The CFR -- ORGANIZATION & CONTENTS

CFR

What is the Code of Federal Regulations ?

- **The CFR contains Federal rules that have:**
  - ✧ **General applicability to the public**
  - ✧ **Current and future effect as of the date specified**
- **Always published first in the FR as amendments to the CFR**
- **The CFR is published in a set of about 200 volumes**
  - ✧ **Printed soft cover books**
  - ✧ **Microfiche**
  - ✧ **Online at: www.access.gpo.gov/nara**

CFR

How is the CFR organized ?

- **Federal regulations are organized into:**
  - ✧ **50 titles**
  - ✧ **Broad subject matter categories**
    - » **Environment, Defense, Public Health, Transportation**

- **Each title is completely revised and reissued once each year on a staggered schedule.**

  - ✧ **Titles 1 -- 16 updated as of January 1**
  - ✧ **Titles 17 -- 27 updated as of April 1**
  - ✧ **Titles 28 -- 41 updated as of July 1**
  - ✧ **Titles 42 -- 50 updated as of October 1**

CFR

What is the CFR numbering system ?

- **The CFR has a uniform numbering system**
  - ✧ **Titles 3, 41, and 48 have significant variations**
- **The section is the basic unit of the CFR**
- **Cite the CFR by title and section: 12 CFR 303.1**
- **Text is divided into descending levels of units**

CFR Structure

Title	**12**	**Broad subject area of regulations**
Chapter	**III**	**Rules of individual agency**
Part	**303**	**Rules on a single program or function**
Section	**303.1**	**One provision of program/function rules**
Paragraph	**303.1(a)**	**Detailed, specific requirements**

Paragraph Levels

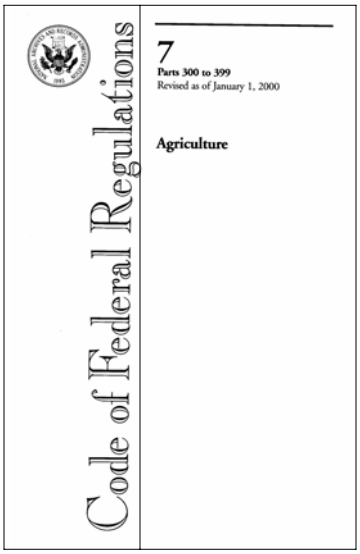
Sections may contain up to 6 levels of paragraphs.

- **We strongly recommend no more than 3 levels.**

Paragraph	Designations	Cite paragraph as
Level 1	(a), (b), (c), etc.	§ 303.1(a)
Level 2	(1), (2), (3), etc.	§ 303.1(a)(1)
Level 3	(i), (ii), (iii), etc.	§ 303.1(a)(1)(i)
Level 4	(A), (B), (C), etc.	§ 303.1(a)(1)(i)(A)
Level 5	*(1), (2), (3)*, etc.	§ 303.1(a)(1)(i)(A)*(1)*
Level 6	*(i), (ii), (iii)*, etc.	§ 303.1(a)(1)(i)(A)*(1)(i)*

How are rules codified in the CFR ?

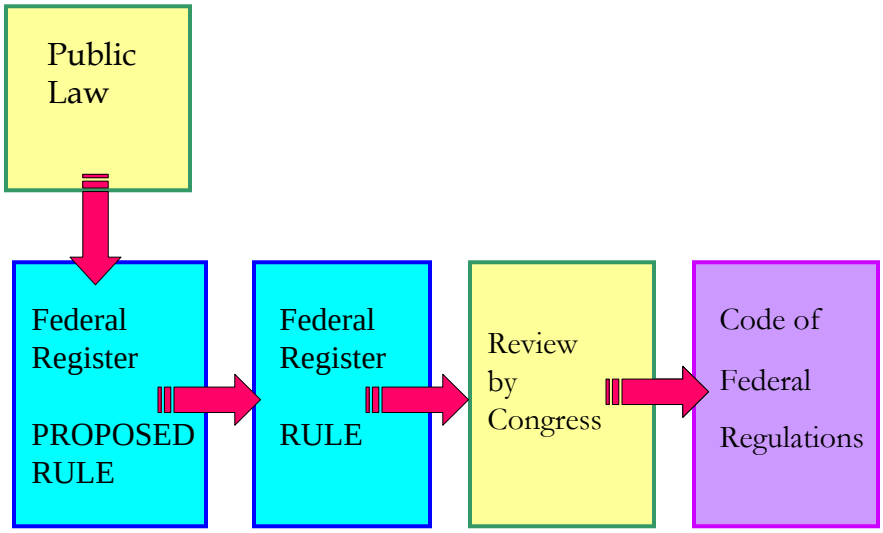
The Rulemaking Process from Start to Finish



