This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

Final Draft 6/30/93

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH'S INVESTIGATIONAL DEVICE EXEMPTION (IDE) REFUSE TO ACCEPT POLICY

PURPOSE

The Office of Device Evaluation (ODE) receives approximately 225 original Investigational Device Exemption (IDE) submissions each year. Many of these applications are incomplete or grossly inadequate, i.e., they fail to contain information clearly required under the regulations and they fail to contain the components necessary to allow substantive review. Further, they inappropriately consume the Center's scientific resources. As a means to employ more effectively the Center's scientific resources, procedures will be implemented to ensure that IDEs meet a minimum threshold of acceptability; otherwise, the Center will refuse to accept the application. These procedures will benefit both FDA and IDE sponsors.

DISCUSSION

An IDE application that is missing any of the elements of 21 CFR 812.20, is technically an incomplete application and, therefore, not subject to the 30 day review clock. In the past, however, the Center has accepted all but the most incomplete IDE applications. The inadequate or incomplete application was reviewed and subsequently disapproved in accordance with 812.30. Typically, there are several cycles of FDA review and manufacturer response before the IDE is sufficiently complete and approvable. This process is inefficient and wasteful of resources, both FDA's and the manufacturer's.

The Center's goal in establishing Refuse to Accept criteria is to improve the utilization of our review resources by ensuring that they are focused on the review of reasonably complete and well-supported applications. Often, during initial scientific review, the Center has found that crucial information necessary to make a decision to approve or disapprove an IDE has been omitted. When making a decision to accept or not to accept an application, the Center will identify those applications in which sufficient information is submitted to allow a decision on the approvability of the investigation (i.e. the application is complete on its face). By establishing a Refuse to Accept Policy with criteria for completeness of an application that are clear, consistent, and available to sponsors, sponsors will know what is expected of them for each submission and device they intend to investigate. Sponsors will be likely to comply to speed the time to substantive review of and a final decision on their application.

In general, there are three bases for refusal to accept an IDE:

1. An approved IDE in not required for the investigations.

2. The application omits a section of the IDE required under 21 CFR 812.20, 812.25 or 812.27 or 813.

3. The application fails to address scientific/technical issues clearly described in publicly available, general, device-specific, and crosscutting guidance documents.

While we can establish minimum completeness criteria based upon the content requirements in the regulations, this alone will not lead to upgraded scientific information in incoming IDEs. Separately, we will continue to promulgate product specific guidelines or guidance documents describing our scientific/technical expectations. In instances where we have established clear expectations through a guidance document, we will evaluate completeness against the consideration the sponsor has given the scientific/technical issues addressed in the guidance.

The threshold determination for accepting the IDE application, whether the application merits a substantive evaluation by Center scientists, will be made in accord with the IDE Refuse to Accept Criteria document attached.

RECOMMENDATIONS

As a result of the above considerations, the following recommendations are hereby made to establish and implement a Refuse to Accept Policy for IDEs:

1. Train reviewers (Branch Chiefs, reviewers) to implement the Refuse to Accept Policy. The Program Operations Staff will conduct the initial training and provide ongoing support for the implementation of the policy within the review divisions.

2. Implement a checklist to use in the initial review of all IDEs. An example of the proposed checklist for IDEs can be found in attached to this document. Divisions may modify or supplement this general checklist based on available guidance documents appropriate to their specific product areas.

3. Guidelines or guidance documents should be promulgated wherever needs are identified. Guidances should provide specific details about what is expected and acceptable for all components of the submissions. Each product specific guideline should include a checklist to be used by a) the applicant in preparing the submission and b) FDA reviewers during the initial evaluation to consider accepting the application for full review. Checklists should also be prepared for existing guidelines. These checklists and guidance documents should be made available to industry through the Division of Small Manufacturers' Assistance. This will save time and provide consistency across submissions. Emphasis should be placed on improved communication with industry.

IMPLEMENTATION:

The Refuse to Accept Policy will be implemented by the review divisions within the Center's Office of Device Evaluation utilizing the procedures provided in the document IDE Refuse to Accept Criteria as of this date.

