April 20, 2017

VIA ELECTRONIC MAIL

[redacted]

Re: Entry No. [redacted] Thiopental Sodium[1]
imported by Arizona Department of Corrections

Dear [redacted]

I am writing in response to your May 20, 2016, letter on behalf of the Arizona Department of Corrections (ADC), which responded to the Food and Drug Administration's (FDA) letter of April 15, 2016, setting forth the Agency's tentative decision regarding the admissibility of Entry Number [redacted] That entry consists of [redacted] one-gram vials of a drug product labeled as [redacted] (Thiopental Sodium USP), which were offered for importation by ADC on or about July 27, 2015. ADC has notified FDA that it is importing the detained drugs for use in administering lethal injection.

As we noted in our April 15 letter, for decades, FDA generally exercised enforcement discretion regarding sodium thiopental used for capital punishment purposes. Ref. 8 at 5[2]; *see Heckler v. Chaney*, 470 U.S. 821, 835-36 (1985); *see also* Ref. 1, Ex. 11 at 8-9 (2010 FDA statement explaining that FDA was exercising enforcement discretion). In February 2011, a group of prisoners on death row in Arizona, California, and Tennessee filed suit challenging FDA's release of imported thiopental sodium for use as an anesthetic as part of lethal injection. The plaintiffs argued that FDA acted contrary to law, in an arbitrary and capricious manner, and in abuse of its discretion when the Agency allowed shipments of the misbranded and unapproved new drug thiopental to be imported into the U.S. In March 2012, the United States District Court for the District of Columbia granted the plaintiffs' motion for summary judgment. *See Beaty v. FDA*, 853 F. Supp. 2d 30 (D.D.C. 2012), *aff'd in part, rev'd in part sub nom. Cook v. FDA*, 733 F.3d 1 (D.C. Cir. 2013) ("*Beaty/Cook*"). The District Court's March 2012 order, as modified in June 2012, permanently enjoins FDA from "permitting the entry of, or releasing any future

[1] Thiopental sodium is also known as sodium thiopental. In this letter, "thiopental sodium" and "sodium thiopental" are used interchangeably.

[2] To avoid confusion, we have maintained the reference numbers from FDA's tentative decision in this final decision. As a result, FDA's letter dated April 15, 2016 is listed as Reference 8.

shipments of, foreign manufactured thiopental that appears to be misbranded or in violation of 21 U.S.C. [§] 355 [as an unapproved new drug]."

ADC contends that *Beaty/Cook* was "wrongly decided," Ref. 9 at 13, but FDA is bound by the terms of the order issued by the District Court in that case. That order requires the Agency to refuse admission to import entries of foreign-manufactured sodium thiopental if the sodium thiopental appears to be an unapproved new drug or a misbranded drug. *See* Refs. 4&5. Therefore, we disagree with ADC's contention that FDA has room to exercise discretion regarding the foreign-manufactured sodium thiopental ADC wishes to import.

We have carefully considered all of the arguments and information in the May 20, 2016, letter, as well as ADC's previous submissions on behalf of the detained drugs. Based on a review of the entire record in this matter, for the reasons detailed below, we have concluded that the detained drugs in Entry No. [redacted] appear to be unapproved new drugs and misbranded drugs within the meaning of 21 U.S.C. §§ 352(f)(1) & 355(a).

In reaching this conclusion, we reject ADC's assertion in its May 20 letter that FDA's "interpretations amount to a federal ban on use of thiopental sodium for lethal injection." *See* Ref. 9 at 10. Nor is it FDA's purpose or intention to interfere with lawfully conducted capital punishment carried out by lethal injection. As noted below, FDA's determination that the detained drugs cannot be imported under the *Beaty/Cook* order because they appear to be unapproved new drugs and misbranded drugs has no effect on importation of foreign-manufactured sodium thiopental that has an FDA approval and is properly labeled and, thus, is not in violation of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). Nor does it require FDA to take action against domestic distribution of sodium thiopental, whether or not it is unapproved or misbranded.

I. Background

A. Statutory Framework

Under the FD&C Act, the Secretary of Health and Human Services may request "samples of food, drugs, devices, tobacco products, and cosmetics which are being imported or offered for import into the United States . . . ." 21 U.S.C. § 381(a). The FD&C Act further provides that "[i]f it appears from the examination of such samples or otherwise that . . . (3) such article is adulterated, misbranded, or in violation of [21 U.S.C. § 355], . . . then such article shall be refused admission, except as provided in" 21 U.S.C. § 381(b). 21 U.S.C. § 381(a)(3) (emphasis added).

