

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1300

[Docket No. DEA-260F]

RIN 1117-AA94

Definition of "Positional Isomer" as It Pertains to the Control of Schedule I Controlled Substances

AGENCY: Drug Enforcement Administration (DEA), Department of Justice.

ACTION: Final Rule.

SUMMARY: On May 25, 2006, DEA published a Notice of Proposed Rulemaking which proposed the addition of a specific definition for the term "positional isomer" to allow for the systematic determination of which isomers of schedule I substances would be considered to be "positional," and therefore, subject to schedule I control. This rulemaking finalizes that definition.

The Controlled Substances Act (CSA) and its implementing regulations specify which hallucinogenic substances are considered schedule I controlled substances. The CSA states that all salts, isomers, and salts of isomers of these substances are also schedule I controlled substances. In non-technical terms, an isomer of a substance is a different compound, but a compound which has the same number and kind of atoms. The terms "optical isomer" and "geometric isomer" are specific scientific terms and it is easy to determine whether one substance is an optical or geometric isomer of another. The term "positional isomer," however, is subject to scientific interpretation.

The addition of a definition for the term "positional isomer" will assist legitimate research[ers] and industry in determining the control status of materials that are "positional isomers" of schedule I hallucinogens. While the DEA will remain the authority for ultimately determining the control status of a given material, providing a specific definition for "positional isomer" will ensure consistent criteria are utilized in making these determinations.

This rule does not change existing laws, regulations, policies, processes, and procedures regarding the determination of control status for schedule I hallucinogenic substances. This rule merely makes available to the public the longstanding definition of "positional isomer" which DEA has

used when making these scheduling determinations.

This rule is relevant only to specialized forensic or research chemists. Most of these individuals are existing DEA registrants who are authorized by the DEA to handle schedule I hallucinogenic substances.

DATES: Effective January 2, 2008.

FOR FURTHER INFORMATION CONTACT: Christine A. Sannerud, Ph.D., Chief, Drug and Chemical Evaluation Section, Office of Diversion Control, Drug Enforcement Administration, Washington, DC 20537 at (202) 307-7183.

SUPPLEMENTARY INFORMATION:**Background**

On May 25, 2006, DEA published a Notice of Proposed Rulemaking (NPRM) [71 FR 30097] which proposed the addition of a specific definition for the term "positional isomer." As DEA discussed in the NPRM, in many instances, the control of a substance under the CSA often includes the specific substance listed under the CSA, as well as the substance's salts, isomers, and/or salts of isomers. In most instances, the term isomer includes only optical isomers. In other instances, however, the term isomer includes positional and/or geometric isomers.

As DEA discussed in its NPRM, in non-technical terms, isomers are different compounds that have the same molecular formula (the same number and types of atoms). The terms "optical isomer" and "geometric isomer" are specifically defined and well understood scientific terms, and it is easy to determine whether one substance is an optical or geometric isomer of another. The term "positional isomer," however, is not universally defined, and, therefore, is subject to scientific interpretation. In order to ensure that consistent criteria are utilized in determining whether one substance is considered a "positional isomer" of another, the DEA is establishing a specific definition for "positional isomer." This definition will be added to 21 CFR 1300.01(b)(21).

Existing CSA and CFR References to "Positional Isomers"

The CSA and its implementing regulations (21 CFR 1308.11(d)) specify which hallucinogenic substances are considered schedule I controlled substances. Under the CSA and its implementing regulations, there are only three references to the term "positional isomer":

(1) Pursuant to 21 U.S.C. 802(14), "the term 'isomer' means the optical isomer,

except as used in schedule I(c) and schedule II(a)(4). As used in schedule I(c), the term 'isomer' means any optical, positional, or geometric isomer. As used in schedule II(a)(4), the term 'isomer' means any optical or geometric isomer."

(2) Under 21 CFR 1300.01(b)(21), "The term 'isomer' means the optical isomer, except as used in §§ 1308.11(d) and 1308.12(b)(4) of this chapter. As used in § 1308.11(d) of this chapter, the term 'isomer' means the optical, positional, or geometric isomer. As used in § 1308.12(b)(4) of this chapter, the term 'isomer' means the optical or geometric isomer."

