E 4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 10, 56, 106, 201, 251, 310, 312, 314, 329, 600, 803, 862, 866, 870, 882, 1114

[Docket No. FDA-2026-N-2886]

RIN 0910-AJ26

Modification of Certain Terminology in Title 21

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing a proposed rule to modify certain terminology in Title 21 of the Code of Federal Regulations (CFR) to comply with Executive Order (E.O.) 14168, "Defending Women From Gender Ideology Extremism and Restoring Biological Truth to the Federal Government," issued on January 20, 2025. Specifically, this proposed rule, if finalized, will remove the term "gender" wherever it appears and either replace it with the term "sex," or delete reference to gender, as applicable, along with other editorial changes to improve readability.

DATES: Submit either electronic or written comments on the proposed rule by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]**. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions.")

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2026-N-2886 for "Modification of Certain Terminology in Title 21." Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted

as “Confidential Submissions,” publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: http://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Swati Kabaria, Office of Policy, Office of Policy, Legislation, and International Affairs, Office of the Commissioner, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 1-888-463-6332.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to amend certain terminology in Title 21 of the CFR to remove the term "gender" wherever it appears, to either replace it with the term "sex," or delete reference to gender, as applicable, and make other editorial changes to the relevant sections for readability.

FDA is taking this action to comply with E.O. 14168, "Defending Women From Gender Ideology Extremism and Restoring Biological Truth to the Federal Government.[1]"

B. Summary of the Major Provisions of the Proposed Rule

The proposed rule would remove the term "gender" wherever it appears, to either replace it with the term "sex," or delete reference to gender, as applicable, and make other editorial changes for readability, in the following regulations in Title 21 of the CFR: 21 CFR 10.65, 56.107, 106.121, 201.57, 251.18, 310.305, 312.33, 312.42, 314.50, 314.80, 329.100, 600.80, 803.32, 803.42, 803.52, 862.1840, 866.3215, 866.5950, 870.1415, 870.2200, 870.2210, 870.2220, 870.5600, 882.1455, 882.1471, 1114.3, and 1114.41.

C. Legal Authority

FDA proposes to issue this rule under the following authorities: The Federal Food, Drug, and Cosmetic Act (FD&C Act) at 21 U.S.C. 321 et seq. and specifically, sections 321-397; the Public Health Service (PHS Act) at 42 U.S.C. 201, 216, 241, 242(a), 262, 263a, 263b, 264; 15 U.S.C. 1451-1461; 5 U.S.C. 551-558, 701-706; 21 U.S.C. 141-149, 467f, 679, 821, 1034; 28 U.S.C. 2112; and section 111 of the Consolidated Appropriations Act, 2022 (Pub. L. 117-103), 136 Stat. 49 at 789. FDA also has general authority to issue regulations for the efficient enforcement of the FD&C Act and the PHS Act under section 701 of the FD&C Act (21 U.S.C. 371) and section 351(j) of the PHS Act.

D. Costs and Benefits

FDA is proposing to remove the term "gender" wherever it appears, and either replace it with the term "sex," or delete reference to gender, as applicable, and make other editorial changes for readability. This proposed rule reflects editorial changes that affect FDA and does not impact industry practices. Consequently, we do not anticipate any measurable change in industry resulting from this proposed rule. We also expect the economic impact on FDA to be

1 https://www.federalregister.gov/documents/2025/01/30/2025-02090/defending-women-from-gender-ideology-extremism-and-restoring-biological-truth-to-the-federal

minimal. This proposed rule will produce no quantifiable savings, costs, or transfers. We do not expect any loss of public health benefits as a result of this rule. We estimate that the annualized benefits over 10 years would be $0 at both 3 and 7 percent discount rate. The annualized costs would also be $0 at both 3 and 7 percent discount rate.