The FD&C Act thus does not require FDA to find that an article that is offered for importation is actually adulterated, misbranded, or in violation of 21 U.S.C. § 355 in order to refuse admission to that article; rather, the Agency has "broad authority to prohibit import" of any article that "appears" to violate the FD&C Act. *Continental Seafoods, Inc. v. Schweiker,* 674 F.2d 38, 43 (D.C. Cir. 1982) (emphasis added); *see Goodwin v. United States,* 371 F. Supp. 433, 436 (S.D. Cal. 1972); *see also United States v. Food, 2998 Cases,* 64 F.3d 984, 992 (5th Cir.

1995) (FDA "can pursue the administrative procedures of § 381 and simply require reexportation of the goods," even where "the government lacks the ability to prove a violation of the [FD&C Act] by a preponderance of the evidence."); *Sugarman v. Forbragd,* 267 F. Supp. 817, 824 (N.D. Cal. 1967), *aff'd,* 405 F.2d 1189 (9th Cir. 1968); *K&K Merch. Group, Inc. v. Shalala,* No. 95Civl0082, 1996 U.S. Dist. LEXIS 4880, *22-23 (S.D.N.Y. 1996) (noting "the wide discretionary power FDA enjoys to determine the factors regarding its decision to grant or refuse admission of imported goods").[3] If an article is refused admission, it must be exported or destroyed within ninety days. 21 U.S.C. § 381(a).

B. The Proceedings

On or about July 27, 2015, ADC offered for import [redacted] one-gram vials of a product labeled as [redacted] (Thiopental Sodium USP). On August 5, 2015, U.S. Customs and Border Protection (CBP) detained the shipment. Ref. 1, Ex. 8 at 1. On August 18, 2015, [redacted] co-counsel for ADC, requested that FDA instruct CBP to lift the detention and let the product proceed to destination. Ref. 1, Ex. 9 at 1. By letter dated August 24, 2015, FDA denied that request. Ref. 1, Ex. 10 at 1.

On August 21, 2015, FDA issued a "Notice of FDA Action" explaining that Entry [redacted] was detained and subject to refusal of admission based on the following: the product appeared to be misbranded under 21 U.S.C. § 352(f)(1) because its labeling appeared to lack adequate directions for use; the product appeared to be misbranded under 21 U.S.C. § 352(f)(2) because its labeling appeared to lack adequate warning against use in a pathological condition or by children where it may be dangerous to health or against an unsafe dose, method, administering duration, application, in manner/form, to protect users; and the product appeared to be a new drug that lacked an approved new drug application as required by 21 U.S.C. § 355. Ref. 1, Ex. 1 at 1-2. The notice, which was sent to ADC as the listed consignee of the entry, specified that testimony regarding the admissibility of the entry must be submitted to FDA by September 11, 2015. *Id.* at 2.

On September 10, 2015, ADC, through counsel, requested an extension to respond to the Notice of FDA Action. On the same day, FDA granted an extension until October 23, 2015. *See* Ref. 1, Ex. 1 at 3-4.

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[3] As part of its assertion that "no deference is due" to "any of the regulatory or statutory interpretations" in FDA's decision, ADC appears to argue that the only questions the Agency is called upon to resolve in this matter are "pure questions of law" to which section 381(a)'s "appearance" standard does not apply. *See* Ref. 9 at 8-9. Although we agree with ADC that some of the facts in this matter (e.g., that the detained products are drugs and they lack an approved application) are not in dispute, this matter does not present only undisputed facts and purely legal questions. For example, it involves FDA's determination regarding what conditions are suggested in the detained drugs' labeling.

On October 23, 2015, ADC, through counsel, submitted written testimony regarding the detained drugs. Ref. 1. The letter explained ADC's position that the detained drugs should not be refused admission and requested an in-person hearing with appropriate FDA personnel. *Id.* at 1. In submitting the written testimony, ADC also requested that FDA transfer the matter to the Director, Office of Enforcement and Import Operations ("OEIO") or his designee, who would serve as the hearing officer for this detention. In a telephone discussion on December 10, 2015, FDA counsel informed you that the Agency did not intend to transfer the matter to OEIO. In a subsequent telephone discussion with FDA counsel on February 2, 2016, FDA asked whether ADC still wanted to present information regarding the detained drugs in person. Subsequently, in a series of phone communications on March 11, 2016, you stated that ADC concurred with an approach in which FDA would send a written, tentative decision and provide ADC with the opportunity to respond before reaching a final decision.

