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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Regulation No.	11/15/99
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Certifier	[Signature]

Food and Drug Administration

21 CFR Part 310

[Docket No. 99N-0188]

Progestational Drug Products for Human Use; Requirements for Labeling Directed to the Patient

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revoking its regulation requiring patient labeling for progestational drug products. Patient labeling had been required to inform patients of an increased risk of birth defects reported to be associated with the use of these drugs during the first 4 months of pregnancy. FDA concluded that, based on a review of the scientific data, such labeling for all progestogens is not warranted. In addition, the diversity of drugs that can be described as progestational and the diversity of conditions these drugs may be used to treat make it inappropriate to consider these drugs a single class for labeling purposes. This action is intended to provide consumers with more appropriate labeling for certain drug products.

EFFECTIVE DATE: *(Insert date 1 year after date of publication in the Federal Register.)*

FOR FURTHER INFORMATION CONTACT: Diane V. Moore, Center for Drug Evaluation and Research (HFD-580), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4260.

SUPPLEMENTARY INFORMATION:

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I. Background

In the 1970's, there were several reports suggesting "an association between intrauterine exposure to sex hormone treatment and congenital anomalies, including congenital heart defects and limb reduction defects" (42 FR 37646, July 22, 1977). Based on these reports, FDA published a proposed rule to require patient labeling for progestational drug products (42 FR 37643, July 22, 1977). The category "progestational drug products" included natural progesterone and all synthetic progestins. The regulation was finalized on October 13, 1978 (43 FR 47178), and was codified at § 310.516 (21 CFR 310.516). It required that progestational drug products be dispensed with a patient package insert containing a "brief discussion of the nature of the risks of birth defects resulting from the use of these drugs during the first 4 months of pregnancy" (§ 310.516(b)(4)). The regulation applied to any drug product that contains a progestogen, with the exceptions of contraceptives and oral dosage forms labeled solely for the treatment of advanced cancer¹ (310.516(e)(4)).

II. The Final Rule

In the **Federal Register** of April 13, 1999 (64 FR 17985), FDA published a proposed rule to revoke its regulation requiring patient labeling for progestational drug products. FDA concluded that, based on a review of the scientific data, such labeling for all progestogens is not warranted. In addition, the diversity of drugs that can be described as progestational and the diversity of conditions these drugs may be used to treat make it inappropriate to consider these drugs a single class for labeling purposes. For more detailed descriptions of the scientific basis for revoking the rule and the history of the rule's adoption, see the proposed rule (64 FR 17985).

FDA received only three comments on the proposed rule, two from university professors and one from a trade association of pharmacists. Two comments commended FDA's action. The third

¹ The original regulation exempted contraceptives, which were required to comply with the labeling requirements of 21 CFR 310.501. In 1981, the regulation was amended to exempt advanced cancer drugs (46 FR 53656, October 30, 1981).

comment stated that each individual progestational drug product should carry warnings appropriate to that particular product and that a teratogenic warning might be appropriate for a particular progestin. FDA agrees and will require labeling that is appropriate to the dose and indication of each progestational drug product. Thus, FDA is adopting the rule as proposed.

III. Guidance Texts

In 1977, when FDA proposed the rule concerning progestational drug products, it published guidance texts for physician and patient labeling warning of possible heart and limb defects (42 FR 37647 and 37648, July 22, 1977). FDA revised these guidance texts in the **Federal Register** of January 12, 1989 (54 FR 1243). The revised texts deleted the warning about possible congenital heart defects and limb reduction defects and added a warning about an increased risk of certain genital abnormalities. Concurrently with the 1999 proposed rule to revoke § 310.516, FDA published a notice announcing that it intended to revoke the guidance texts for physician and patient labeling (64 FR 18035, April 13, 1999). FDA received no comments concerning the revocation of the guidance texts. Elsewhere in this issue of the **Federal Register**, FDA is publishing a notice revoking those guidance texts.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (Public Law 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). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant impact on small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities. The Unfunded Mandates Reform Act (in section 202) requires that agencies prepare an assessment

of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million or more (adjusted annually for inflation).

The agency has reviewed this final rule and has determined that it is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and these two statutes. With respect to the Regulatory Flexibility Act, the agency certifies that the rule will not have a significant effect on a substantial number of small entities. Because the final rule does not impose any mandates on State, local, or tribal governments or the private sector that will result in a 1-year expenditure of \$100 million or more, FDA is not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act. FDA received no comments on the proposed Analysis of Impacts.

The final rule removes the requirement that sponsors include certain information in the professional labeling of affected drug products. The revised labeling may be filed in the next annual report. The agency has identified 13 sponsors and 16 distinct professional labeling inserts that will need to be changed to comply with this rule. Any professional skills necessary for implementation of this rule should already exist within the sponsor's firm and should not need to be newly acquired. Using a pharmaceutical labeling cost model developed for the agency by its contractor, Eastern Research Group, Inc., the average cost for this labeling change is \$1,317 per insert, assuming a compliance period of 1 year. Applying this cost to the 16 professional labeling inserts results in a one-time cost of compliance of \$21,000. There will also be an additional minor cost of lost inventory. Of the 13 sponsors affected, fewer than 5 would meet the Small Business Administration's definition of a small entity. No additional burdens are imposed upon manufacturers. Therefore, in accordance with the Regulatory Flexibility Act, FDA certifies that this rule will not have a significant economic impact on a substantial number of small entities.

V. Paperwork Reduction Act of 1995

FDA concludes that this final rule contains no collections of information. The final rule removes the requirement that certain information be included in the labeling of affected drug products. The revised labeling may be filed in the next annual report, which is already required under FDA regulations and is already approved by the Office of Management and Budget (OMB) as a collection of information (OMB control no. 0910–0001). Therefore, clearance by OMB under the Paperwork Reduction Act of 1995 is not required.

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a class of actions 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.

VII. Effective Date

This final rule becomes effective 1 year after its date of publication in the **Federal Register**.

List of Subjects in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under the authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

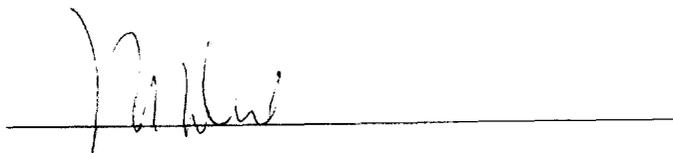
Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

§ 310.516 [Removed]

2. Section 310.516 *Progestational drug products; labeling directed to the patient* is removed.

Dated: 11/4/99

November 4, 1999



Margaret M. Dotzel
Acting Associate Commissioner
for Policy

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL



[FR Doc. 99-???? Filed ??-??-99; 8:45 am]

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