(3) 21 CFR 1308.11(d) states, "*Hallucinogenic substances*. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation, which contains any quantity of the following hallucinogenic substances, or which contains any of its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation (for purposes of this paragraph only, the term 'isomer' includes the optical, positional and geometric isomers)."

Why Definition Is Needed

As DEA discussed in the NPRM, the CSA (21 U.S.C. 802(14) and 21 U.S.C. 812(c)(I)(c)) and its implementing regulations (21 CFR 1308.11(d)) specify which hallucinogenic substances are considered schedule I controlled substances. The CSA further states that all salts, isomers, and salts of isomers of these substances are also schedule I controlled substances.

Under the definition of "isomer" found in 21 CFR 1300.01(b)(21), "The term 'isomer' means the optical isomer, except as used in §§ 1308.11(d) and 1308.12(b)(4) of this chapter. As used in § 1308.11(d) of this chapter, the term 'isomer' means the optical, positional, or geometric isomer. As used in § 1308.12(b)(4) of this chapter, the term 'isomer' means the optical or geometric isomer."

Therefore, according to this definition as it specifically applies to hallucinogens, the term "isomer" includes all optical, positional, or geometric isomers. As such, all salts, isomers (including optical, positional, or geometric isomers), and salts of isomers (including optical, positional, or geometric isomers) of the hallucinogenic substances listed in 21 U.S.C. 812(c)(I)(c) and 21 CFR 1308.11(d) are considered schedule I controlled substances.

Because the determination as to whether a substance is considered a "positional isomer" can be subject to scientific interpretation, the DEA believes it is necessary to specifically define the term "positional isomer". This definition will only pertain to those substances that are "positional isomers" of schedule I controlled substances pursuant to 21 U.S.C. 812(c)(1)(c) and 21 CFR 1308.11(d).

As DEA noted in the NPRM, DEA is not establishing definitions for either optical or geometric isomers. The DEA believes that these terms are highly specific and are not subject to differing scientific interpretation.

Comments

The definition of "positional isomer" will be used in the determination of the control status of substances as schedule I controlled substances pursuant to 21 CFR 1308.11(d). This definition is highly technical in nature and the DEA has sought to provide specific criteria for determination as to whether a substance is a "positional isomer" of schedule I hallucinogens. In writing the definition contained in this rulemaking, DEA consulted a wide variety of reference sources including, but not limited to, Chemical Abstracts, the IUPAC Compendium of Chemical Terminology, World Health Organization (WHO) documents, and various encyclopedias and chemistry textbooks.

The NPRM sought input from all interested parties regarding the proposed definition of "positional isomer." DEA received one comment in response to the proposed definition. That comment did not raise any specific objections to the definition, but expressed the opinion that instead of DEA adding this definition, this duty should be the responsibility of Congress and the definition added via legislation.

DEA disagrees. 21 U.S.C. 821 authorizes the Attorney General to "promulgate rules and regulations and to charge reasonable fees relating to the registration and control of the manufacture, distribution, and dispensing of controlled substances." Expanding on this authority, 21 U.S.C. 871(b) further provides that the Attorney General "may promulgate and enforce any rules, regulations, and procedures which he may deem necessary and appropriate for the efficient execution of his functions." The authority has been delegated by the Attorney General to the Administrator of DEA pursuant to 28 CFR 0.100, and redelegated to the Deputy Administrator pursuant to 28 CFR 0.104.

It is, therefore, well within the Deputy Administrator's purview to issue a notice of proposed rulemaking to define a term relating to the control of certain schedule I controlled substances. By inviting comment to the proposed definition, DEA ensured that potentially affected persons, such as researchers, were given the opportunity to review the definition and submit comments or changes. No other comments were received by DEA. Therefore, this rulemaking finalizes the definition exactly as it was proposed in the NPRM.

Criteria That Will Apply to Positional Isomers

Pursuant to 21 U.S.C. 802(14), 21 U.S.C. 812(c)(1)(c), and 21 CFR 1308.11(d), positional isomers of schedule I hallucinogens are any and all substances which:

- (1) Are not already controlled in a different schedule I category, or are listed in another schedule, or are specifically exempted from control by law; and
- (2) Have the same molecular formula and core structure as a schedule I hallucinogen; and
- (3) Have the same functional group(s) and/or substituent(s) as those found in the respective schedule I hallucinogen, attached at any position(s) on the core structure, but in such manner that no new chemical functionalities are created and no existing chemical functionalities are destroyed relative to the respective schedule I hallucinogen; except that
- (4) Rearrangements of alkyl moieties within or between functional group(s) or substituent(s), or divisions or combinations of alkyl moieties, that do not create new chemical functionalities or destroy existing chemical functionalities, would be within the definition of positional isomer (and therefore be controlled).

