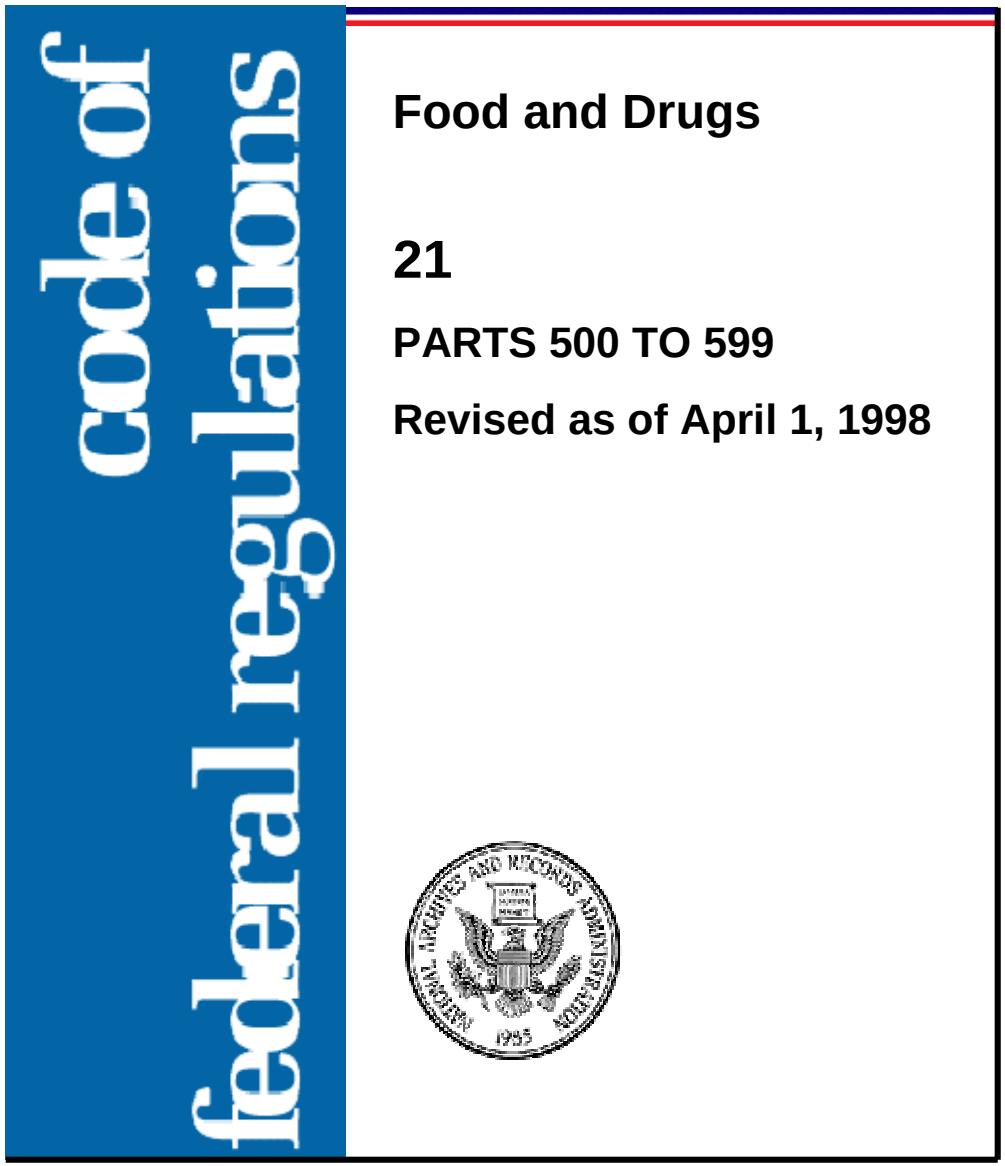
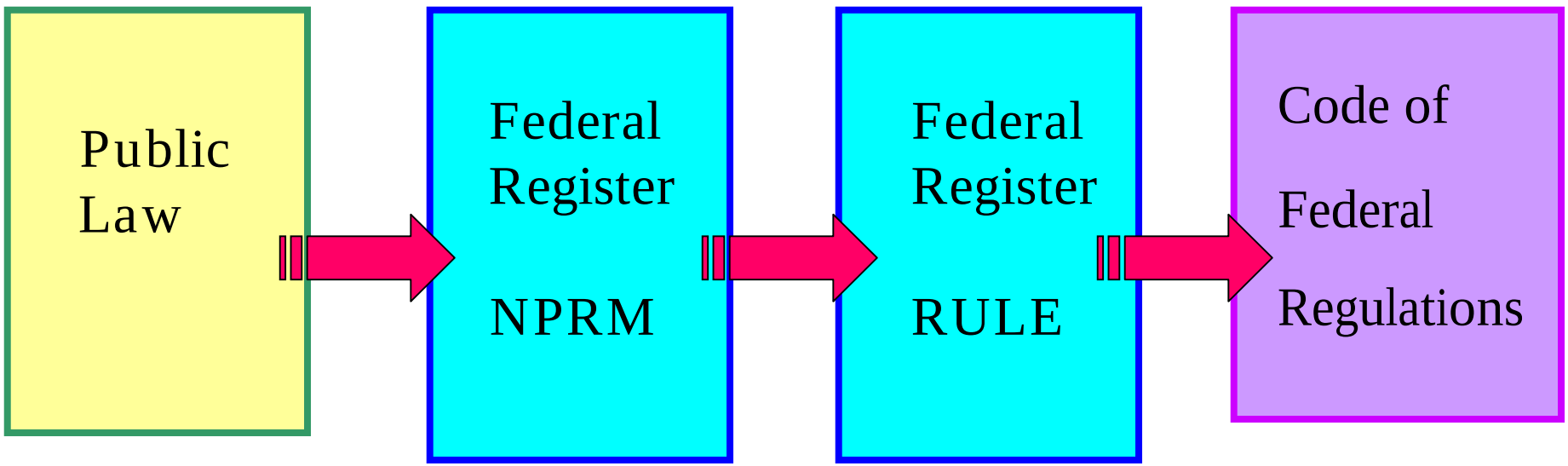
How are rules codified in the CFR ?

