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Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 3, et al.

Removal of Regulations Regarding Certification of Drugs Composed Wholly or Partly of Insulin; Proposed Rule and Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 3, 5, 10, 16, 25, 50, 56, 58, 71, 200, 201, 207, 210, 211, 310, 312, 314, 369, 429, 800, and 812

[Docket No. 98N–0210]

Removal of Regulations Regarding Certification of Drugs Composed Wholly or Partly of Insulin; Companion Document to Direct Final Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is publishing this companion proposed rule to the direct final rule, published elsewhere in this issue of the **Federal Register**, which is intended to repeal FDA's regulations governing certification of drugs containing insulin and make conforming amendments to other sections of the agency's regulations. The agency is taking this action in accordance with provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA repealed the statutory provision in the Federal Food, Drug, and Cosmetic Act (the act) under which the agency certified drugs containing insulin. FDAMA also made conforming amendments to the act.

DATES: Comments must be received on or before July 27, 1998.

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: Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

Section 125(a) of FDAMA (Pub. L. 105–115) repealed section 506 of the act (21 U.S.C. 356) and made other conforming amendments to the act and another provision of Federal law. Section 506 was the statutory provision in the act under which the agency certified drugs containing insulin. FDA is proposing to remove all regulations relating to the certification of insulin products, remove citations to section 506 of the act in various authority sections in title 21 of the Code of Federal Regulations (CFR), and eliminate citations to section 506 in regulations that do not deal primarily with the certification of insulin. FDA is also proposing to eliminate out-of-date provisions dealing with labeling and testing of insulin and to update the definition of insulin found in 21 CFR 200.15.

II. Additional Information

This proposed rule is a companion to the direct final rule published elsewhere in this issue of the **Federal Register**. The companion proposed rule and the direct final rule are identical. This companion proposed rule will provide the procedural framework to finalize the rule in the event the direct final rule receives significant adverse comment and is withdrawn. The comment period for the companion proposed rule runs concurrently with the comment period of the direct final rule. Any comments received under the companion proposed rule will be treated as comments regarding the direct final rule.

Most of the amendments in this rule are a direct result of the repeal of the statutory certification provision. The remainder of the amendments repeal or update out-of-date, noncontroversial regulations dealing with insulin. If no significant adverse comment is received in response to the direct final rule, no further action will be taken related to the companion proposed rule. Instead, FDA will publish a confirmation document within 30 days after the comment period ends confirming that the direct final rule will go into effect on September 25, 1998. If FDA receives significant adverse comments, the agency will withdraw the direct final rule. FDA will proceed to respond to all of the comments received regarding the rule and, if appropriate, the rule will be finalized under this companion proposed rule using usual notice-and-comment procedures.

For additional information, see the corresponding direct final rule published elsewhere in this issue of the **Federal Register**. All persons who wish to comment should review the detailed rationale for these amendments set out in the preamble discussion of the direct final rule. A significant adverse comment is one that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. A comment recommending a rule change in addition to this rule will not be considered a significant adverse comment, unless the comment states why this rule would be ineffective without the additional change.

III. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Analysis of Impacts

FDA has examined the impacts of this companion proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of $100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant impact on small entities. The only two current manufacturers marketing insulin drug products in the United States are not small entities. Furthermore, by eliminating the certification process, this direct final rule would lower market entry barriers for small entities. The agency certifies that the proposed rule will not have a significant impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The Unfunded Mandates Act requires an agency to prepare a budgetary impact statement before issuing any rule likely to result in a Federal mandate that may result in expenditures by State, local, and tribal governments or the private sector of $100 million (adjusted annually for inflation) in any 1 year. The elimination of the insulin certification program will lower the

costs of marketing insulin drug products by eliminating both the direct cost of applying for certification and the cost of holding batches of insulin while awaiting certification. Because this rule will not result in an expenditure of $100 million or more on any governmental entity or the private sector, no budgetary impact statement is required.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (Pub. L. 104–13) is not required.

VI. Request for Comments

Interested persons may, on or before September 27, 1998, submit to the Dockets Management Branch (address above) written comments regarding this proposal. This comment period runs concurrently with the comment period for the direct final rule; any comments received will be considered as comments regarding the direct final rule. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 3

Administrative practice and procedure, Biologics, Drugs, Medical devices.

21 CFR Part 5

Authority delegations (Government agencies), Imports, Organization and functions (Government agencies).

21 CFR Part 10

Administrative practice and procedure, News media.

21 CFR Part 16

Administrative practice and procedure.

21 CFR Part 25

Environmental impact statements, Foreign relations, Reporting and recordkeeping requirements.

21 CFR Part 50

Human research subjects, Prisoners, Reporting and recordkeeping requirements, Safety.