As clarification, note that the "core structure" is the parent molecule that is the common basis for the class; for example, tryptamine, phenethylamine, or ergoline. The following are examples of rearrangements resulting in creation and/or destruction of chemical functionalities. These rearrangements result in compounds which are not positional isomers: ethoxy to *alpha*-hydroxyethyl, hydroxy and methyl to methoxy, or the repositioning of a phenolic or alcoholic hydroxy group to create a hydroxyamine. Examples of rearrangements resulting in compounds that would be positional isomers include, but are not limited to: *tert*-butyl to *sec*-butyl, methoxy and ethyl to isopropoxy, *N,N*-diethyl to *N*-methyl-*N*-propyl, or *alpha*-methylamino to *N*-methylamino.

Impact of Rule Limited to Specialized Forensic or Research Chemists

As DEA discussed in the NPRM, the addition of a definition for the term "positional isomer" as it applies to 21 CFR 1308.11(d) will assist legitimate research[ers] and industry in determining the control status of substances that are isomers of schedule I hallucinogens. While the DEA will remain the authority on ultimately determining the control status of a given substance, providing a specific definition for "positional isomer" will greatly reduce any potential confusion or inconsistencies in making these determinations.

This definition will enable researchers and industry to determine definitively whether a substance is a "positional isomer" of a schedule I hallucinogen. As such, they will be able to know the control status of a particular substance when considering new research.

This rule is relevant only to specialized forensic or research chemists. Most of these individuals are existing DEA registrants who are authorized by the DEA to handle schedule I hallucinogenic substances.

Specific Changes and Definition

As currently defined in 21 CFR 1300.01(b)(21), the term "isomer" means the optical isomer, except as used in § 1308.11(d) and § 1308.12(b)(4) of this chapter. As used in § 1308.11(d) of this chapter, the term "isomer" means any optical, positional, or geometric isomer. As used in § 1308.12(b)(4) of this chapter, the term "isomer" means any optical or geometric isomer.

Pursuant to this Final Rule, 21 CFR 1300.01(b)(21) is revised to include a specific definition for the term "positional isomer". The modification specifies that, as used in § 1308.11(d), the term "positional isomer" means any substance possessing the same molecular formula and core structure and having the same functional group(s) and/or substituent(s) as those found in the respective schedule I hallucinogen, attached at any position(s) on the core structure, but in such manner that no new chemical functionalities are created and no existing chemical functionalities are destroyed relative to the respective schedule I hallucinogen. Rearrangements of alkyl moieties within or between functional group(s) or substituent(s), or divisions or combinations of alkyl moieties that do not create new chemical functionalities or destroy existing chemical functionalities, would be within the

definition of positional isomer. For purposes of this definition, the "core structure" is the parent molecule that is the common basis for the class. Some examples would include tryptamine, phenethylamine, or ergoline. Examples of non-permissible rearrangements resulting in creation and/or destruction of chemical functionalities (that therefore would not be considered positional isomers) include, but are not limited to: ethoxy to *alpha*-hydroxyethyl, hydroxy and methyl to methoxy, or the repositioning of a phenolic or alcoholic hydroxy group to create a hydroxyamine. Examples of permissible rearrangements (that are within the definition of positional isomers) include: *tert*-butyl to *sec*-butyl, methoxy and ethyl to isopropoxy, N,N-diethyl to N-methyl-N-propyl, or *alpha*-methylamino to N-methylamino.

Scientific/Technical Nature of Definition

As DEA discussed in its NPRM, DEA understands that the definition is highly technical and laden with scientific terms. However, the DEA believes that such a highly technical definition is necessary to ensure that consistent criteria are utilized in determining whether one substance is a "positional isomer" of another.