What Triggers Rulemaking ?

- Legislation, Congressional hearings/reports
- Executive orders and OMB Circulars
- Court Orders
- Agencies act on own initiative to carry out mission
- Petitions for Rulemaking and informal requests from affected parties
- Federal Advisory Committee Recommendations
- Emergency situations, technological developments
- Political Factors

The Regulatory Process

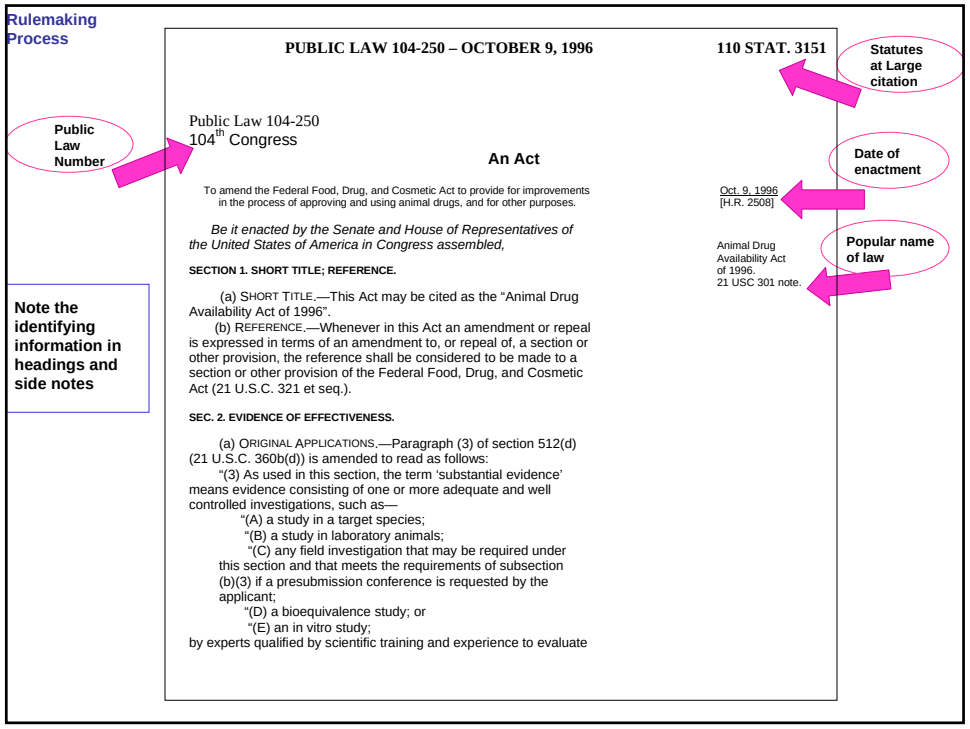


Authorization in Public Law

Rulemaking usually begins with Congressional action.

For Example:

- **The Animal Drug Availability Act of 1996 (ADAA) (Public Law 104- 250), enacted October 9, 1996, amended the Food, Drug and Cosmetic Act.**
  - **Signaled Congressional intent for Food and Drug Administration (FDA) to administer the regulations on behalf of the Secretary of Health and Human Services (HHS).**