This proposed rule, if finalized, is not expected to be an Executive Order 14192 regulatory action. We estimate that this proposed rule would generate $0 in net cost savings.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
CFR	Code of Federal Regulations
E.O.	Executive Order
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA or Agency	Food and Drug Administration
IDE	Investigational Device Exemption
IND	Investigational New Drug
NDA	New Drug Application
OMB	Office of Management and Budget
PHS Act	Public Health Service Act

III. Background

A. Need for the Regulation

On January 20, 2025, the President issued E.O. 14168, "Defending Women From Gender Ideology Extremism and Restoring Biological Truth to the Federal Government," which, among other things, requires executive agencies to use the term "sex" and not "gender" when administering or enforcing sex-based distinctions, in all applicable Federal policies and documents.

Accordingly, this proposed rule would, if finalized, amend certain terminology in FDA regulations, specifically by removing the word "gender" wherever it appears, to either replace it with the term "sex," or delete reference to gender, as applicable, and make other appropriate editorial changes for readability.

B. FDA's Current Regulatory Framework

The terms "gender" and "sex" appear in various contexts in FDA regulations, including in requirements related to Institutional Review Board (IRB) membership (see 21 CFR 56.107), records and reporting requirements for product applications and approvals (see, e.g., 21 CFR 312.42, 314.50, 314.80, 600.80, 803.32), and device classification regulations (see, e.g., 21 CFR 862.1840, 866.3215, 866.5950). Section 2(a) of E.O. 14168 defines "sex" as referring to an individual's immutable biological classification as either male or female. Section 3(c) of E.O. 14168 requires, among other things, that "[w]hen administering or enforcing sex-based distinctions, every agency and all Federal employees acting in an official capacity on behalf of their agency shall use the term "sex" and not "gender" in all applicable Federal policies and documents." After reviewing them, FDA is modifying regulations to remove the term "gender" wherever it appears, to either replace it with the term "sex," or delete reference to gender, as applicable.

IV. Legal Authority

FDA is proposing this rule under the authority granted to it by the FD&C Act (21 U.S.C. 301 *et seq.*),the PHS Act (42 U.S.C. 201 *et seq.*), 15 U.S.C. 1451-1461; 5 U.S.C. 551-558, 701-706; 21 U.S.C. 141-149, 467f, 679, 821, 1034; 28 U.S.C. 2112; and section 111 of the Consolidated Appropriations Act, 2022. The statutory authorities supporting this rulemaking are those authorizing the regulations which are to be amended. Specifically, FDA is proposing this rule under the following statutes and public laws: 21 U.S.C. 321-397; 42 U.S.C. 201, 216, 241, 242(a), 262, 263a, 263b, 264; 15 U.S.C. 1451-1461; 5 U.S.C. 551-558, 701-706; 21 U.S.C. 141-149, 467f, 679, 821, 1034; 28 U.S.C. 2112; and section 111 of the Consolidated Appropriations Act of 2022. By delegation from the Secretary of the Department of Health and Human Services, FDA is authorized to issue regulations for the efficient enforcement of the FD&C Act (21 U.S.C. 371) and section 351(j) of the PHS Act (42 USC 262(j)). Any final rule upon which this proposal is based would help with the efficient enforcement of provisions relating to the following: (1) IRBs; (2) infant formula; (3) human and animal drugs, biological products, and

medical devices; (4) drug, biological product, and device labeling and reporting; (5) drug importation; and (6) premarket tobacco product applications.