1. Processing

   a. The ODE Document Mail Center (DMC) will log in, jacket, and distribute the IDE to the appropriate review division within 2 days of receipt of the application in the DMC or as quickly as available resources allow.

   b. A designated reviewer (Branch Chief, Reviewer, CSO, CST) using the IDE Refuse to Accept Checklist and other appropriate device-appropriate checklists, will determine whether the IDE is sufficiently complete to allow substantive review and make a recommendation within 10 days of DMC's receipt. The division should consult with the Program Operations Staff (POS) on any decisions that are particularly difficult or controversial.

c. Refuse to Accept recommendations will be forwarded to the appropriate supervisor for concurrence. If an application is found sufficiently complete to allow substantive review, review will continue.

d. Upon the supervisor's concurrence with the Refuse to Accept recommendation, a Refuse to Accept letter will be prepared for the Division Director's signature.

e. A Refuse to Accept letter, detailing the omissions or inadequacies that lead to the decision not to accept the application and clearly stating whether a complete, new application must be submitted or specifying which portion of the application must be provided if the sponsor wishes to pursue the investigation, will issue within 15 days of receipt of the original IDE.

2. Industry Inquiries

In the event that the sponsor has questions regarding the Refuse to Accept letter, the sponsor may contact the appropriate Division Director, via phone or FAX, regarding the decision.

3. Monitoring

The implementation of the IDE Refuse to Accept Policy will be reviewed by the Office of the Director, ODE, at three month intervals to determine the number of incomplete and/or inadequate applications not accepted, the consistency with which the criteria are applied, further necessary refinements to the process, and the overall impact on the IDE program.

The Center will continue to disseminate written guidance and will communicate with sponsors to help improve applications and to help ensure that applications are complete and reviewable. Nonetheless, we will no longer accept applications that will not allow the Center to conduct a substantive review.

EFFECTIVE DATE

The IDE Refuse to Accept Policy is effective immediately.

CONCURRENCE

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IDE Refuse to Accept Criteria

As a means to more effectively utilize review resources and to improve the timeliness of the device evaluation process, the Office of Device Evaluation is establishing a Refuse to Accept Policy for Investigational Device Exemptions (IDEs).

With IDEs, immediately following receipt is the appropriate time to make a threshold determination regarding the quality of the submission and whether the application merits substantive evaluation by Center scientists.

The purpose of the attached IDE Checklist is to: provide uniform guidance as to when an IDE should be accepted or not accepted; ensure that regulatory obligations are met; ensure consistency of reviews among the Divisions; and to upgrade the quality of applications. The checklist is intended to identify those original IDE applications which are administratively incomplete and therefore should not undergo substantive review and to identify those IDE applications which, although are administratively complete, have scientific/technical omissions which should result in a decision not to accept for review.

This checklist is intended for use by the reviewing Divisions, and may be modified by the Divisions to adequately reflect their specific needs. The reviewers should keep in mind that the purpose of this review is to ensure reviewability, not approvability of the IDE.

Sponsors are still expected to submit information as required by the Act, the implementing regulations and as described in the IDE Manual. The IDE Checklist is an aid to the sponsor and the reviewer and is NOT a new IDE contents outline.

To use this checklist place a check mark in the "Yes" block (left column) when: the item is present or a justification for its omission has been provided, or a waiver of the item has been requested. Place a check mark in the "No" block (right column) when the item is grossly inadequate or omitted without a valid justification.

Section I, "Screening Information", will permit quick identification of IDE applications which should not be reviewed because of either inappropriate submission by the sponsor (e.g., an exempt device), or because of other regulatory concerns (e.g., integrity investigation). In Section I, any question receiving a "no" response results in termination of the review.

Section II, "Format for Submission", lists those features of an IDE application which are believed to be important to permit a substantive review.

Section III, "Required elements for application", presents those sections of an IDE application which must be submitted in order for a substantive review to occur.

An inadequate or omitted required element may not be, in itself, a reason not to accept the IDE. Upon completion of the checklist, the reviewer will determine if the application is complete enough to allow a substantive review, given the omissions. Any inadequate required element will be conveyed to the sponsor.

It is intended that this approach to reviewing original IDE applications will conserve resources by eliminating early those applications which fail to meet the minimum requirements for a substantive review.