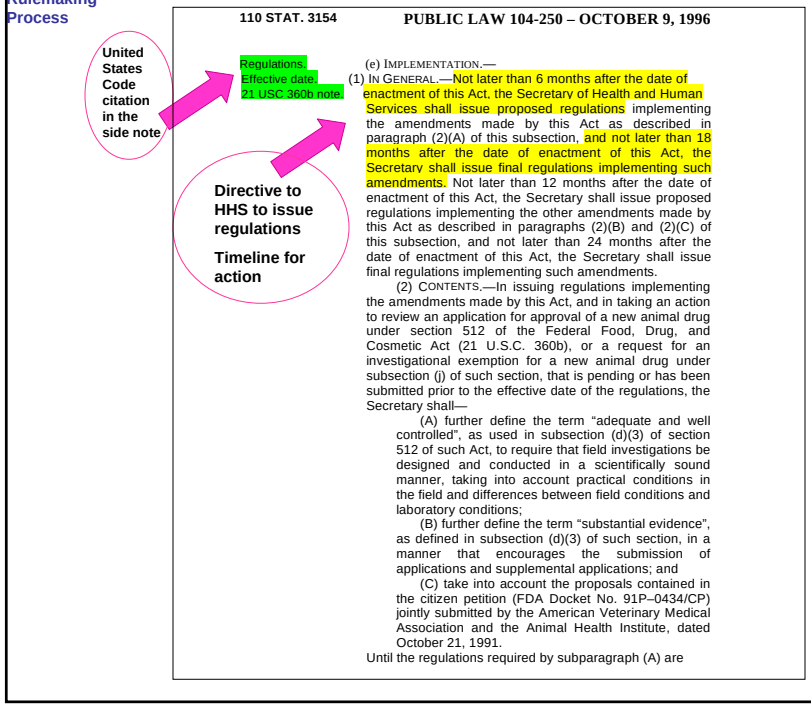
Rulemaking Process

Rulemaking Instructions in the Law

FDA must issue regulations to implement the law.

- ✧ **Law sets a schedule for issuing proposed and final rules**
- ✧ **The agency must publish in *Federal Register* and follow APA notice and comment rulemaking process.**

Rulemaking Process



Rulemaking Process

Proposed Rulemaking

ADAA Example

- **Statute set a 6 month time limit for a Proposed Rule**
- **FDA published the proposed rule on May 8, 1997, about 7 months after the law was enacted, slightly past the deadline**

Rulemaking Process

Federal Register/Vol. 62, No. 89/ Thursday, May 8, 1997/Proposed Rules 25153

NPRM published May 8, 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 514

[Docket No. 97N-0141]

Adequate and Well-Controlled Studies for Investigational Use and Approval of New Animal Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA), as directed by the Animal Drug Availability Act of 1996 (ADAA), is publishing a proposed regulation to further define the term "adequate and well-controlled" to require that field investigations be designed and conducted in a scientifically sound manner. Elsewhere in this issue of the Federal Register, FDA is reopening docket number 96N-0411 to receive comments regarding a concept, "good study practices," that is related to the definition of adequate and well-controlled studies.

DATES: Written comments by July 22, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Herman M. Schoenemann, Center for Veterinary Medicine (HFV-126), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1638.

SUPPLEMENTARY INFORMATION:

I. Background

Congress enacted the ADAA (Pub. L. 104-250) on October 9, 1996. Section 2(e) of the ADAA directs FDA to issue, within 6 months of its enactment, proposed regulations to further define the term "adequate and well-controlled" to require that field

The public has 75 days to comment

Rulemaking Process

Federal Register / Vol. 62, No. 89 / May 8, 1997/ Proposed Rules 25157

Proposed Amendment to the CFR

3. New Sec. 514.117 is added to subpart B to read as follows:

§ 514.117 Adequate and well-controlled studies.

(a) *Purpose*. The primary purpose of conducting adequate and well-controlled studies of a new animal drug is to distinguish the effect of the new animal drug from other influences, such as spontaneous change in the course of the disease, normal animal production performance, or biased observation. One or more adequate and well-controlled studies are required to establish, by substantial evidence, that a new animal drug is effective. The characteristics described in paragraph (b) of this section have been developed over a period of years and are generally recognized as the essentials of an adequate and well-controlled study. Well-controlled, as used in the phrase adequate and well-controlled, emphasizes an important aspect of adequacy. FDA considers these characteristics in determining whether a study is adequate and well-controlled for purposes of section 512 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b).. . .