V. Description of the Proposed Rule

We propose to amend regulations concerning IRBs; infant formula; human and animal drugs, biological products, and medical devices; drug, biological product, and device labeling and reporting; drug importation; and premarket tobacco product applications by removing the term "gender" wherever it appears, to either replace it with the term "sex," or delete reference to gender, as applicable, and make other appropriate editorial changes for readability in Title 21 of the CFR:

	Chapter/Subchapter	*Heading*
1	§10.65(d)(3)	Meetings and correspondence
2	§56.107(a)	IRB membership
3	§56.107(b)	IRB membership
4	§106.121(a)(2)	Quality factor assurances for infant formulas
5	§201.57(c)(13)(i)(C)	Specific requirements on content and format of labeling for human prescription drug and biological products described in Sec. 201.56(b)(1)
6	§251.18(d)(7)(i)(C)	Post-importation requirements
7	§310.305(d)(1)(iii)	Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications
8	§312.33 (a)(2)	Annual reports
9	§312.42(b)(1)(v)	Clinical holds and requests for modification
10	§312.42(b)(1)(v)(A)	Clinical holds and requests for modification
11	§312.42(b)(1)(v)(B)	Clinical holds and requests for modification
12	§314.50(d)(5)(v)	Content and format of an NDA
13	§314.50(d)(5)(vi)	Content and format of an NDA
14	§314.80(f)(1)(iii)	Postmarketing reporting of adverse drug experiences
15	§329.100(b)(1)(iii)	Postmarketing reporting of adverse drug events under section 760 of the Federal Food, Drug, and Cosmetic Act
16	§600.80(f)(1)(iii)	Postmarketing reporting of adverse experiences
17	§600.80(g)(1)(iii)	Postmarketing reporting of adverse experiences

18	§803.32(a)(3)	If I am a user facility, what information must I submit in my individual adverse event reports?
19	§803.42 (a)(3)	If I am an importer, what information must I submit in my individual adverse event reports?
20	§803.52(a)(3)	If I am a manufacturer, what information must I submit in my individual adverse event reports?
21	§862.1840(b)(3)	Total 25-hydroxyvitamin D mass spectrometry test system
22	§866.3215(b)(5)	Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis
23	§866.5950(b)(3)(ii)(B)	Genetic health risk assessment system
24	§866.5950(b)(3)(iii)(J)(1)(viii)	Genetic health risk assessment system
25	§870.1415(b)(6)(v)	Coronary vascular physiologic simulation software device
26	§870.2200(b)(5)(vii)	Adjunctive cardiovascular status indicator
27	§870.2210(b)(5)(viii)	Adjunctive predictive cardiovascular indicator
28	§870.2220(b)(5)(v)	Adjunctive hemodynamic indicator with decision point
29	§870.5600(b)(5)(ix)	Adjunctive open loop fluid therapy recommender
30	§882.1455(b)(6)(ii)(E)	Traumatic brain injury eye movement assessment aid
31	§882.1471(b)(3)(i)(D)(5)	Computerized cognitive assessment aid for concussion
32	§1114.3	Definitions
33	§1114.41(a)(1)(vi)(C)	Reporting requirements
34	§1114.41(a)(1)(xvi)	Reporting requirements

VI. Proposed Effective Date

We propose that any final rule resulting from this rulemaking would become effective 30 days after the date of the final rule's publication in the *Federal Register*.

VII. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under E.O. 12866, E.O. 13563, E.O. 14192, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Executive Orders 12866 and 13563 direct us to assess all benefits and costs of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. Rules are economically significant under E.O. 12866 if they have an

annual effect on the economy of $100 million or more; or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities. The Office of Information and Regulatory Affairs (OIRA) has determined that this proposed rule is not a significant regulatory action under E.O. 12866.

E.O. 14192 requires that any new incremental costs associated with certain significant regulatory actions "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least 10 prior regulations." This proposed rule, if finalized as proposed, is not expected to be an E.O. 14192 regulatory action because this rule is not significant under E.O. 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule reflects editorial changes and does not add any new regulatory burden on the industry, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $193 million, using the most current (2025) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

FDA is proposing to remove the term "gender" wherever it appears, and either replace it with the term "sex," or delete reference to gender, as applicable, and make other editorial changes for readability. This proposed rule reflects editorial changes that affect FDA and does

not impact industry practices. Consequently, we do not anticipate any measurable change in industry resulting from this proposed rule. We also expect the economic impact on FDA to be minimal. This proposed rule will produce no quantifiable savings, costs, or transfers. We do not expect any loss of public health benefits as a result of this rule.

