full compensation. All that is required is that a full explanation be provided. The agency does not find that the wording of § 50.25(a)(8) is ambiguous on this point and the comments are rejected.

41. One comment on proposed § 50.25(b) stated that the regulations could allow IRB's and investigators to deny human subjects information necessary for informed consent because that information was listed under "Additional elements."

FDA disagrees with this interpretation. The elements of informed consent listed as "additional" are not needed in every clinical investigation. However, when any of those additional elements would be appropriate, § 50.25(b) requires that the additional information be provided to the subject.

42. Several comments suggested that the "Additional elements" of proposed § 50.25(b) be required as basic because they are all material to informed consent.

FDA disagrees with the suggestion. The elements listed as "additional" are not material to every clinical investigation. For example, the requirement of § 50.25(b)(5) in the final rule that significant new findings be communicated to the subject if those findings might affect the patient's willingness to continue participation in the study, is not relevant to single-dose studies.

43. One comment on proposed § 50.25(b)(1) suggested that this "additional" element as written was overbroad.

The agency does not agree that the element is overbroad. However, for clarity, § 50.25(b)(1) has been revised and has been shortened by deleting the second sentence.

44. Two comments suggested that proposed § 50.25(b)(2) be deleted. The comments argued that the required information was inherent in the required disclosure of foreseeable risks or discomforts and that providing information about foreseeable circumstances under which a subject's participation may be terminated would be impractical because such possible circumstances were "infinite."

The agency disagrees. Not every hypothetical circumstance in which a subject's participation might be terminated need be disclosed. The regulation requires only a discussion of anticipated circumstances. It might well be sufficient to state that a subject's participation might be terminated when, in the judgment of the clinical investigator, it is in the subject's best interests although in such a case some illustrative situations should be provided. For clarity, the word "anticipated" has been substituted for the word "forseeable" as used in the proposed regulation to describe circumstances.

45. One comment on proposed § 50.25(b)(3) suggested that the requirement that information on possible additional costs "to others" besides the subject be provided was unclear, would have infrequent application, and could be misleading because it might refer to additional costs to the investigator or the sponsor.

The agency agrees and has deleted the words "to others." Section 50.25(b)(3) now requires that information be provided only on possible resulting additional costs to the subject.

46. One comment on proposed § 50.25(b)(5) (§ 50.25(b)(4) in the final rule) stated that providing information on the consequences of a decision to withdraw from a study was unnecessary because the information would duplicate the requirements of other sections of the informed consent regulations.

The agency does not agree. There may be studies in which specific information on the consequences of a decision to withdraw will be of particular importance. The information need only be provided in those cases. IRB review should help identify those studies in which the information would be appropriate.

47. As discussed in responses to comments 29 through 31, the proposed requirement of § 50.25(a)(6) to provide to all subjects in any investigation, a statement regarding new " information" has been determined to be more appropriately an additional element of consent and included in the final rule as § 50.25(b)(5).

48. A number of comments on proposed § 50.25(b)(4) (§ 50.25(b)(6) in the final rule) stated that disclosing the name of the sponsor, the responsible institution, and who was funding the study would add nothing to the quality of a subject's consent because none of the items of information were likely to be important to a subject's decision to participate in research.

The agency agrees that, for the most part, the items of information proposed need not be specifically provided and has, therefore, deleted the language regarding funding, responsible institution, and sponsor. Because the approximate number of subjects participating may have a bearing on a subject's decision to participate, however, that requirement is retained in § 50.25(b)(6). Where multi-institutional studies are involved, an indication of the number of institutions and the approximate number of subjects will be sufficient.

49. On the agency's own initiative, two new paragraphs have been added to § 50.25. Section 50.25(c), which states that the requirements of these regulations are not intended to preempt any applicable Federal, state, or local laws which require additional information to be disclosed, is added to make the policy clear and to conform to the HHS language. Section 50.25(d), which states that these regulations are not intended to limit the authority of a physician to provide emergency medical care to the extent permitted under other applicable statutes, was initially proposed as § 50.23(d). It has been finalized without change and moved to conform to the HHS placement.

50. Section 50.27 requiring an investigator to document informed consent has been revised and shortened. The language of the section conforms to the language of the HHS regulation.

51. Several comments stated that to require a long, detailed consent form would be confusing and would detract from the intended purpose of the regulation that relevant information about a study be conveyed to the human subject.