The Rulemaking Process from Start to Finish



The following discussion and examples track a rule from the grant of authority in law to the proposed rule, the final rule, and codification in the CFR



What Triggers Rulemaking ?

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

Authorization in Public Law

Rulemaking usually begins with Congressional action.

The next example shows a grant of rulemaking authority:

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

Statutes at Large citation

Public Law Number

Public Law 104-250
104th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to provide for improvements in the process of approving and using animal drugs, and for other purposes.

Oct. 9, 1996
[H.R. 2508]

Date of enactment

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Animal Drug Availability Act of 1996.
21 USC 301 note.

Popular name of law

SECTION 1. SHORT TITLE; REFERENCE.

(a) SHORT TITLE.—This Act may be cited as the "Animal Drug Availability Act of 1996".

(b) REFERENCE.—Whenever in this Act an amendment or repeal is expressed in terms of an amendment to, or repeal of, a section or other provision, the reference shall be considered to be made to a section or other provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.).

SEC. 2. EVIDENCE OF EFFECTIVENESS.

(a) ORIGINAL APPLICATIONS.—Paragraph (3) of section 512(d) (21 U.S.C. 360b(d)) is amended to read as follows:

"(3) As used in this section, the term 'substantial evidence' means evidence consisting of one or more adequate and well controlled investigations, such as—

"(A) a study in a target species;

"(B) a study in laboratory animals;

"(C) any field investigation that may be required under this section and that meets the requirements of subsection (b)(3) if a presubmission conference is requested by the applicant;

"(D) a bioequivalence study; or

"(E) an in vitro study;

by experts qualified by scientific training and experience to evaluate

Note the identifying information in headings and side notes

Rulemaking Instructions in the Law

FDA must issue regulations to implement the law.

- ✧ **Law sets a schedule for issuing proposed and final rules**
- ✧ **Instruction to publish "regulations" will not always make explicit reference to FR, but the agency must publish in *Federal Register* and follow APA notice and comment rulemaking process.**

United States Code citation in the side note

Regulations.
Effective date.
21 USC 360b note.

Directive to HHS to issue regulations

Timeline for action

(e) IMPLEMENTATION.—

(1) IN GENERAL.—Not later than 6 months after the date of enactment of this Act, the Secretary of Health and Human Services shall issue proposed regulations implementing the amendments made by this Act as described in paragraph (2)(A) of this subsection, and not later than 18 months after the date of enactment of this Act, the Secretary shall issue final regulations implementing such amendments. Not later than 12 months after the date of enactment of this Act, the Secretary shall issue proposed regulations implementing the other amendments made by this Act as described in paragraphs (2)(B) and (2)(C) of this subsection, and not later than 24 months after the date of enactment of this Act, the Secretary shall issue final regulations implementing such amendments.

(2) CONTENTS.—In issuing regulations implementing the amendments made by this Act, and in taking an action to review an application for approval of a new animal drug under section 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b), or a request for an investigational exemption for a new animal drug under subsection (j) of such section, that is pending or has been submitted prior to the effective date of the regulations, the Secretary shall—

(A) further define the term "adequate and well controlled", as used in subsection (d)(3) of section 512 of such Act, 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;

(B) further define the term "substantial evidence", as defined in subsection (d)(3) of such section, in a manner that encourages the submission of applications and supplemental applications; and

(C) take into account the proposals contained in the citizen petition (FDA Docket No. 91P–0434/CP) jointly submitted by the American Veterinary Medical Association and the Animal Health Institute, dated October 21, 1991.

Until the regulations required by subparagraph (A) are

Proposed Rulemaking

The APA requires agencies to give the public the opportunity to comment by submitting:

- ✧ **Written data**
- ✧ **Views or arguments**

The time needed to issue an NPRM varies

- ✧ **The animal drug law set a 6 month time limit**

In the next example:

- ✧ **FDA published the proposed rule on May 8, 1997, about 7 months after the law was enacted, slightly past the deadline**

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.