The Agency set forth its tentative conclusions in a letter dated April 15, 2016. Ref. 8. In that letter, the Agency provided ADC with the opportunity to respond to the tentative conclusions, either in writing or in a meeting, and assured ADC that the Agency would take any information provided in response to the April 15 letter into account in reaching a final conclusion regarding the admissibility of the detained drugs. The letter specified that additional testimony regarding the admissibility of the entry must be submitted within 20 calendar days of receipt. *Id.* at 15. After receiving the letter, ADC, through counsel, requested an extension to May 20, which FDA granted. *See* Ref. 10 at 1. ADC responded to FDA's tentative conclusions in the May 20 letter, which included five attachments.

C. The Detained Drugs

Entry No. [redacted] consists of [redacted] one-gram vials of [redacted] (Thiopental Sodium USP). Ref. 2 at 2. The labels on the vials of thiopental sodium state:

1 gm
[redacted]
Thiopental Sodium USP
Sterile

Rx Only CIII
[redacted]
manufacturer and distribution services
For law enforcement purpose only.

[redacted]

Marketed by:
[redacted]

Ref. 3 at 19-22. The label bears no other information. *Id.*; Ref. 1, Ex. 2 at 1. *See also* Ref. 1 at 2 ("Aside from the information printed on the label . . . , there is no additional labeling accompanying the drug specifying information about its properties or uses."). Stickers on the outside of each box of vials repeat the information on the vial label. Ref. 3 at 25. The boxes contain no package inserts, leaflets, or other materials with directions for use or warnings about the use of the thiopental sodium. An outside box label lists the Arizona Department of Corrections as the consignee. *Id.* at 9-11. In addition to the label listing "[redacted]" the certificate of analysis in the entry documentation for the thiopental sodium states that it is "[m]anufactured by" "[redacted]" Ref. 2 at 6.

Thiopental sodium is a barbiturate that depresses nervous system function to render a person unconscious, Ref. 1, Ex. 13 at 3-5 (Goodman and Gilman's, *The Pharmacological Basis of Therapeutics*, 11th ed., at 347-49), which can cause death in a large enough dose. Ref. 1, Ex. 14 at 10 (History of Barbiturates, at 338). As classified among anesthetics, it is an ultrashort-acting agent. *Id.* Like other anesthetics, its effects vary based on patient-specific factors such as weight and age, and its use must be calibrated. Ref. 1, Ex. 13 at 3-5 (Goodman and Gilman's, at 347-349). In addition, thiopental sodium can produce allergic reactions in some individuals. *Id.* at 6 (Goodman and Gilman's, at 350). It is a schedule III controlled substance. Ref. 1 at 2; Ref. 1, Ex. 2.

ADC agrees that the detained thiopental sodium is a drug within the meaning of the FD&C Act[4] and does not dispute that the detained drugs are not the subject of an approved new drug application, an approved abbreviated new drug application [redacted] In fact, there are no FDA-approved sodium thiopental products that are currently being marketed for any use.[5]

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[4] In its initial submission, ADC acknowledged that the thiopental sodium is a drug, because it is intended to affect the structure and function of the body. Ref. 1 at 6 (discussing 21 U.S.C. § 321(g)(1)(C) and stating that "[t]his second definition applies here"). Moreover, in the May 20 letter, ADC repeatedly refers to the detained thiopental sodium as "detained drugs." *See* Ref. 9 *passim*.

[5] Previously, for example, Abbott Laboratories held an NDA (NDA 11-679) for Pentothal Sodium (thiopental sodium) Suspension. FDA withdrew that NDA in 2001 at Abbott's request because the drug was no longer marketed. *See* 66 Fed. Reg. 43017 (Aug. 16, 2001). NDA 11-679 remains listed in FDA's Orange Book, meaning that FDA has not determined that Abbott's thiopental sodium drug product was withdrawn for safety or efficacy reasons. Unless FDA makes such a determination, NDA 11-679 can be cited in applications for approval using the abbreviated pathways established in the FD&C Act.