The agency, as noted in responses to comments on proposed § 50.25, has simplified the informational requirements of the regulation and has required that the information given to a subject be in understandable language. FDA recognizes that the documentation of informed consent represents only one part of the entire consent process. The consent form itself is merely an aid to assure that a required minimum of information is provided to the subject and that the subject consents. The entire informed consent process involves giving the subject all the information concerning the study that the subject would reasonably want to know; assuring that the subject has comprehended this information; and finally, obtaining the subject's consent to participate. The process, to be meaningful, should involve an opportunity for both parties, the investigator and the subject, to exchange information and ask questions. The consent form, thus, should not be viewed as an end point. Rather, it is the beginning. The agency concludes that the comments do not justify any specific changes to § 50.27, although, as stated in comment 50, the regulation has for other reasons been revised and shortened.

52. One comment stated that the documentation of informed consent by a short form will not ensure that subjects understand the oral explanations. The comment further stated that subjects would have to rely solely on the interpretation given to them by the investigator.

FDA disagrees with the comment. The same quantum and quality of information, i.e., that information required by § 50.25, must be provided to a subject whether a long form, a short form, or no form is used (see also § 56.109(c)). The fact that a short form is used to document informed consent does not mean that the subject will get less information than if handed a long, detailed written document. When a "short form" is used, the IRB must first approve a written summary of what is to be said, and a witness must be present to attest to the adequacy of the consent process and to the voluntariness of the

subject's consent. Section 50.27(b)(2) also requires that a copy of that summary be given to the subject. FDA believes that in many cases an oral presentation and written summary will be an effective method of disclosing necessary information. All the "form" provides, in either case, is evidence that the information required by § 50.25 has been provided to a prospective subject. The "form" itself cannot subsitute for the communicative process that it represents and, as noted in response to comment 51, it is not intended to.

53. The agency received no comments on the proposed conforming amendments and except for combining the proposed amendments relating to Parts 50 and 56, they are issued as proposed.

54. On its own initiative, the agency is revising 21 CFR 312.20(b)(1)(iv) by replacing the 1964 Declaration of Helsinki with the revised version adopted by the World Medical Assembly in 1975. The Declaration, first adopted by the World Medical Assembly in 1964 (see 44 FR 47715), was revised by that group, and the revision adopted at the 29th World Medical Assembly held in Tokyo, in October 1975. The revision includes a number of new requirements, among them the requirement that a research protocol be reviewed by a specially appointed independent committee.

55. On its own initiative, the agency is also adopting amendments to the Investigational Device Exemptions (IDE) regulations (21 CFR Part 812) to conform them to Part 50. The IDE regulations were promulgated by FDA on January 18, 1980 (45 FR 3732) after the August 14, 1979 proposal of these regulations.

References

The following material has been placed on file in the Dockets Management Branch, Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be seen by interested persons from 9 a.m. to 4 p.m., Monday through Friday.

1. Annas, G. J., "The Law of Informed Consent to Human Experimentation: An Introduction with Specific Reference to the Hospital Patient and the Normal Volunteer," prepared for the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, NIH Contract No. NO1–HU–6–2120, June 1976.

2. H.R. Rept. No. 94–1090, 94th Cong., 2d Sess. (1976).

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701(a), 706, and 8901, 52 Stat. 1049–1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 52 Stat. 463 as amended, 68 Stat. 511–517 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 76 Stat. 794–795 as amended, 90 Stat. 540–560, 562–574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 301, 351, 354–360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 241, 262, 263b–263n)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

SUBCHAPTER A—GENERAL

PART 50—PROTECTION OF HUMAN SUBJECTS

1. In Part 50:

a. In § 50.3 by adding paragraphs (a) and (c) through (m), to read as follows:

§ 50.3 Definitions.

* * * * *

(a) "Act" means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201–902, 52 Stat. 1040 et seq. as amended (21 U.S.C. 321–392)).

* * * * *

(c) "Clinical investigation" means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of Part 58 of this chapter, regarding nonclinical laboratory studies.

(d) "Investigator" means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) "Sponsor" means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(f) "Sponsor-investigator" means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g) "Human subject" means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h) "Institution" means any public or private entity or agency (including Federal, State, and other agencies). The word "facility" as used in section 520(g) of the act is deemed to be synonymous with the term "institution" for purposes of this part.