Final Rulemaking

ADAA

- ✧ FDA published the final rule on March 5, 1998, in time to meet the 18 month statutory deadline

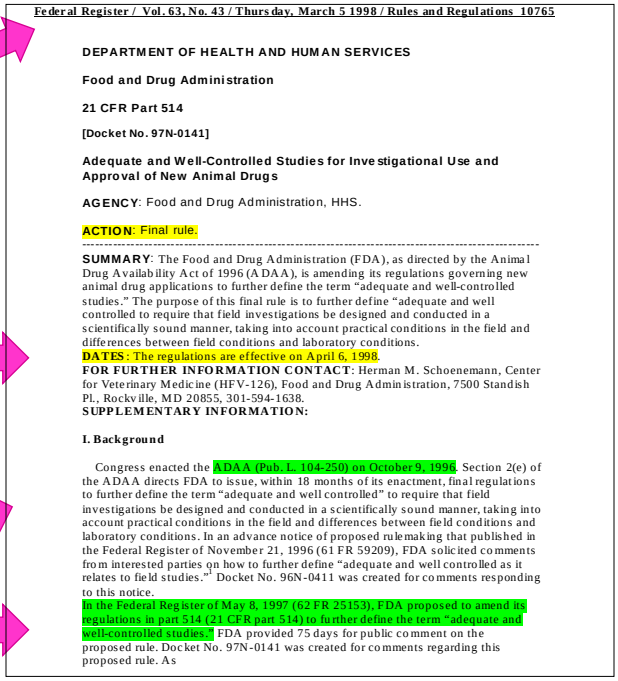
The preamble of a final rule typically contains:

- ✧ Statement of the requirements in the law
- ✧ Cite to proposed rule and other rulemaking history
- ✧ Discussion and analysis of public comments received
- ✧ Justification for agency's final decisions

Final rule published in FR on March 5, 1998

Rule is effective 18 months from enactment of public law

References to public law and proposed rule



Federal Register / Vol. 63, No. 43 / Thursday, March 5 1998 / Rules and Regulations 10765

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 514

[Docket No. 97N-0141]

Adequate and Well-Controlled Studies for Investigational Use and Approval of New Animal Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA), as directed by the Animal Drug Availability Act of 1996 (ADAA), is amending its regulations governing new animal drug applications to further define the term "adequate and well-controlled studies." The purpose of this final rule is to further define "adequate and well controlled to require that field investigations be designed and conducted in a scientifically sound manner, taking into account practical conditions in the field and differences between field conditions and laboratory conditions.

DATES: The regulations are effective on April 6, 1998.

FOR FURTHER INFORMATION CONTACT: Herman M. Schoenemann, Center for Veterinary Medicine (HFV-126), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1638.

SUPPLEMENTARY INFORMATION:

I. Background

Congress enacted the ADAA (Pub. L. 104-250) on October 9, 1996. Section 2(e) of the ADAA directs FDA to issue, within 18 months of its enactment, final regulations to further define the term "adequate and well controlled" to require that field investigations be designed and conducted in a scientifically sound manner, taking into account practical conditions in the field and differences between field conditions and laboratory conditions. In an advance notice of proposed rulemaking that published in the Federal Register of November 21, 1996 (61 FR 59209), FDA solicited comments from interested parties on how to further define "adequate and well controlled as it relates to field studies."[1] Docket No. 96N-0411 was created for comments responding to this notice.

In the Federal Register of May 8, 1997 (62 FR 25153), FDA proposed to amend its regulations in part 514 (21 CFR part 514) to further define the term "adequate and well-controlled studies." FDA provided 75 days for public comment on the proposed rule. Docket No. 97N-0141 was created for comments regarding this proposed rule. As

Rulemaking Process

Federal Register / Vol. 63, No. 43 / Thursday, March 5, 1998 / …. 10768

Point-by-point analysis and response to public comments

Discussion of variations between proposed rule and final rule

A. Section 514.117(a)

1. AHI recommended that FDA clarify in proposed Sec. 514.117(a) that reports of adequate and well-controlled studies refer to reports of adequate and well-controlled "effectiveness" studies. Based on the following discussion, FDA does not find it necessary to make such a clarification.