ADC is importing the detained drugs for use in administering lethal injection. Ref. 1, Ex. 12 ¶ 3; Ref. 1 at 4-5. Specifically, ADC states that in the "past 23 years, ADC has executed 35 prisoners by administering lethal injection" and there are more than 100 prisoners in Arizona "who are awaiting execution, through lethal injection or lethal gas." Ref. 9, Attch. D ¶ 3. ADC states that because it likely "will continue to execute additional prisoners on a recurring and continuing basis for the foreseeable future, ADC needs a continuing and recurring supply of drugs to be used for lethal injection." *Id.* Thiopental sodium "is one of the drugs used in Arizona's lethal injection protocol." *Id.*; *see also* Ref. 1, Ex. 12 ¶ 3 (drugs like the detained sodium thiopental are to be used "only to carry out executions by lethal injection . . . , and not for any other purpose.").

II. FDA Is Bound by Judicial Order to Refuse Entry to the Detained Sodium Thiopental If It Appears to be an Unapproved New Drug or Misbranded

As noted above, the District Court's March 2012 order, as modified in June 2012, permanently enjoins FDA from "permitting the entry of, or releasing any future shipments of, foreign manufactured thiopental that appears to be misbranded or in violation of 21 U.S.C. [§] 355 [as an unapproved new drug]." Ref. 4 at 1-2; Ref. 5 at 2. We interpret the order to mean what it says: namely, that FDA is required to refuse entry to thiopental produced abroad when it appears that the thiopental is misbranded or an unapproved new drug.

ADC argues that, even if FDA concludes that the detained drugs appear to be unapproved new drugs and/or misbranded drugs, the Agency can and should exercise enforcement discretion to admit Entry [redacted] Ref. 9 at 13. In particular, ADC contends that the *Beaty/Cook* decision is distinguishable from the present circumstances because the parties to that case stipulated that the drugs at issue were unapproved new drugs and misbranded. But the question here is not whether this case is similar to *Beaty/Cook* or whether *Beaty/Cook* is persuasive authority that FDA should follow. Rather, the question is whether the terms of the *Beaty/Cook* order cover the circumstances presented in this case. So long as the import entry at issue is "foreign manufactured thiopental that appears to be misbranded or in violation of 21 U.S.C. [§] 355," the District Court's order constrains FDA's enforcement discretion.

Similarly, we reject ADC's argument that FDA should have discretion to admit the thiopental because *Beaty/Cook* was (in ADC's view) "wrongly decided." Ref. 9 at 13. ADC's argument on this ground is effectively a collateral attack on the District Court's order. But the *Beaty/Cook* decision cannot be subjected to collateral attack through this proceeding; the order could only be modified through further judicial action. Until the Court lifts or modifies its injunction order, that order continues to govern FDA's review of thiopental import entries. *See, e.g., GTE Sylvania, Inc. v. Consumers Union of the U.S.*, 445 U.S. 375, 386 (1980) ("persons subject to an injunctive order issued by a court with jurisdiction are expected to obey that decree until it is modified or reversed . . . .").

Because, as discussed below, we conclude that the thiopental at issue here appears to be a misbranded and unapproved new drug, under the injunction order, FDA is without discretion to

permit entry to the foreign-manufactured sodium thiopental ADC wishes to import. Consistent with the District Court's order, FDA must refuse entry of this thiopental into the United States.

III. The Detained Thiopental Sodium Appears To Be An Unapproved New Drug

In the April 15 letter, FDA tentatively concluded that the labeling of the detained thiopental sodium suggests the conditions under which it will be used: for lethal injection. ADC challenges that tentative conclusion on several grounds. First, ADC argues that although FDA may look beyond a product's labeling to determine "whether an article is a 'drug' in the first place . . . based on [its] intended use," the Agency may consider only statements in a drug's labeling to determine whether the drug is a "new drug" under 21 U.S.C. § 321(p). *See* Ref. 9 at 6. Based on this assertion, ADC contends that the Agency's tentative conclusion that the detained drugs are new drugs is "erroneous" because the Agency reached its conclusion by relying "primarily on information that is not labeling . . . ." *See id.* (emphasis in original). Second, ADC argues that FDA erred in concluding that the labeling of the detained drugs "suggest[s] any condition of use." *Id.* at 7. Third, ADC claims that FDA had "no basis for concluding that the detained drugs are not generally accepted [sic] as safe and effective for any use simply because FDA could not find scientific literature documenting studies with this particular distributor's product." *See id.* at 8. We address each of these arguments below.

A. The Meaning of "Conditions . . . Suggested in the Labeling"

In this matter, FDA must determine whether a detained drug that is not approved for any use appears to be a "new drug" as defined in 21 U.S.C. § 321(p). Before turning to ADC's specific arguments, we begin by addressing the meaning of "suggested" in this inquiry.