(i) "Institutional review board" (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase "institutional review committee" as used in section 520(g) of the act.

(j) "Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(k) "Test article" means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354–360F of the Public Health Service Act (42 U.S.C. 262 and 263b–263n).

(l) "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(m) "Legally authorized representative" means an individual or

judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

b. By adding new Subpart B to read as follows:

Subpart B—Informed Consent of Human Subjects

Sec.
50.20 General requirements for informed consent.
50.21 Effective date.
50.23 Exception from general requirements.
50.25 Elements of informed consent.
50.27 Documention of informed consent.

Subpart B—Informed Consent of Human Subjects

§ 50.20 General requirements for informed consent.

Except as provided in § 50.23, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

§ 50.21 Effective date.

The requirements for informed consent set out in this part apply to all human subjects entering a clinical investigation that commences on or after July 27, 1981.

§ 50.23 Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

§ 50.25 Elements of informed consent.

(a) *Basic elements of informed consent.* In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantâgeous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) *Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

§ 50.27 Documentation of informed consent.

(a) Except as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in § 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(2) A "short form" written consent document stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

PART 71—COLOR ADDITIVE PETITIONS

2. Part 71 is amended:

a. In § 71.1 by adding new paragraph (i) to read as follows:

§ 71.1 Petitions

* * * * *

(i) If clinical investigations involving human subjects are involved, petitions filed with the Commissioner under section 706(b) of the act shall include statements regarding each such clinical investigation contained in the petition that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

b. In § 71.6 by adding a new sentence at the end of paragraph (b) to read as follows:

§ 71.6 Extension of time for studying petitions; substantive amendments; withdrawal of petitions without prejudice.

* * * * *

(b) * * * If clinical investigations involving human subjects are involved, additional information or data submitted in support of filed petitions shall include statements regarding each such clinical investigation from which the information or data are derived, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

* * * * *

SUBCHAPTER B—FOOD FOR HUMAN CONSUMPTION

PART 171—FOOD ADDITIVE PETITIONS

3. Part 171 is amended:

a. In § 171.1 by adding new paragraph (m) to read as follows:

§ 171.1 Petitions.

* * * * *

(m) If clinical investigations involving human subjects are involved, petitions filed with the Commissioner under section 409(b) of the act shall include statements regarding each such clinical investigation relied upon in the petition that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

b. In § 171.6 by adding a new sentence at the end of the paragraph to read as follows:

§ 171.6 Amendment of petition.

* * * If clinical investigations involving human subjects are involved, additional information and data submitted in support of filed petitions shall include statements regarding each clinical investigation from which the information or data are derived, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

PART 180—FOOD ADDITIVES PERMITTED IN FOOD ON AN INTERIM BASIS OR IN CONTACT WITH FOOD PENDING ADDITIONAL STUDY

4. Part 180 is amended in § 180.1 by adding new paragraph (c)(6) to read as follows:

§ 180.1 General.

* * * * *

(c) * * *

(6) If clinical investigations involving human subjects are involved, such investigations filed with the Commissioner shall include, with respect to each investigation, statement that the investigation either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it has been or will be conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

* * * * *

SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 310—NEW DRUGS

§ 310.3 [Amended]

5. Part 310 is amended in § 310.3 *Definitions and interpretations*, by removing and reserving paragraph (i).

§ 310.102 [Removed]

6. Part 310 is amended by removing § 310.102 *Consent for use of investigational new drugs (IND) on humans: statement of policy.*

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

7. Part 312 is amended:

a. In § 312.1 by revising paragraph (a)(2) item c of Form FD–1571, item 3 of Form FD–1572, and item 2a of Form FD–1573, and redesignating paragraph (d)(11) and (12) as (d)(12) and (13), respectively, and adding new paragraph (d)(11) to read as follows:

§ 312.1 Conditions for exemption of new drugs for investigational use.

(a) * * *

(2) * * *

c. *Institutional review board (IRB).* The sponsor must give assurance that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The sponsor must also provide assurance that the investigators will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that the investigators will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazard to the human subjects. FDA will regard the signing of the Form FD–1571 as providing the necessary assurances above.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the

additional phase or phases is submitted before such additional phases begin. A limitation on an exemption does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaulation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records maintained for each subject to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given, and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

* * * * *

3. The investigator assures that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator also assures that he/she will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that he/she will not make any changes in the research that would increase the risks to human subjects without IRB approval. FDA will regard the signing of the Form FD–1572 as providing the necessary assurances stated above.