Regulatory Certifications

Regulatory Flexibility Act

The Deputy Administrator hereby certifies that this rulemaking has been drafted in accordance with the Regulatory Flexibility Act (5 U.S.C. 605(b)), has reviewed this regulation, and by approving it certifies that this regulation will not have a significant economic impact on a substantial number of small entities. The inclusion of the definition of positional isomer set forth herein is unlikely to subject any new substances to CSA control. Also, this rule does not require the obtaining of new DEA registrations. Most persons affected by this rule are already DEA registrants (or would have to become registrants even absent this rule in order to handle schedule I hallucinogens). Further, this rule does not impose any additional regulatory burden on the regulated community. The change simply will ensure that consistent criteria are utilized in making scheduling determinations.

Executive Order 12866

The Deputy Administrator further certifies that this rulemaking has been drafted in accordance with the principles in Executive Order 12866 § 1(b). It has been determined that this is a significant regulatory action.

Therefore, this action has been reviewed by the Office of Management and Budget.

Executive Order 12988

This regulation meets the applicable standards set forth in §§ 3(a) and 3(b)(2) of Executive Order 12988 Civil Justice Reform.

Executive Order 13132

This rulemaking does not preempt or modify any provision of state law; nor does it impose enforcement responsibilities on any state; nor does it diminish the power of any state to enforce its own laws. Accordingly, this rulemaking does not have federalism implications warranting the application of Executive Order 13132.

Unfunded Mandates Reform Act of 1995

This rule will not result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$120,000,000 or more (adjusted for inflation) in any one year, and will not significantly or uniquely affect small governments. Therefore, no actions were deemed necessary under the provisions of the Unfunded Mandates Reform Act of 1995.

Congressional Review Act

This rule is not a major rule as defined by section 804 of the Small Business Regulatory Enforcement Fairness Act of 1996 (Congressional Review Act). This rule will not result in an annual effect on the economy of \$114,000,000 or more; a major increase in costs or prices; or significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based companies to compete with foreign-based companies in domestic and export markets.

List of Subjects in 21 CFR Part 1300

Controlled substances, Definitions, Drug Traffic Control.

■ For the reasons set out above, 21 CFR part 1300 is amended as follows:

PART 1300—DEFINITIONS [AMENDED]

■ 1. The authority citation for Part 1300 continues to read as follows:

Authority: 21 U.S.C. 802, 871(b), 951, 958(f).

■ 2. Section 1300.01 is amended by revising paragraph (b)(21) to read as follows:

§ 1300.01 Definitions relating to controlled substances.

* * * * *

(b) * * *

(21) (i) *The term isomer means the optical isomer, except as used in § 1308.11(d) and § 1308.12(b)(4) of this chapter. As used in § 1308.11(d) of this chapter, the term "isomer" means any optical, positional, or geometric isomer. As used in § 1308.12(b)(4) of this chapter, the term "isomer" means any optical or geometric isomer.*

(ii) As used in § 1308.11(d) of this chapter, the term "positional isomer" means any substance possessing the same molecular formula and core structure and having the same functional group(s) and/or substituent(s) as those found in the respective schedule I hallucinogen, attached at any position(s) on the core structure, but in such manner that no new chemical functionalities are created and no existing chemical functionalities are destroyed relative to the respective schedule I hallucinogen.

Rearrangements of alkyl moieties within or between functional group(s) or substituent(s), or divisions or combinations of alkyl moieties, that do not create new chemical functionalities or destroy existing chemical functionalities, are allowed i.e., result in compounds which are positional isomers. For purposes of this definition, the "core structure" is the parent molecule that is the common basis for the class; for example, tryptamine, phenethylamine, or ergoline. Examples of rearrangements resulting in creation and/or destruction of chemical functionalities (and therefore resulting in compounds which are not positional isomers) include, but are not limited to: ethoxy to *alpha*-hydroxyethyl, hydroxy and methyl to methoxy, or the repositioning of a phenolic or alcoholic hydroxy group to create a hydroxyamine. Examples of rearrangements resulting in compounds which would be positional isomers include: *tert*-butyl to *sec*-butyl, methoxy and ethyl to isopropoxy, N,N-diethyl to N-methyl-N-propyl, or *alpha*-methylamino to N-methylamino.

* * * * *

Dated: November 21, 2007.

Michele M. Leonhart,

Deputy Administrator,

[FR Doc. E7-23413 Filed 11-30-07; 8:45 am]

BILLING CODE 4410-09-P