The public has 75 days to comment

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

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

It is not unusual for more than a year to pass between proposed and final rules.

- ✧ **In the next example, 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**

Rulemaking Process

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

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

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

Amendatory instructions

Text of new section 514.117 in part 514 of title 21

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.

* * * * *

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.

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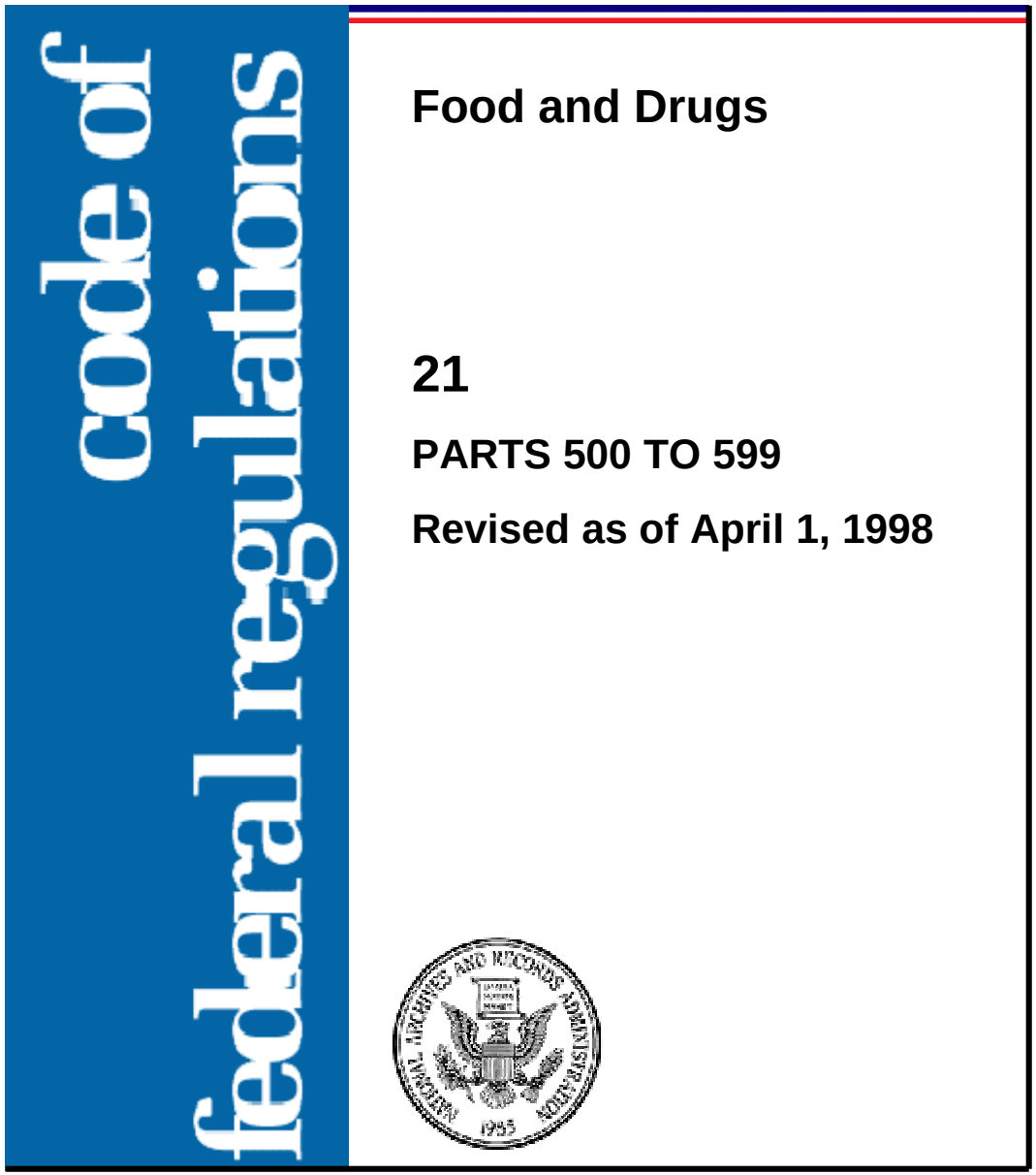
CFR Codification

In the next example:

- **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.

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

The next example shows:

- **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:**
  - ✧ **Refers readers to the agency's statutory, Presidential or internal authority to issue regulations in this part**

- **The source note below the authority cite:**
  - ✧ **Indicates when the part was last published in full, citing the volume, page and date**

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

In the next example:

- **The text of new section 514.117 has been inserted into CFR Title 21, Chapter I, Part 514, Subpart B according to instructions in final rule**

- **A source note follows the text of the section to indicate the recent amendment that added this section**

- **No separate authority citation for this section**
  - ✧ **The section level authority for this section is the same as the part level authority**

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]

continue >