Table 1 summarizes the estimated benefits and costs of the proposed rule. We estimate that the annualized benefits over 10 years would be $0 at both 3 and 7 percent discount rate. The annualized costs would also be $0 at both 3 and 7 percent discount rate. We request comments on our estimates of benefits, costs, and transfers of this proposed rule.

Table 1. Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule (millions of 2024 dollars)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($millions/year)	$0	$0	$0		7%		
						3%		
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized ($millions/year)	$0	$0	$0		7%		
						3%		
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized ($millions/year)					7%		
						3%		
		From:			To:			
	Other Annualized Monetized ($millions/year)					7%		
						3%		
		From:			To:			
Effects	State, Local or Tribal Government: none Small Business: none Wages: none Growth: none							

In line with E.O. 14192, in Table 2 we estimate present and annualized values of costs, cost savings, and net costs over a perpetual time horizon. This proposed rule, if finalized as proposed, is not expected to be an E.O. 14192 regulatory action. We estimate that this proposed rule would generate $0 in net cost savings.

Table 2. Executive Order 14192 Summary Table (millions of 2024 dollars, discounted over a perpetual time horizon relative to year 2024 at a 7 percent discount rate)

	Primary Estimate	Low Estimate	High Estimate
Present Value of Costs	$0	$0	$0
Present Value of Cost Savings	$0	$0	$0
Present Value of Net Costs	$0	$0	$0
Annualized Costs	$0	$0	$0
Annualized Cost Savings	$0	$0	$0
Annualized Net Costs	$0	$0	$0

VIII. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521) is not required.

IX. Analysis of Environmental Impact

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

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in E.O. 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the E.O. and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in E.O. 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the

Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

List of Subjects

21 CFR Part 10

Administrative practice and procedure; News media.

21 CFR Part 56

Human research subjects; Reporting and recordkeeping requirements; Safety.

21 CFR Part 106

Food grades and standards; Infants and children; Nutrition; Reporting and Recordkeeping Requirements.

21 CFR Part 201

Drugs; Labeling; Reporting and recordkeeping requirements.

21 CFR Part 251

Exports; Labeling; Packaging and containers; Prescription drugs; Reporting and recordkeeping requirements.

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.

21 CFR Part 314

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

21 CFR Part 329

Alcohol and alcoholic beverages; Over-the-counter drugs; Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics; Reporting and recordkeeping requirements.

21 CFR Part 803

Imports; Medical devices; Reporting and recordkeeping requirements.

21 CFR Part 862

Medical devices.

21 CFR Part 866

Biologics; Laboratories; Medical devices.

21 CFR Part 870

Medical devices.

21 CFR Part 882

Medical devices.

21 CFR Part 1114

Administrative practice and procedure; Cigars and cigarettes; Smoking; Tobacco.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR parts 10, 56, 106, 201, 251, 310, 312, 314, 329, 600, 803, 862, 866, 870, 882, and 1114 be amended as follows:

PART 10 – ADMINISTRATIVE PRACTICES AND PROCEDURE

1. The authority citation for part 10 continues to read as follows:

Authority: 5 U.S.C. 551-558, 701-706; 15 U.S 1451-1461; 21 U.S.C. 141-149, 321-397, 467f, 679, 821, 1034; 28 U.S.C. 2112; 42 U.S.C. 201, 262, 263b, 264.

2. Revise § 10.65 to read as follows:

§ 10.65 Meetings and correspondence.

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(d) ***

(3) An agency representative may not knowingly participate in a meeting that is closed on the basis of sex, race, or religion.