ORIGINAL IDE CHECKLIST FOR ADMINISTRATIVE REVIEW

Filing Review Elements	Yes Present Omission Justified	No Inadequate Omitted
I. Screening Information		
A. Is the investigation within the categories of investigations that are not exempt from the IDE regulation under 812.2(c)?	☐	☐
B. Is this a significant risk device investigation? (21 CFR 812.3(m) and 812.20(a)(1))	☐	☐
C. If there has been an Integrity Investigation, has the ODE integrity officer given permission to proceed with review? (If no integrity investigation, check yes)	☐	☐
D. U.S. sponsor, address, telephone number and contact person identified (Note: IDE application will not be approved without a U.S. sponsor) (21 CFR 812.18(a))	☐	☐
II. Format for submission		
A. Table of contents (21 CFR 812.20(b))	☐	☐
B. Submission clearly paginated	☐	☐
C. 3 copies included (21 CFR 812.20(a)(3))	☐	☐

III. Required elements for application

A. Report of prior investigations (Are the following items present in the application?) (21 CFR 812.27)

1. Report of clinical, animal and laboratory testing	☐	☐
2. Bibliography of all relevant publications	☐	☐
3. Copies of published and unpublished adverse information	☐	☐
4. Summary of all other unpublished information	☐	☐
5. Statement whether nonclinical tests comply with GLP regulation or justification for noncompliance	☐	☐

B. Investigational Plan (21 CFR 812.25)

1. Purpose: Are the following items clearly defined?

a. Name and intended use of the device	☐	☐
b. Objectives of the investigation	☐	☐
c. Duration of the investigation (Example: specify-months and years)	☐	☐

2. Protocol: Are the following items present?

a. Written protocol describing methodology including:

i. objectives, hypothesis to be tested, or question to be answered	☐	☐

ii. description of the type of trial (i.e., controlled/open, double-blind/single-blind, etc.)	☐	☐
iii. detailed description of the conduct of the trial	☐	☐
iv. description of statistical methods	☐	☐
v. case report forms	☐	☐
3. Risk Analysis: Are the following items present in the application?		
a. Description and analysis of all risks to subjects	☐	☐
b. Justification for the investigation	☐	☐
4. Description of the Device: Are the following items present?		
a. Description of each important component, ingredient and property	☐	☐
b. Principle of Operation	☐	☐
c. Copies of all labeling for the device	☐	☐
5. Monitoring Procedures: Are the following items present?		
a. Written procedures for monitoring	☐	☐
b. Name and address of the individual(s) who will monitor the study	☐	☐

C. Manufacturing Information (21 CFR 812.20(b)(3): Does the application contain a description of methods, facilities and controls used for:

1. Manufacturing	☐	☐
2. Processing	☐	☐
3. Packing	☐	☐
4. Storage	☐	☐
5. Installation	☐	☐

D. Investigator Information (21 CFR 812.20(b)(4): Are the following items included?

1. Example of investigator agreement in accordance with 21 CFR 812.43(c)	☐	☐
2. Certification that all participating investigators will or have signed the agreement and that no investigator will be added until the agreement is signed (21 CFR 812.20(b)(5)	☐	☐

E. Sales information (21 CFR 812.7(b)): Is the following information provided?

1. Is the device to be sold?	☐	☐
2. Explanation of why sale does not constitute commercialization	☐	☐

F. Labeling (21 CFR 812.5)

Is a sample of the proposed labeling complete and included in the submission?	☐	☐

G. Informed Consent Materials (21 CFR 50.20 and 812.25(g):

Are <u>all</u> forms and informational materials to be presented to the subjects submitted?	☐	☐

H. Environmental Impact Assessment (21 CFR 25.31 and 812.20(b)(9): Has the sponsor provided:

1. An environmental impact assessment describing the potential environmental impact of manufacturing and investigating a device	☐	☐
2. A claim for categorical exclusion from the requirement	☐	☐

<u>RECOMMENDATION</u>

Do indepth review ____ Prepare incomplete letter ____

REVIEWED BY: _____
(REVIEWER'S SIGNATURE)

BRANCH: _____ DIVISION: _____

DATE: _____

CONCURRENCES BY: _____
(SUPERVISOR'S SIGNATURE)

DATE: _____