* * * * *

2a. The investigator assures that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator also assures that he/she will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that he/she will not make any changes in the research that would increase the risks to human subjects without IRB approval. FDA will regard the signing of the Form FD–1573 as providing the necessary assurances stated above.

* * * * *

(d) * * *

(11) The clinical investigations are not being conducted in compliance with the requirements regarding institutional review set forth in this part or in Part 56 of this chapter, or informed consent set forth in Part 50 of this chapter; or

* * * * *

b. In § 312.20(b)(1)(iv) by replacing the 1964 "Declaration of Helsinki" with the revised version to read as follows:

§ 312.20 Clinical data generated outside the United States and not subject to a "Notice of Claimed Investigational Exemption for a New Drug."

* * * * *

(b) * * *

(1) * * *

(iv) * * *

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that her or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined With Professional Care (Clinical Research)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic methods.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

* * * * *

PART 314—NEW DRUG APPLICATIONS

8. Part 314 is amended:

a. In § 314.1 by adding new item 17 to Form FD–356H in paragraph (c)(2) and by redesignating paragraph (f)(7) and (8) as (f)(8) and (9), and adding new paragraph (f)(7) to read as follows:

§ 314.1 Applications.

* * * * *

(c) * * *

(2) * * *

Form FD–356H—Rev. 1974:

* * * * *

17. *Conduct of clinical investigations.* Statements contained in the application regarding each clinical investigation involving human subjects, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

* * * * *

(f) * * *

(7) Statements contained in the application regarding each clinical investigation involving human subjects, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

* * * * *

b. In § 314.8 by adding new paragraph (n) to read as follows:

§ 314.8 Supplemental applications.

* * * * *

(n) A supplemental application that contains clinical investigations involving human subjects shall include statements by the applicant regarding each such investigation, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

c. In § 314.9 by adding new paragraph (e) to read as follows:

§ 314.9 Insufficient information in application.

* * * * *

(e) The information contained in an application shall be considered insufficient to determine whether a drug is safe and effective for use unless the application includes statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

d. In § 314.12 by adding new paragraph (e) to read as follows:

§ 314.12 Untrue statements in application.

* * * * *

(e) Any clinical investigation involving human subjects contained in the application subject to the requirements for informed consent set forth in Part 50 of this chapter either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was not conducted in compliance with such requirements.

e. In § 314.110 by adding new paragraph (a)(11) to read as follows:

§ 314.110 Reasons for refusing to file applications.

(a) * * *

(11) The applicant fails to include in the application statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

* * * * *

f. In § 314.111 by adding new paragraph (a)(11) to read as follows:

§ 314.111 Refusal to approve the application.

(a) * * *

(11) Any clinical investigation involving human subjects contained in the application subject to the requirements for institutional review set forth in Part 56 of this chapter, or informed consent set forth in Part 50 of this chapter was not conducted in compliance with such requirements.

* * * * *

g. In § 314.115 by adding new paragraph (c)(7) to read as follows:

§ 314.115 Withdrawal of approval of an application.

* * * * *

(c) * * *

(7) That any clinical investigation involving human subjects contained in the application subject to the requirements for institutional review set forth in Part 56 of this chapter, or informed consent set forth in Part 50 of this chapter was not conducted in compliance with such requirements.

* * * * *

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

g. Part 320 is amended:

a. In § 320.31 by adding new paragraph (f) to read as follows:

§ 320.31 Applicability of requirements regarding a "Notice of Claimed Investigational Exemption for a New Drug."

* * * * *

(f) An in vivo bioavailability study in humans shall be conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, and informed consent set forth in Part 50 of this chapter, regardless of whether the study is conducted under a "Notice of Claimed Investigational Exemption for a New Drug."

b. In § 320.57 by adding new paragraph (e) to read as follows:

§ 320.57 Requirements of the conduct of in vivo bioequivalence testing in humans.

* * * * *

(e) If a bioequivalence requirement provides for in vivo testing in humans, any person conducting such testing shall

comply with the requirements of § 320.31.

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

10. Part 330 is amended in § 330.10 by adding new paragraph (e) to read as follows:

§ 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.