As discussed in greater detail below, under the FD&C Act, a "drug" is a "new drug" unless, among other things, it is generally recognized among qualified experts as being "safe and effective for use under the conditions prescribed, recommended, or suggested in [its] labeling." *See* 21 U.S.C. § 321(p)(1) (emphasis added). In this proceeding, ADC has equated the phrase "prescribed, recommended, or suggested" with the conditions being "stated" or "specified" in the labeling. For example, in the October 23, 2015, letter, ADC argued, "[f]or FDA to establish that a drug is a 'new drug,' the agency must demonstrate that the drug is not generally recognized as safe and effective with respect to specific conditions of use stated in the labeling. When no conditions for use are so specified, it is not possible for FDA to establish that a drug is a 'new drug.'" Ref. 1 at 8 (emphasis added). In its May 20 letter, ADC contends that the "plain meaning of the term 'suggested' is 'proposed.'" Ref. 9 at 7 n.10.

The three terms "prescribed," "recommended," and "suggested" each must be given an independent, non-superfluous meaning. According to Webster's New International Dictionary

Second Edition Unabridged (G&C Merriam Co. 1940) [6] (Ref. 11), prescribe means "[t]o lay down authoritatively as a guide, direction, or rule of action" and, as used in medicine, "[t]o direct, designate, or order the use of, as a remedy; as, the doctor *prescribed* medicine." *Id.* at 1 (italics in original). "Recommend" in turn is defined in part as "[t]o commend, or bring forward explicitly, as meriting consideration, acceptance, adoption, election, or the like." *Id.* at 2 (emphasis added).

By comparison, the first definition of "suggest" is "[t]o put (something) into one's mind; to arouse or awaken, often by indirect means, the thought or feeling of, the desire for, the temptation to commit, the will to do, or the like; as, plays that harm by *suggesting* evil; now, often, to propose tentatively; to mention as a hint, a possible explanation or course, etc.; as, to *suggest* a walk in the country, a moratorium; to *suggest* that a change of government is necessary." *See* Ref. 11 at 3 (italics in original, emphasis added). Thus, "suggest" is not limited to things that are explicitly stated, specified, or proposed, as ADC contends. "Suggested" has a broader meaning, and something can be "suggested" even if only proposed or hinted at indirectly.

This broader meaning of "suggested" is confirmed by Congress's inclusion of "suggested" following "prescribed" and "recommended." Having already covered conditions of use that are either "prescribed" or "recommended" in the labeling, Congress's inclusion of "suggested" must mean that it applies to situations where the conditions for use are not "la[id] down authoritatively," "direct[ed]," or "commend[ed] . . . explicitly." Thus, because no indications for use are explicitly "prescribed" or "recommended" in the labeling of the detained drugs, it is necessary to consider here what is "suggested" in the drugs' labeling.

B. Statements on the Label of the Detained Sodium Thiopental Suggest Its Use for Lethal Injection

ADC contends that FDA may consider only statements in a drug's labeling[7] in determining whether the drug is a "new drug" under 21 U.S.C. § 321(p). *See* Ref. 9 at 6. Based on this assertion, ADC argues that the Agency's tentative conclusion that the detained drugs are new drugs is "erroneous" because the Agency based its conclusion "primarily on information that is not labeling . . . ." *See id.* (emphasis in original).[8] We disagree.

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[6] *See, e.g., Taniguchi v. Kan Pacific Saipan, Ltd.*, 566 U.S. 560, 566-67 (2012) (explaining "When a term goes undefined in a statute, we give the term its ordinary meaning," and considering dictionaries contemporaneous to the regulatory enactment).

[7] As used in the FD&C Act, "label" means "a display of written, printed, or graphic matter upon the immediate container of any article . . . ." 21 U.S.C. § 321(k) (emphasis added). "Labeling" means "all labels and other written, printed, or graphic matter" that is either "upon any article or any of its containers or wrappers" or "accompanying such article." 21 U.S.C. § 321(m).

[8] ADC's position appears to be that an importer can avoid having a drug that is not approved for any use classified as a "new drug" – and thereby bypass entirely the premarket approval scheme for new drugs mandated by Congress – simply by removing from the drug's labeling any explicit

Four statements appear on the labels of the detained drugs: "Thiopental Sodium USP," "Sterile," "Rx only," and "For law enforcement purpose only." Ref. 3 at 19-22; Ref. 1, Ex. 2 at 1. These statements are indisputably "labeling" because the drugs' labels are part of their "labeling." 21 U.S.C. § 321(m). Taken together, these four statements suggest the conditions under which this unapproved drug will be used: for lethal injection. "Rx only" makes clear that the detained drugs are prescription drugs,[9] meaning that due to their "toxicity or other potentiality for harmful effect, or the method of [their] use, or the collateral measures necessary to [their] use, [they are] not safe for use except under the supervision of a" licensed practitioner. *See, e.g.*, 21 U.S.C. § 353(b)(1)(A). "Sterile" on the label of this single-glass-vial drug suggests that the drugs are likely to be administered by injection, where sterility is critical.