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PART 56 – INSTITUTIONAL REVIEW BOARDS

1. The authority citation for part 56 continues to read as follows:

Authority: 21 U.S.C. 321, 343, 346, 346a, 350a, 351, 352, 353, 355, 360, 360c-360f, 360h, 360i, 360j, 360hh-360ss, 371, 379e, 381; 42 U.S.C 216, 241, 262.

2. Revise § 56.107 to read as follows:

§ 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, sex, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. * * * The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

* * *

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of sex. No IRB may consist entirely of members of one profession.

* * *

PART 106 – INFANT FORMULA REQUIREMENTS PERTAINING TO CURRENT GOOD MANUFACTURING PRACTICE, QUALITY CONTROL PROCEDURES, QUALITY FACTORS, RECORDS AND REPORTS, AND NOTIFICATIONS

1. The authority citation for part 106 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 350a, 371.

2. Revise § 106.121 to read as follows:

§ 106.121 Quality factor assurances for infant formulas.

(a) ***

(2) Records that contain the information required by §106.96(b) to be collected during the study for each infant enrolled in the study. The records shall be identified by subject number, age, feeding group, sex, and study day of collection.

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PART 201 - LABELING

1. The authority citation for part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 343, 351, 352, 353, 355, 358, 360, 360b, 360ccc, 360ccc-1, 360ee, 360gg-360ss, 371, 374, 379e, 42 U.S.C. 216, 241, 262, 264.

2. Revise § 201.57 to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

***

(c) ***

(13) ***

(i) ***

(C) *12.3 Pharmacokinetics.* This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (C_{min}), maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), pertinent half-lives ($t_{1/2}$), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (V_d) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data. Dosing recommendations based on clinically significant factors that change the product's pharmacokinetics (e.g., age, sex, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., "Warnings and Precautions," "Dosage and Administration," or "Use in Specific Populations") must not be repeated in this subsection, but the location of such recommendations must be referenced.

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PART 251 – SECTION 804 IMPORTATION PROGRAM

1. The authority citation for part 251 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353, 355, 360, 360eee-1, 371, 374, 381, 384.

2. Revise § 251.18 to read as follows:

§ 251.18 Post-importation requirements.

***

(d) ***

(7) ***

(i) ***

(C) Patient sex; and

***

PART 310 – NEW DRUGS

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

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 360hh-360ss, 361(a), 371, 374, 375, 379e, 379k-1; 42 U.S.C. 216, 241, 242(a), 262.

2. Revise § 310.305 to read as follows:

§ 310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.

***

(d) ***

(1) ***

(iii) Patient sex; and

***

PART 312 – INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.

2. Revise § 312.33 to read as follows:

§ 312.33 Annual reports.

(a) ***

(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, sex, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason

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3. Revise § 312.42 to read as follows:

§ 312.42 Clinical holds and requests for modification.

***

(b) ***

(1) ***

(v) The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both sexes, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk or potential risk from use of the investigational drug of reproductive toxicity (*i.e.*, affecting reproductive organs) or developmental toxicity (*i.e.*, affecting potential offspring). The phrase "women with reproductive potential" does not include pregnant women. For purposes of this paragraph, "life-threatening illnesses or diseases" are defined as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted." The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies pertinent only to one sex (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function);

(B) Only in men or women, as long as a study that does not exclude members of the other sex with reproductive potential is being conducted concurrently, has been conducted, or will take place within a reasonable time agreed upon by the agency; or

***

PART 314 – APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1. The authority citation for part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 355f, 356, 356a, 356b, 356c, 356e, 360cc, 371, 374, 379e, 379k-1.

2. Revise § 314.50 to read as follows:

§ 314.50 Content and format of an NDA.

***

(d) ***

(5) ***

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended. The effectiveness data must be presented by sex, age, and racial subgroups and must identify any modifications of dose or dose interval needed for specific subgroups. Effectiveness data from other subgroups of the population of patients treated, when appropriate, such as patients with renal failure or patients with different levels of severity of the disease, also must be presented.