21 CFR Part 56

Human research subjects, Reporting and recordkeeping requirements, Safety.

21 CFR Part 58

Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 71

Administrative practice and procedure, Color additives, Confidential business information, Cosmetics, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 200

Drugs, Prescription drugs.

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR 207

Drugs, Reporting and recordkeeping requirements.

21 CFR 210

Drugs, Packaging and containers.

21 CFR Part 211

Drugs, Labeling, Laboratories, Packaging and containers, Prescription drugs, Reporting and recordkeeping requirements, Warehouses.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

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

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

21 CFR Part 429

Administrative practice and procedure, Drugs, Labeling, Packaging and containers, Reporting and recordkeeping requirements.

21 CFR Part 800

Administrative practice and procedure, Medical devices, Ophthalmic goods and services, Packaging and containers, Reporting and recordkeeping requirements.

21 CFR Part 812

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 3, 5, 10, 16, 25, 50, 56, 58, 71, 200, 201, 207, 210, 211, 310, 312, 314, 369, 429, 800, and 812 be amended as follows:

PART 3—PRODUCT JURISDICTION

1. The authority citation for 21 CFR part 3 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 357, 360, 360c–360f, 360h–360j, 360gg–360ss, 371(a), 379e, 381, 394; 42 U.S.C. 216, 262.

PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION

2. The authority citation for 21 CFR part 5 continues to read as follows:

Authority: 5 U.S.C. 504, 552, App. 2; 7 U.S.C. 138a, 2271; 15 U.S.C. 638, 1261–1282, 3701–3711a; 15 U.S.C. 1451–1461; 21 U.S.C. 41–50, 61–63, 141–149, 321–394, 467f, 679(b), 801–886, 1031–1309; 35 U.S.C. 156; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 264, 265, 300u–300u–5, 300aa–1; 1395y, 3246b, 4332, 4831(a), 10007–10008; E.O. 11921, 41 FR 24294, 3 CFR, 1977 Comp., p. 124–131; E.O. 12591, 52 FR 13414, 3 CFR, 1988 Comp., p. 220–223.

§ 5.31 [Amended]

3. Section 5.31 *Petitions under part 10* is amended by removing and reserving paragraphs (f)(2)(iii) and (f)(2)(iv).

§ 5.73 [Removed]

4. Section 5.73 *Certification of insulin* is removed.

§ 5.74 [Removed]

5. Section 5.74 *Issuance, amendment, or repeal of regulations pertaining to drugs containing insulin* is removed.

PART 10—ADMINISTRATIVE PRACTICES AND PROCEDURES

6. The authority citation for 21 CFR part 10 continues to read as follows:

Authority: 21 U.S.C. 41–50, 141–149, 321–394, 467f, 679, 821, 1034; 42 U.S.C. 201, 262, 263b, 264; 15 U.S.C. 1451–1461; 5 U.S.C. 551–558, 701–721; 28 U.S.C. 2112.

§ 10.50 [Amended]

7. Section 10.50 *Promulgation of regulations and orders after an opportunity for a formal evidentiary public hearing* is amended by removing and reserving paragraph (c)(10).

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

8. The authority citation for 21 CFR part 16 continues to read as follows:

Authority: 21 U.S.C. 41–50, 141–149, 321–394, 467f, 679, 821, 1034; 42 U.S.C. 201, 262, 264; 15 U.S.C. 1451–1461; 28 U.S.C. 2112.

§ 16.1 [Amended]

9. Section 16.1 *Scope* is amended in paragraph (b)(2) by removing the entry for ''§ 429.50.''

PART 25—ENVIRONMENTAL IMPACT CONSIDERATIONS

10. The authority citation for 21 CFR part 25 continues to read as follows:

Authority: 21 U.S.C. 321–393; 42 U.S.C. 262, 263b–264; 42 U.S.C. 4321, 4332; 40 CFR parts 1500–1508; E.O. 11514, 35 FR 4247, 3 CFR, 1971 Comp., p. 531–533 as amended by E.O. 11991, 42 FR 26967, 3 CFR, 1978 Comp., p. 123–124 and E.O. 12114, 44 FR 1957, 3 CFR, 1980 Comp., p. 356–360.

§ 25.31 [Amended]

11. Section 25.31 *Human drugs and biologics* is amended in paragraph (f) by removing the words ''or insulin.''

PART 50—PROTECTION OF HUMAN SUBJECTS

12. The authority citation for 21 CFR part 50 is revised to read as follows:

Authority: 21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 357, 360, 360c–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b–263n.