As ADC has acknowledged, there are several well-known uses of thiopental sodium. *See* Ref. 9 at 7. Currently, one of the best-known uses of thiopental sodium is for lethal injection, most often for anesthesia in multi-drug protocols, but sometimes as the lethal agent itself. [10] Indeed, sodium thiopental has been described as "the key drug in the three drug protocol used in most executions since lethal injection began in 1982," *see* Owen Dyer, *The Slow Death of Lethal Injection*, 348 BMJ 2670 (2014), and is "one of the drugs used in Arizona's lethal injection protocol." Ref. 9, Attch. D ¶ 4.

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description of the purposes for which it is to be used, while at the same time submitting sworn testimony stating unequivocally the purpose for which that very drug will be used. We do not agree that ADC's position is correct, but it is not necessary to address it because the labeling of these detained drugs does in fact suggest their conditions of use.

[9] In fact, if the detained drugs are not prescription drugs despite being labeled as such, they are misbranded. *See* 21 U.S.C. § 353(b)(4)(B) (a drug that is not a prescription drug "shall be deemed to be misbranded if at any time prior to dispensing the label of the drug bears the symbol" Rx only).

[10] *See, e.g.*, *Glossip v. Gross*, 135 S. Ct. 2726, 2732 (2015) ("By 2008, at least 30 of the 36 States that used lethal injection employed" a "three-drug protocol" for lethal injection that included sodium thiopental); *Baze v. Rees*, 553 U.S. 35, 53 (2008) ("Thirty States, as well as the Federal Government, use a series of sodium thiopental, pancuronium bromide, and potassium chloride, in varying amounts."); *Cook*, 733 F.3d at 4 (noting that when the complaint was filed in that case, the states in which the plaintiffs had been sentenced to death "and many others executed prisoners by injecting them with a sequence of three drugs" that included sodium thiopental); Death Penalty Information Center, *State by State Lethal Injection*, http://www.deathpenaltyinfo.org/state-lethal-injection (describing States' use of thiopental sodium in both three-drug and single-drug protocols); Jennifer Horne, *Lethal Injection Drug Shortage*, COUNCIL OF STATE GOVERNMENTS E-NEWSLETTER (Feb. 17, 2011), http://www.csg.org/pubs/capitolideas/enews/issue65_4.aspx; Emma Marris, *Death-row drug dilemma*, NATURE (Jan. 27, 2011) (available at http://www.nature.com/news/2011/110121/full/news.2011.53.html); Jennifer Sullivan, *Killer on Death Row 16 ½ Years is Executed*, Seattle Times (Sept. 10, 2010) (available at http://www.seattletimes.com/ seattle-news/killer-on-death-row-16-years-is-executed).

ADC does not dispute that this is a widely-recognized use of the drug, but notes that "thiopental sodium may be used for a variety of different purposes other than lethal injection." Ref. 9 at 7. In particular, ADC has asserted that "[t]he standard reference source for pharmacology indicates that sodium thiopental is a barbiturate that produces unconsciousness and anesthesia" and that "[t]his effect is well known; the drug has been used for purposes of anesthesia since before the [FD&C Act] was enacted in 1938." Ref. 1 at 5 n.5.

Because there are possible purposes for sodium thiopental other than use in lethal injection, ADC contends "the drug's name does not suggest any particular condition of use." Ref. 9 at 7. But a drug must be GRAS/E for all of the conditions of use suggested in its labeling,[11] and, as discussed below, the detained sodium thiopental is not GRAS/E under any conditions of use. In any event, here, the fourth statement on the detained drugs' label—"For law enforcement purpose only," in combination with the name of the drug and other statements, "suggests" that the drug is for use in lethal injection. ADC implicitly acknowledges as much when it argues, "The 'law enforcement purpose only' legend . . . provides a warning not to use the product for any medical purpose . . . ." *Id.* at 7 (emphasis added). Because, as ADC notes, the "law enforcement purpose only" legend conveys that the drugs are not to be used for any "medical purpose" – that is, not for their anesthetic or barbiturate effects apart from lethal injection – we conclude that the statements on the labels of these unapproved drugs collectively suggest (i.e., propose or hint at indirectly) use of the detained drugs in lethal injection.