* * * * *

(e) *Institutional review and informed consent.* Information and data submitted under this section after (July 27, 1981) shall include statements regarding each clinical investigation involving human subjects, from which the information and data are derived, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, areas not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

PART 361—PRESCRIPTION DRUGS FOR HUMAN USE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED: DRUGS USED IN RESEARCH

11. Part 361 is amended in § 361.1 by revising paragraph (d)(5) to read as follows:

§ 361.1 Radioactive drugs for certain research uses.

* * * * *

(d) * * *

(5) *Human research subjects.* Each investigator shall select appropriate human subjects and shall obtain the review and approval of an institutional review board that conforms to the requirements of Part 56 of this chapter, and shall obtain the consent of the subjects or their legal representatives in accordance with Part 50 of this chapter. The research subjects shall be at least 18 years of age and legally competent. Exceptions are permitted only in those special situations when it can be demonstrated to the committee that the study presents a unique opportunity to gain information not currently available, requires the use of research subjects less than 18 years of age, and is without significant risk to the subject. Studies involving minors shall be supported with review by qualified pediatric consultants to the Radioactive Drug Research Committee. Each female research subject of childbearing potential shall state in writing that she is not pregnant, or, on the basis of a pregnancy test be confirmed as not pregnant, before she may participate in any study.

* * * * *

PART 430—ANTIBIOTIC DRUGS; GENERAL

12. Part 430 is amended in § 430.20 by adding new paragraph (g) to read as follows:

§ 430.20 Procedure for the issuance, amendment, or repeal of regulations.

* * * * *

(g) No regulation providing for the certification of an antibiotic drug for human use shall be issued or amended unless each clinical investigation involving human subjects on which the issuance or amendment of the regulation is based was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and for informed consent set forth in Part 50 of this chapter.

PART 431—CERTIFICATION OF ANTIBIOTIC DRUGS

13. Part 431 is amended in § 431.17 by adding new paragraph (l) to read as follows:

§ 431.17 New antibiotic and antibiotic-containing products.

* * * * *

(l) Statements regarding each clinical investigation involving human subjects contained in the request, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and for informed consent set forth in Part 50 of this chapter.

SUBCHAPTER F—BIOLOGICS

PART 601—LICENSING

14. Part 601 is amended:

a. In § 601.2 by revising paragraph (a) to read as follows:

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Bureau of Biologics, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and was conducted in compliance with requirements for informed consent set forth in Part 50 of this chapter, a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent information and data have been received from the manufacturer by the Bureau of Biologics. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section.

* * * * *

b. In § 601.25 by revising paragraph (h)(1) and adding new paragraph (1) to read as follows:

§ 601.25 Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use.

* * * * *

(h) *Additional studies.* (1) Within 30 days following publication of the final order, each licensee for a biological product designed as requiring further study to justify continued marketing on an interim basis, under paragraph (f)(3) of this section, shall satisfy the Commissioner of Food and Drugs in writing that studies adequate and appropriate to resolve the questions raised about the product have been undertaken, or the Federal government may undertake these studies. Any study involving a clinical investigation that

involves human subjects shall be conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, unless it is not subject to such requirements in accordance with §§ 56.104 or 56.105, and for informed consent set forth in Part 50 of this chapter. The Commissioner may extend this 30-day period if necessary, either to review and act on proposed protocols or upon indication from the licensee that the studies will commence at a specified reasonable time. If no such commitment is made, or adequate and appropriate studies are not undertaken, the product licenses shall be revoked.

* * * * *

(1) *Institutional review and informed consent.* Information and data submitted under this section after July 27, 1981 shall include statements regarding each clinical investigation involving human subjects, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter, or was not subject to such requirements in accordance with §§ 56.104 or 56.105, and that it was conducted in compliance with the requirements for informed consent set forth in Part 50 of this chapter.

* * * * *

c. By revising § 601.30 to read as follows:

§ 601.30 Licenses required; products for controlled investigation only.

Any biological or trivalent organic arsenical manufactured in any foreign country and intended for sale, barter, or exchange shall be refused entry by collectors of customs unless manufactured in an establishment holding an unsuspended and unrevoked establishment license and license for the product. Unlicensed products that are not imported for sale, barter, or exchange and that are intended solely for purposes of controlled investigation are admissible only if the investigation is conducted in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act and the requirements set forth in Parts 50, 56 unless exempted under § 56.104 as granted a waiver under § 56.105, 58, and 312 of this chapter.