(vi) ***

(a) The applicant must submit an integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data must be presented by sex, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also must be presented, such as for patients with renal failure or patients with different levels of severity of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

***

3. Revise § 314.80 to read as follows:

§ 314.80 Postmarketing reporting of adverse drug experiences.

***

(f) ***

(1) ***

(iii) Patient sex; and

***

PART 329 – NONPRESCRIPTION HUMAN DRUG PRODUCTS SUBJECT TO SECTION 760 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

1. The authority citation for part 329 continues to read as follows:

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

2. Revise § 329.100 to read as follows:

§ 329.100 Postmarketing reporting of adverse drug events under section 760 of the Federal Food, Drug, and Cosmetic Act.

***

(b) ***

(1) ***

(iii) Patient sex; and

***

PART 600 – BIOLOGICAL PRODUCTS: GENERAL

1. The authority citation for part 600 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 353, 355, 356C, 356e, 360, 360i, 371, 374, 379k-1; 42 U.S.C. 216, 262, 263, 263a, 264.

2. Revise § 600.80 to read as follows:

§ 600.80 Postmarketing reporting of adverse experiences.

***

(f) ***

(1) ***

(iii) Patient sex; and

***

(g) ***

(1) ***

(iii) Patient sex; and

***

PART 803 – MEDICAL DEVICE REPORTING

1. The authority citation for part 803 continues to read as follows:

Authority: 21 U.S.C. 352, 360, 360i, 0360j, 371, 374.

2. Revise § 803.32 to read as follows:

§ 803.32 If I am a user facility, what information must I submit in my individual adverse event reports?

***

(a) ***

(3) Patient sex; and

***

3. Revise § 803.42 to read as follows:

§ 803.42 If I am an importer, what information must I submit in my individual adverse event reports?

***

(a) ***

(3) Patient sex; and

***

4. Revise § 803.52 to read as follows:

§ 803.52 If I am a manufacturer, what information must I submit in my individual adverse event reports?

***

(a) ***

(3) Patient sex; and

***

PART 862 – CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES

1. The authority citation for part 862 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Revise § 862.1840 to read as follows:

§ 862.1840 Total 25-hydroxyvitamin D mass spectrometry test system.

***

(b) ***

(3) The 21 CFR 809.10(b) compliant labeling must be supported by a reference range study representative of the performance of the device. The study must be conducted using samples collected from apparently healthy male and female adults at least 21 years of age and older from at least 3 distinct climatic regions within the United States in different weather seasons. Demographic characteristics (*e.g.*, ethnic, racial, and sex distribution) of this study population must be representative of the U.S. population demographics.

***

PART 866 – IMMUNOLOGY AND MICROBIOLOGY DEVICES

1. The authority citation for part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Revise § 866.3215 to read as follows:

§ 866.3215 Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis.

***

(b) ***

(5) Premarket notification submissions must include evaluation of the level of the non-microbial analyte in asymptomatic patients with demographic characteristics (*e.g.,* age, racial, ethnic, and sex distribution) similar to the Intended Use population.

***

3. Revise § 866.5950 to read as follows:

§ 866.5950 Genetic health risk assessment system.

***

(b) ***

(3) ***

(ii) **

(B) Clear context for the user to understand the context in which the cited clinical performance data support the risk reported. This includes, but is not limited to, any risks that are influenced by ethnicity, age, sex, environment, and lifestyle choices.

***

(iii) ***

(J) ***

(1) ***

(viii) Information must be reported on the Technical Positive Predictive Value (TPPV) related to the analytical (technical) performance of the device for genotypes in each relevant subpopulation (*e.g.,* ethnicity, sex, age, geographical location, etc.). TPPV is the percentage of individuals with the genotype truly present among individuals whose test reports indicate that this genotype is present. The TPPV depends on the accuracy measures of percent agreements and on the frequency of the genotypes in the subpopulation being studied. The f(DD) is the frequency of DD and f(Dd) is the frequency of Dd in the subpopulation being studied; TPPV must be calculated as described in paragraphs (b)(3)(iii)(J)(*1*)(*ix*) through (*xi*) of this section.