§ 50.1 [Amended]

13. Section 50.1 *Scope* is amended in the last sentence of paragraph (a) by removing the number ''506,''.

PART 56—INSTITUTIONAL REVIEW BOARDS

14. The authority citation for 21 CFR part 56 is revised to read as follows:

Authority: 21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 357, 360, 360c–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b–263n.

PART 58—GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES

15. The authority citation for 21 CFR part 58 is revised to read as follows:

Authority: 21 U.S.C. 342, 346, 346a, 348, 351, 352, 353, 355, 357, 360, 360b–360f, 360h–360j, 371, 379e, 381; 42 U.S.C. 216, 262, 263b–263n.

PART 71—COLOR ADDITIVE PETITIONS

16. The authority citation for 21 CFR part 71 is revised to read as follows:

Authority: 21 U.S.C. 321, 342, 348, 351, 355, 357, 360, 360b–360f, 360h–360j, 361, 371, 379e, 381; 42 U.S.C. 216, 262.

PART 200—GENERAL

17. The authority citation for 21 CFR part 200 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 358, 360e, 371, 374, 375.

18. Section 200.15 is revised to read as follows:

§ 200.15 Definition of term ''insulin.''

For purposes of sections 801 and 802 of the act and this title, the term insulin means the active principle of the pancreas that affects the metabolism of carbohydrates in the animal body and which is of value in the treatment of diabetes mellitus. The term includes synthetic and biotechnologically derived products that are the same as, or similar to, naturally occurring insulins in structure, use, and intended effect and are of value in the treatment of diabetes mellitus.

PART 201—LABELING

19. The authority citation for 21 CFR part 201 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

§ 201.50 [Amended]

20. Section 201.50 *Statement of identity* is amended in paragraph (b) by removing the second sentence.

§ 201.100 [Amended]

21. Section 201.100 *Prescription drugs for human use* is amended in paragraph (c)(2) by removing the number '', 506,''.

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION

22. The authority citation for 21 CFR part 207 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 355, 357, 360, 360b, 371, 374; 42 U.S.C. 262.

§ 207.25 [Amended]

23. Section 207.25 *Information required in registration and drug listing* is amended in paragraphs (b)(2), (b)(5), and (b)(6) by removing the number ''506,'' and in paragraph (b)(4) by removing the number '', 506,''.

§ 207.31 [Amended]

24. Section 207.31 *Additional drug listing information* is amended in paragraph (a)(1) by removing the number '', 506,'', and in paragraphs (a)(2), (a)(3), and (c) by removing the number ''506,''.

§ 207.37 [Amended]

25. Section 207.37 *Inspection of registrations and drug listings* is amended in paragraph (a)(2)(i) by removing the number ''506,''.

PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

26. The authority citation for 21 CFR part 210 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 357, 360b, 371, 374.

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

27. The authority citation for 21 CFR part 211 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 357, 360b, 371, 374.

PART 310—NEW DRUGS

28. The authority citation for 21 CFR part 310 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

29. The authority citation for 21 CFR part 312 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371; 42 U.S.C. 262.

30. The authority citation for 21 CFR part 312, subpart E is revised to read as follows:

Authority: 21 U.S.C. 351, 352, 353, 355, 357, 371; 42 U.S.C. 262.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

31. The authority citation for 21 CFR part 314 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371, 374, 379e.

§ 314.170 [Amended]

32. Section 314.170 *Adulteration and misbranding of an approved drug* is amended in the first sentence by removing the phrase ''under sections 505, 506, and 507'' and adding in its place the phrase ''under sections 505(j) and 507''.

§ 314.430 [Amended]

33. Section 314.430 *Availability for public disclosure of data and*

information in an application or abbreviated application is amended in paragraph (f)(6) by removing the phrase ''under sections 505(j), 506, and 507'' and adding in its place the phrase ''under sections 505(j) and 507''.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER–THE–COUNTER SALE

34. The authority citation for 21 CFR part 369 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371.

§ 369.5 [Removed]

35. Section 369.5 *Warning required on insulin intended for over-the-counter sale* is removed

§ 369.21 [Amended]

36. Section 369.21 *Drugs; warning and caution statements required by regulations* is amended by removing the entry for ''INSULIN''.

PART 429—DRUGS COMPOSED WHOLLY OR PARTLY OF INSULIN

37. Under authority of section 701(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 371(a)) and section 125(a) of the Food and Drug Modernization Act (Pub. L. 105–115), amend Title 21 of the Code of Federal Regulations by removing part 429.

PART 800—GENERAL

38. The authority citation for 21 CFR part 800 is revised to read as follows:

Authority: 21 U.S.C. 321, 334, 351, 352, 355, 357, 360e, 360i, 360k, 361, 362, 371.

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

39. The authority citation for 21 CFR part 812 is revised to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 357, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b–263n.

Dated: April 17, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

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