PART 630—ADDITIONAL STANDARDS FOR VIRAL VACCINES

15. Part 630 is amended:

a. In § 630.11 by revising the first sentence to read as follows:

§ 630.11 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design conducted in compliance with Part 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and with Part 50 of this chapter. * * *

b. In § 630.31 by adding a new sentence at the end of the section to read as follows:

§ 630.31 Clinical trials to qualify for license.

* * * Such clinical trials shall be conducted in compliance with Part 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and with the requirements for informed consent set forth in Part 50 of this chapter.

c. By revising § 630.51 to read as follows:

§ 630.51 Clinical trials to qualify for license.

To qualify for license, the antigenicity of Mumps Virus Vaccine, Live; shall be determined by clinical trials, conducted in compliance with Part 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and with Part 50 of this chapter, that follow the procedures prescribed in § 630.31, except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of mumps-susceptible individuals, each having received the parenteral administration of a virus vaccine dose not greater than that demonstrated to be safe in field studies (§ 630.50(b)) when used under comparable conditions.

d. By revising § 630.61 to read as follows:

§ 630.61 Clinical trials to qualify for license.

To qualify for license, the antigenicity of Rubella Virus Vaccine, Live, shall be determined by clinical trials, conducted in compliance with Part 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and with Part 50 of this chapter, that follow the procedures prescribed in § 630.31, except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of rubella-susceptible individuals, each having received the parenteral administration of a virus vaccine dose not greater than that demonstrated to be safe in field studies when used under comparable conditions.

e. In § 630.81 by revising the first sentence to read as follows:

§ 630.81 Clinical trials to qualify for license.

In addition to demonstrating that the measles component meet the requirements of § 630.31, the measles and smallpox antigenicity of the final product shall be determined by clinical trials of adequate statistical design conducted in compliance with Part 56 of this chapter unless exempted under § 56.104 or granted a waiver under § 56.105, and with Part 50 of this chapter and with three consecutive lots of final vaccine manufactured by the same methods and administered as recommeded by the manufacturer. * * *

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

16. Part 812 is amended:

a. In § 812.2 by revising paragraph (b)(1)(iii) to read as follows:

§ 812.21 Applicability.

(b) * * *

(1) * * *

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under Part 50 and documents it, unless documentation is waived by an IRB under § 56.109(c).

b. In § 812.3 by revising paragraph (f) to read as follows:

§ 812.3 Definitions.

* * * * *

(f) "Institutional review board" (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving subjects and established, operated, and functioning in conformance with Part 56. The term has the same meaning as "institutional review committee" in section 520(g) of the act.

c. In § 812.20 by removing paragraph (a)(2), and by redesignating (a)(3) as (a)(2) and revising it, and by redesignating (a)(4) as (a)(3) as follows:

§ 812.20 Application.

(a) * * *

(2) A sponsor shall not begin an investigation for which FDA's approval of an application is required until FDA has approved the application.

* * * * *

d. In § 812.35 by revising paragraphs (a) and (b) to read as follows:

§ 812.35 Supplemental applications.

(a) *Changes in investigational plan.* A sponsor shall: (1) Submit to FDA a supplemental application if the sponsor or an investigator proposes a change in the investigational plan and (2) obtain IRB approval (see § 56.110(b)) and FDA approval of the change before implementation.

(b) *IRB approval.* A sponsor shall submit to FDA, in a supplemental application, the certification of any IRB approval of an investigation or a part of an investigation not included in the IDE application.

e. By adding new § 812.42 to read as follows:

§ 812.42 FDA and IRB approval.

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation.

f. By revising the heading of Subpart D to read as follows:

Subpart D—IRB Review and Approval

g. By revising § 812.60 to read as follows:

§ 812.60 IRB composition, duties, and functions.

An IRB reviewing and approving investigations under this part shall comply with the requirements of Part 56 in all respects, including its composition, duties, and functions.

h. In § 812.62 by revising the section heading and the section to read as follows:

§ 812.62 IRB approval.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all investigations covered by this part.

(b) If no IRB exists or if FDA finds that an IRB's review is inadequate, a sponsor may submit an application to FDA.

i. By adding new § 812.64 to read as follows:

§ 812.64 IRB's continuing review.