Under section 512(d)(1)(E) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b(d)(1)(E)), FDA must refuse to approve a new animal drug application if there is a lack of substantial evidence that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling. By definition, substantial evidence consists of one or more adequate and well-controlled studies on the basis of which experts qualified by scientific training and experience to evaluate the effectiveness of the drug could fairly and reasonably conclude that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling (section 512(d)(3) of the act). Thus, it is clear and well established that adequate and well-controlled studies are studies intended to determine whether or not a drug is effective.

Because it is adequate and well-controlled studies and not just reports of adequate and well-controlled studies that provide a basis for determining whether a new animal drug is effective, and in some instances support a claim of target animal safety, FDA is deleting "Reports of" in the second to last sentence in proposed Sec. 514.117(a).

In that same sentence, FDA is also clarifying that adequate and well-controlled studies may be relied upon to support target animal safety but are not necessary to support claims of target animal safety. Studies intended to demonstrate safety need not be adequate and well-controlled studies (see section 512(d)(1) of the act, which states that in order to secure approval of a new animal drug, a sponsor must conduct adequate tests by all methods reasonably applicable to show whether or not such drug is safe). In proposed Sec. 514.117(a), FDA intended only to note that adequate and well-controlled studies intended to demonstrate whether a new animal drug is effective may be designed in a manner that also permits sponsors to simultaneously collect target animal safety data. If a sponsor needs to demonstrate through a field study that a new animal drug is safe for use in the target animal, the sponsor may do so by adequate tests by methods that are reasonably applicable or as part of an adequate and well-controlled study that is designed to determine the effectiveness of the new animal drug. Accordingly the second to last sentence in Sec. 514.117(a) will now provide that adequate and well-controlled studies, in addition to providing a basis for determining whether a new animal drug is effective, may also be relied upon to support target animal safety.

Rulemaking Process

Federal Register / Vol. 63, No. 43 / Thursday, March 5, 1998 …. 10770

Lists of Subjects in 21 CFR Part 514

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 514 is amended as follows:

PART 514--NEW ANIMAL DRUG APPLICATIONS

1. The authority citation for 21 CFR part 514 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 360b, 371, 379e, 381.

2. Section 514.111 is amended by revising paragraph (a)(5) to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(5) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of one or more adequate and well-controlled studies by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

* * * * *

Amendatory instructions

3. New Sec. 514.117 is added to subpart B to read as follows:

Text of new section 514.117 in part 514 of title 21

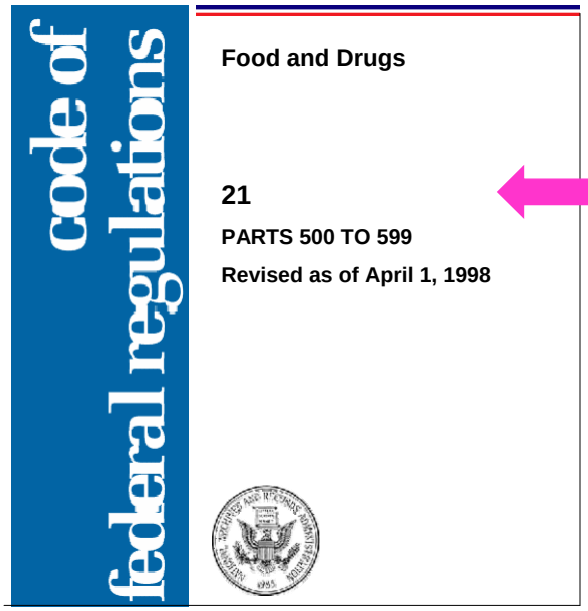
§ 514.117 Adequate and well-controlled studies.

(a) *Purpose*. The primary purpose of conducting adequate and well-controlled studies of a new animal drug is to distinguish the effect of the new animal drug from other influences, such as spontaneous change in the course of the disease, normal animal production performance, or biased observation. One or more adequate and well-controlled studies are required to establish, by substantial evidence, that a new animal drug is effective. The characteristics described in paragraph (b) of this section have been developed over a period of years and are generally recognized as the essentials of an adequate and well-controlled study.