As noted in the tentative decision, the Agency's interpretation of the detained drug's use is confirmed by ADC's submissions. *See, e.g.*, Ref. 1, Ex. 12 ¶ 3 ("the sodium thiopental currently detained by FDA" is to be "used only to carry out executions by lethal injection pursuant to Warrants of Execution issued by the Arizona Supreme Court, and not for any other purpose"); Ref. 1 at 4-5 (the detained drug will be used "to effectuate lawfully-imposed capital sentences through lethal injection"); Ref. 9, Attch. D at ¶ 3 (explaining that sodium thiopental is "one of the drugs used in Arizona's lethal injection protocol" and that ADC is importing the detained drugs for use in lethal injection).

We do not agree with ADC's contention that the Agency is relying "primarily on information that is not labeling to conclude that [the detained drugs] are 'new drugs.'" Ref. 9 at 6 (emphasis in original). In particular, ADC points to the tentative conclusion's citation of two court cases and several articles. FDA did not cite those materials as "labeling" for the detained drugs. Rather, the Agency cited the court cases and articles simply to illustrate that sodium thiopental's use in lethal injection is well known. *See* Ref. 8 at 7. Similarly, FDA did not, and does not, rely on ADC's supporting affidavits as part of the Agency's determination of the "new drug" status of the detained drugs. Instead, we simply note that the interpretation of the labeling

[11] *United States v. An Article of Drug... Neo-Terramycin Soluble Powder Concentrate*, 540 F. Supp. 363, 379 (N.D. Tex. 1982) ("a finding that a drug is not generally recognized as effective for one or more of the label claims would result in a determination that the product is a new drug, even if it is assumed that it is generally recognized as effective for the remaining label claims."); *see also United States v. An Article of Drug . . . Quinaglute,* 268 F. Supp. 245, 248-49 (E.D. Mo. 1967).

of the detained drugs as suggesting use of those drugs in lethal injection is "confirmed by" ADC's own statements regarding how it plans to use the drugs.

C. The FD&C Act's Definition of "New Drug"

If a product is a drug, then, as a matter of law, it is a "new drug" that must be approved by FDA before it can be lawfully distributed in interstate commerce, unless it satisfies two requirements.[12] First, it must be generally recognized among qualified experts as being safe and effective ("GRAS/E") "for use under the conditions prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. §§ 321(p)(1), 331(d), 355. Second, even if a drug has become GRAS/E as a "result of investigations to determine its safety and effectiveness for use under such conditions," it remains a new drug unless it has been "used to a material extent or for a material time" other than in those investigations. 21 U.S.C. § 321(p)(2).[13]

1. General Recognition of Safety and Effectiveness

General recognition of effectiveness requires a three-pronged showing. First, there must exist a body of evidence that would at least be sufficient to obtain FDA's approval for the product. *See United States v. 50 Boxes More or Less*, 909 F.2d 24, 26 (1st Cir. 1990); *United States v. 225 Cartons, More or Less, of an Article off Drug ... (Fiorinal)*, 871 F.2d 409, 413 (3d Cir. 1989). As the Supreme Court has explained, "'general recognition of effectiveness' requires at least 'substantial evidence' of effectiveness for approval of [a new drug application]." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629 (1973); *see also United States v. Undetermined Quantities of an Article of Drug (Amucort)*, 709 F. Supp. 511, 514 n.2 (D.N.J. 1987), *aff'd*, 857 F.2d 1464 (3d Cir. 1988). The FD&C Act defines "substantial evidence" as evidence consisting of "adequate and well-controlled investigations, including clinical investigations . . . on the basis of which it could fairly and responsibly be concluded by

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[12] The definition of "new drug" also contains a limited exception for grandfathered drugs. *See* 21 U.S.C. § 321(p)(1) (a drug that does not meet that section's "generally recognized" standard "shall not be deemed to be a 'new drug' if at any time prior to the enactment of [the FD&C Act] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use."); *see also* Public Law 87-781, § 107 (reprinted following 21 U.S.C. § 321) (grandfather clause in 1962 Amendments that was not codified). The two grandfather clauses in the FD&C Act have been interpreted very narrowly. *See, e.g., United States v. Allan Drug Corp.*, 357 F.2d 713, 718-19 (10th Cir. 1966) (holding that a drug product "loses the immunity of the Grandfather clause and becomes a new drug" subject to the FDCA's premarket approval requirements even if there is no more than a "mere change in the labeling after the effective date of the Act"); *United States v. Articles of Drug . . . 5,906 Boxes*, 745 F.2d 105, 113 (1st Cir. 1984). ADC has not claimed, nor does FDA believe, that these provisions apply to the detained sodium thiopental.