The IRB shall conduct its continuing review of an investigation in accordance with Part 56.

j. By adding new § 812.66 to read as follows:

§ 812.66 Significant risk device determinations.

If an IRB determines that an investigation, presented for approval under § 812.2(b)(1)(ii), involves a significant risk device, it shall so notify the investigator and, where appropriate, the sponsor. A sponsor may not begin the investigation except as provided in § 812.30(a).

k. In § 812.100 by revising the second sentence to read as follows:

§ 812.100 General responsibilities of investigators.

* * * An investigator also is responsible for ensuring that informed consent is obtained in accordance with Part 50 of this chapter.* * *

* * * * *

Subpart F [Removed]

l. Part 812 is amended by removing Subpart F—*Informed Consent* and marking it "Reserved."

m. In § 812.140 by revising paragraphs (c), (d), and (e) to read as follows:

§ 812.140 Records

* * * * *

(c) *IRB records.* An IRB shall maintain records in accordance with Part 56 of this chapter.

(d) *Retention period.* An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

(e) *Records custody.* An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of § 812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

n. In § 812.150 by revising paragraph (a)(4) to read as follows:

§ 812.150 Reports.

(a) * * *

(4) *Deviations from the investigational plan.* An investigator shall notify the sponsor and the reviewing IRB (see § 56.108(a)(3) and (4) of any deviation from the investigational plan. In the case of an emergency to protect the life or physical well being of a subject, the investigator shall notify the reviewing IRB withing 48 hours. Prior approval by the sponsor is required for changes in, or deviations from, a plan. FDA approval under § 812.35(a) is also required.

* * * * *

PART 813—INVESTIGATIONAL EXEMPTIONS FOR INTRAOCULAR LENSES

Subpart F [Removed]

17. Part 813 is amended by removing Subpart F—*Informed Consent of Human Subjects* and marking it "Reserved."

SUBCHAPTER J—RADIOLOGICAL HEALTH

PART 1003—NOTIFICATION OF DEFECTS OR FAILURE TO COMPLY

18. Part 1003 is amended in § 1003.31 by revising paragraph (b) to read as follows:

§ 1003.31 Granting the exemption.

* * * * *

(b) Such views and evidence shall be confined to matters relevant to whether the defect in the product or its failure to comply with an applicable Federal standard would create a significant risk to injury, including generic injury, to any person and shall be presented in writing unless the Secretary determines that an oral presentation is desirable. When such evidence includes clinical investigations involving human subjects, the data submitted shall include, with respect to each clinical investigation either a statement that each investigation was conducted in compliance with the requirements set forth in Part 56 of this chapter, or a statement that the investigation is not subject to such requirements in accordance with §§ 56.104 or 56.105, and a statement that each investigations was conducted in compliance with the requirements set forth in Part 50 of this chapter.

* * * * *

PART 1010—PERFORMANCE STANDARDS FOR ELECTRONIC PRODUCTS; GENERAL

19. Part 1010 is amended:

a. In § 1010.4 by adding new paragraph (b)(1)(xi) to read as follows:

§ 1010.4 Variances.

* * * * *

(b) * * *

(1) * * *

(xi) If the electronic product is used in a clinical investigation involving human subjects, is subject to the requirements for institutional review set forth in Part 56 of this chapter, and is subject to the requirements for informed consent set forth in Part 50 of this chapter, the investigation shall be conducted in compliance with such requirements.

* * * * *

b. In § 1010.5 by revising paragraph (c)(12) to read as follows:

§ 1010.5 Exemptions for products intended for United States Government use.

* * * * *

(c) * * *

(12) Such other information required by regulation or by the Director, Bureau of Radiological Health, to evaluate and act on the application. Where such information includes nonclinical laboratory studies, the information shall include, with respect to each nonclinical study, either a statement that each study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations. When such information includes clinical investigations involving human subjects, the information shall include, with respect to each clinical investigation, either a statement that each investigation was conducted in compliance with the requirements set forth in Part 56 of this chapter, or a statement that the investigation is not subject to such requirements in accordance with §§ 56.104 or 56.105 and a statement that each investigation was conducted in compliance with the requirements set forth in Part 50 of this chapter.

* * * * *

Effective date. This regulation shall become effective July 27, 1981.

(Secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701(a), 706, and 801, 52 Stat. 1049–1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511–517 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 76 Stat. 794–795 as amended, 90 Stat. 540–560, 562–574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371(a), 376, and 381); secs. 215, 301, 351, 354–360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 241, 262, 263b–263n))

Dated: January 19, 1981.

Jere E. Goyan,

Commissioner of Food and Drugs.

[FR Doc. 81-2587 Filed 1-21-81; 8:45 am]

BILLING CODE 4110-03-M

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21 CFR Parts 16 and 56

[Docket No. 77N-0350]

Protection of Human Subjects; Standards for Institutional Review Boards for Clinical Investigations

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or agency) is establishing standards governing the composition, operation, and responsibility of institutional review boards (IRBs) that review clinical investigations, involving human subjects, conducted pursuant to requirements for prior submission to FDA or conducted in support of applications for permission to conduct further research or to market regulated products. These regulations and the protection of human research subjects regulations adopted by the Department of Health and Human Services (HHS or Department) published in the January 26, 1981 issue of the **Federal Register**, establish a common framework for the operation of IRBs that review research funded by HHS and research conducted under FDA regulatory requirements. Compliance with these regulations is intended to provide protection of the rights and welfare of human subjects involved in clinical investigations.

EFFECTIVE DATE: July 27, 1981.

FOR FURTHER INFORMATION CONTACT: John C. Petricciani, Office of the Commissioner (HFB–4), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301–496–9320.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of August 8, 1978 (43 FR 35186), FDA published proposed standards for IRBs for clinical investigations. Interested persons were given until December 6, 1978 to submit written comments on the proposal. By notice in the **Federal Register** of December 15, 1978 (43 FR 58574), FDA extended the comment period to June 6, 1979. During the comment period, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) submitted its report and recommendations on IRBs and informed consent, and that document was published in the **Federal Register** of November 30, 1978 (43 FR 56174). In its report, the National Commission recommended revision of the current HHS IRB regulations (45 CFR Part 46). On August 14, 1979 (44 FR 46799), FDA withdrew the August 8, 1978 proposal and published a revised proposal that it had developed in conjunction with HHS in response to the recommendations made by the National Commission.

In addition, the agency held three hearings under § 15.1(a) (21 CFR 15.1(a)) of the administrative practices and procedures regulations in: (1) Bethesda, Maryland, on September 18, 1979; (2) San Francisco, California, on October 2, 1979; and (3) Houston, Texas, on October 16, 1979. These hearings were intended to provide an open forum to present views on the regulations and to foster greater consideration of the proposal among the scientific community, regulated industry, and the public. (Transcripts of these hearings are on file with the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA–305), FDA.)

For the reasons set forth in paragraph 1, the sections of the regulation have been reorganized and renumbered to be parallel with the Department's regulations. The following table correlates the new sections with those proposed.

New section	Old section
56.101	56.1.
56.102	56.3.
56.103	56.5.
56.104	No corresponding section.
56.105	56.6.
56.107	56.21, 56.25, 56.26, and 56.34.
56.108	56.80, 56.81, and 56.87.
56.109	56.82 and 56.87.
56.110	56.83.
56.111	56.86.
56.112	56.8, 56.9, 56.87, and 56.90.
56.113	56.90.
56.114	56.9.
56.115	56.15, 56.21, 56.25, 56.185, and 56.195.
56.120	No corresponding section.
56.121	56.202, 56.206, and 56.210.
56.122	56.213.
56.123	56.219.
56.124	56.215.

FDA will seek Office of Management and Budget (OMB) clearance of the reporting and recordkeeping requirements contained in these regulations prior to the effective date. If OMB does not approve the reporting and recordkeeping requirements without change, the agency will revise the regulations to comply with OMB's recommendations.

The agency received 145 comments on the original proposal and 179 comments on the reproposal. In addition, approximately 100 people appeared at the three public hearings. Following is a summary of the significant comments received and FDA's response to them:

General Comments

1. One of the overriding themes in the comments was that the agency should adopt the same final regulations as the Department.

FDA agrees that the Department's and the agency's regulations should be as consistent as possible, and it recognizes that if such consistency is achieved, IRBs that deal with both FDA and other HHS components will be able to follow a uniform standard. Therefore, FDA participated with other components of the Public Health Service in an intra-departmental task force whose goal was to achieve the maximum degree of