CFR Codification

ADAA

- FDA published the new animal drugs rule on March 5, 1998
- The rule was integrated into the April 1, 1998 revision of title 21 -- “Food and Drugs”



Title 21, like most CFR titles, has multiple volumes. The new rule was codified in the volume containing parts 500-599 of title 21.

Rulemaking Process

Part Level Table of Contents, Authority Citations, and Source Notes

- A new entry in the table of contents at the part level to reflect the newly added section of regulatory text
- The authority citation below the table of contents
- The source note below the authority cite

Rulemaking Process

Table of Contents, Authority Cite, Source Note

Title 21--Food and Drugs

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

PART 514--NEW ANIMAL DRUG APPLICATIONS

Subpart A – General Provisions

* * *

Subpart B – Administrative Actions on Applications

514.100 Evaluation and comment on applications.
514.105 Approval of applications.
514.106 Approval of supplemental applications.
514.110 Reasons for refusing to file applications.
514.111 Refusal to approve an application.
514.112 Return of applications for animal feeds bearing or containing new animal drugs.
514.115 Withdrawal of approval of applications.
514.116 Notice of withdrawal of approval of application.
514.117 Adequate and well-controlled studies.
514.120 Revocation of order refusing to approve an application or suspending or withdrawing approval of an application.
514.121 Service of notices and orders.

Subpart C – Hearing Procedures

* * *

Subparts D-E [Reserved]

Subpart F – Judicial Review

514.235 Judicial review.

AUTHORITY: 21 U.S.C. 351, 352, 360b, 371, 379e, 381

SOURCE: 40 FR 13825, Mar. 27, 1975, unless otherwise noted.

Section 514.117 added to Table of Contents

Authority Citation and Source Note

CFR Text,
Section Level Source Notes,
and Authority Citations

- The text of new section 514.117 inserted into CFR Title 21, Chapter I, Part 514, Subpart B
- A source note
- No separate authority citation for this section

CFR Text

& Section

Source Note

Text of § 514.117 added to CFR

Updated Source Note cites to the final rule

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DE
AND HUMAN SERVICES--(Continued)

PART 514--NEW ANIMAL DRUG APPLICATIONS--Table

Subpart B--Administrative Actions on Applications

§ 514.116 Notice of withdrawal of approval of application.

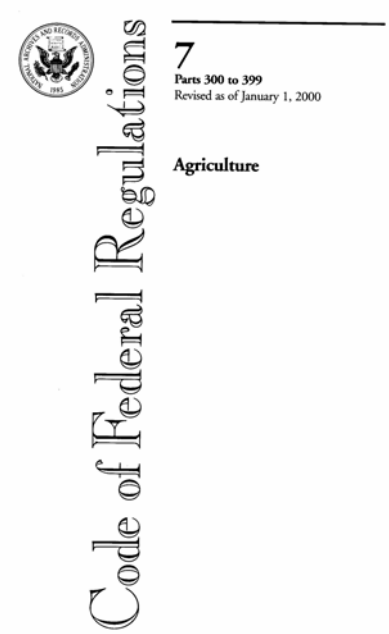
When an approval of an application submitted pursuant to section 512 of the act is withdrawn by the Commissioner, he will give appropriate public notice of such action by publication in the FEDERAL REGISTER.

§ 514.117 Adequate and well-controlled studies.

(a) *Purpose*. The primary purpose of conducting adequate and well-controlled studies of a new animal drug is to distinguish the effect of the new animal drug from other influences, such as spontaneous change in the course of the disease, normal animal production performance, or biased observation. One or more adequate and well-controlled studies are required to establish, by substantial evidence, that a new animal drug is effective. The characteristics described in paragraph (b) of this section have been developed over a period of years and are generally recognized as the essentials of an adequate and well-controlled study. Well controlled, as used in the phrase adequate and well controlled, emphasizes an important aspect of adequacy. The Food and Drug Administration (FDA) considers these characteristics in determining whether a study is adequate and well controlled for purposes of section 512 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b). Adequate and well-controlled studies, in addition to providing a basis for determining whether a new animal drug is effective, may also be relied upon to support target animal safety. /\