***

PART 870 – CARDIOVASCULAR DEVICES

1. The authority citation for part 870 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c 360e, 360j, 360l, 371.

2. Revise § 870.1415 to read as follows:

§ 870.1415 Coronary vascular physiologic simulation software device.

***

(b) ***

(6) ***

(v) A detailed description of the patients studied in the clinical validation (*e.g.,* age, sex, race or ethnicity, clinical stability, current treatment regimen) as well as procedural details of the clinical study (*e.g.,* scanner representation, calcium scores, use of beta-blockers or nitrates); and

***

3. Revise § 870.2200 to read as follows:

§ 870.2200 Adjunctive cardiovascular status indicator.

***

(b) ***

(5) ***

(vii) A detailed description of the patients studied in the clinical validation (*e.g.,* age, sex, race/ethnicity, clinical stability) as well as procedural details of the clinical study.

4. Revise § 870.2210 to read as follows:

§ 870.2210 Adjunctive predictive cardiovascular indicator.

***

(b) ***

(5) ***

(viii) Relevant characteristics of the patients studied in the clinical validation (including age, sex, race or ethnicity, and patient condition) and a summary of validation results.

5. Revise § 870.2220 to read as follows:

§ 870.2220 Adjunctive hemodynamic indicator with decision point.

***

(b) ***

(5) ***

(v) A summary of the clinical validation data, including details of the patient population studied (*e.g.,* age, sex, race/ethnicity), clinical study protocols, and device performance with confidence intervals for all intended use populations.

6. Revise § 870.5600 to read as follows:

§ 870.5600 Adjunctive open loop fluid therapy recommender.

***

(b) ***

(5) ***

(ix) Relevant characteristics of the patients studied in the clinical validation (such as age, sex, race or ethnicity, and patient condition) and a summary of validation results; and

***

PART 882 – NEUROLOGIC DEVICES

1. The authority citation for part 882 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Revise § 882.1455 to read as follows:

§ 882.1455 Traumatic brain injury eye movement assessment aid.

***

(b) ***

(6) ***

(ii) ***

(E) Any adjustments for age and sex.

***

3. Revise § 882.1471 to read as follows:

§ 882.1471 Computerized cognitive assessment aid for concussion.

***

(b) ***

(3) ***

(i) ***

(D) ***

(5) Whether or not the normative database was adjusted due to differences in age and sex.

***

PART 1114 – PREMARKET TOBACCO PRODUCT APPLICATIONS

1. The authority citation for part 1114 continues to read as follows:

Authority: 21 U.S.C. 371, 374, 387a, 387i, 387j; Pub. L. 117-103, 136 Stat. 49.

2. Revise § 1114.3 to read as follows:

§ 1114.3 Definitions.

***

Vulnerable populations means groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation. Vulnerable populations can be based on criteria such as age (e.g., youth and young adults), socioeconomic status, race, ethnicity, rurality, pregnancy status, current or prior military service, and current or prior mental health conditions or substance use disorders.

***

3. Revise § 1114.41 to read as follows:

§ 1114.41 Reporting requirements.

(a) ***

(1) ***

(vi) ***

(C) Demographic characteristics of product(s) purchasers, such as age, sex, race or ethnicity, geographic region, and tobacco use status;

***

(xvi) A summary of media tracking and optimization, by channel, by product, and by audience demographics (*e.g.,* age, sex, race/ethnicity, geographic region), including a summary of any real-time digital media monitoring and including a summary of implementation of any corrective and preventive measures to identify, correct, and prevent delivery of advertising to individuals below the minimum age of sale, not previously submitted;

***

Robert F. Kennedy, Jr.,

Secretary, Department of Health and Human Services.

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