[63 FR 10770, Mar.5, 1998]

CFR Research Tools



Tables of Contents

Incorporation by Reference Tables

Table of CFR Titles and Chapters

Alphabetical List of Agencies Appearing in the CFR

Redesignation Tables

List of CFR Sections Affected

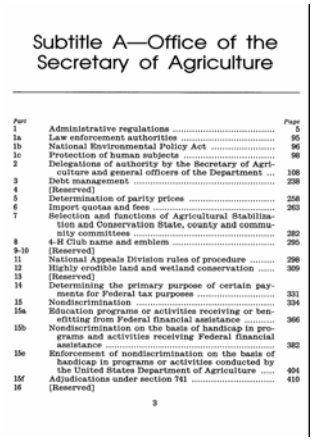
What research tools are in each printed volume of the CFR ?

- **At the front of each CFR volume, look for:**
  - ✧ **Tables of contents to all material within the book**
  - ✧ **Tables of contents to the title, subtitle(s), chapter(s), and subchapter(s) within the book**
- **At the back of each CFR volume, look for:**
  - ✧ **Table of "Material Approved for Incorporation by Reference" (IBR) - *Moved to a sidebar on the e-CFR***
  - ✧ **"Table of CFR Titles and Chapters"**
  - ✧ **"Alphabetical List of Agencies Appearing in the CFR"**
  - ✧ **Redesignation Tables**
  - ✧ **"List of CFR Sections Affected"**

CFR Research Tools

Table of Contents to a Subtitle

Table of Contents shows page numbers for the beginning of each part



Subtitle A—Office of the Secretary of Agriculture

3

CFR Research Tools

Part Level Table of Contents

Table of Contents lists the sections in the part and subparts

PART 1—ADMINISTRATIVE REGULATIONS

Subpart A—Official Records

Subpart B—Departmental Proceedings

Subpart C—Judicial Proceedings

Subpart D—Claims

Subpart E—Cooperative Production of Television Films

Subpart G—Privacy Act Regulations

Subpart H—Rules of Practice Governing Formal Adjudicatory Proceedings Instituted by the Secretary Under Various Statutes

5

Material Approved for Incorporation By Reference

- **IBR material has the force of law as though it were published in full text the FR & CFR**
- **Congress authorized IBR to enforce voluntary standards already used in science & industry**
- **Under the FOIA, the Director of the Federal Register must approve IBR to give it force and effect of law**
- **The incorporation by reference (IBR) table directs you to regulatory material not published in the FR & CFR**
  - **Located in the sidebar of the online e-CFR**

Table of CFR Titles and Chapters

- **A list of all CFR titles, subtitles, chapters, and part spans in numerical order -- titles 1 to 50**
- **Includes the names of agencies assigned to CFR chapters**
- **A more detailed list is located in the *CFR Index and Finding Aids*, a separate publication**

Alphabetical List of Agencies Appearing in the CFR

- A list of all agencies that publish in the CFR
- References to sub-agencies under main agencies
- Location of the regulations of each agency and sub-agency appear in the CFR by title, subtitle and chapter

Redesignation Tables

- A Redesignation Table helps you find the new location of parts and sections of regulations
- An agency publishes this table when it has done extensive reorganization and renumbering
- The table appears in the preamble of the rule document and is then included as a research tool in the back of the CFR

List of CFR Sections Affected (in a specific CFR volume)

- This list helps you track amendments in each CFR volume since 1986 by year and FR page number
- Lists the type of amendment and the text affected down to the paragraph level
- For years before 2000, use the eleven separate volumes of the *List of CFR Sections Affected*
- A cumulative, monthly LSA is also published separately

Federal Register On-line Resources

- **Official Federal Register Publications**
  - ✧www.fdsys.gov
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- **Federal Register Table of Contents ListServ**
  - ✧ **http://listerv.access.gpo.gov**
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  - ✧ **www.archives.gov/federal-register**
- **Public Participation in Rulemaking**
  - ° **Regulations.gov**

The End