[13] FDA recognizes that health care professionals may choose to use approved drugs for unapproved uses. FDA generally does not regulate the conduct of health care professionals in prescribing or using a legally marketed drug for an unapproved use within the practice of medicine.

. . . [qualified] experts that the drug will have the effect it purports or is represented to have . . . ." 21 U.S.C. § 355(d); *Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 151 (3d Cir. 1986).

Second, the investigations must be published in the scientific literature so that they are made generally available to the community of qualified experts and are, thereby, subject to peer evaluation, criticism, and review. *Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 652 (1973); *United States v. Article of Drug . . . 4,680 Pails*, 725 F.2d 976, 987 (5th Cir. 1984); *United States v. Undetermined Quantities of Various Articles of Drug . . . Equidantin Nitrofurantoin*, 675 F.2d 994, 1001 (8th Cir. 1982); *Premo Pharm. Labs., Inc. v. United States*, 629 F.2d 795, 803-04 (2d Cir. 1980); *United States v. Sene X Eleemosynary Corp. Inc.*, 479 F. Supp. 970, 977 (S.D. Fla. 1979) (general recognition of safety and effectiveness cannot be established by anecdotal evidence or the fact that a number of physicians throughout the country prescribe the drug); *United States v. Undetermined Quantities of Articles of Drug, Street Drug Alternatives*, 145 F. Supp. 2d 692, 701 (D. Md. 2001) (absence of literature establishing the safety and efficacy of the product is proof that the requisite general recognition does not exist).

Third, there must be a consensus among the qualified experts, based on the adequate and well-controlled published investigations of the product in question, that the product is safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling. *See, e.g., Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 141 (3d Cir. 1987) ("[E]ither the unawareness of the drug product by experts generally or a genuine dispute among qualified experts regarding a drug product's safety and effectiveness preclude[s] its qualifying for exclusion as 'generally recognized.'") (internal quotation omitted); *Equidantin*, 675 F.2d at 1000-01 (requiring "general consensus of expert opinion in favor of" the drug); *Premo Pharm.*, 629 F.2d at 803 ("genuine dispute among qualified experts regarding a drug product's safety and effectiveness preclude[s] its qualifying for exclusion as 'generally recognized.'"); *United States v. Article of Drug . . . "Entrol-C Medicated"*, 513 F.2d 1127, 1128 (9th Cir. 1975).

A drug product that fails to meet any one of these three conditions is a new drug as a matter of law. *See 4,680 Pails*, 725 F.2d at 985; *United States v. Seven Cardboard Cases . . . Codeine Capsules*, 716 F. Supp. 1221, 1223-24 (E.D. Mo. 1989); *United States v. 118/100 Tablet Bottles*, 662 F. Supp. 511, 513-14 (W.D. La. 1987); *see also United States v. Articles of Drug . . . Promise Toothpaste*, 826 F.2d 564, 569 (7th Cir. 1987).

2. Material Extent or Material Time

As noted, even if a drug is GRAS/E, it remains a "new drug" if the drug has not been used to a "material extent or for a material time under such conditions." 21 U.S.C. § 321(p)(2). *See Hynson*, 412 U.S. at 631 ("a drug cannot transcend 'new drug' status until it has been used 'to a material extent or for a material time'"); *United States v. Articles of Drug . . . HORMONIN*, 498 F. Supp. 424, 432 (D.N.J.) (stating that a drug is a "new drug" even if recognized as GRAS/E, unless it also has been "'used to a material extent or for a material time' under non-investigative conditions"), *aff'd sub nom. Appeal of Carnrick Labs., Inc.*, 672 F.2d 902 (3d Cir. 1981) and *aff'd sub nom. United States v. Articles of Drug*, 672 F.2d 904 (3d Cir. 1981).

D. The Detained Drugs Appear to Be "New Drugs"

In our April 15 letter, FDA explained that there is no approved new drug application for the detained drugs (*i.e.*, [redacted]). FDA also explained that the detained drugs are not GRAS/E. Specifically, FDA explained that the Agency's searches of the published scientific literature found no adequate and well-controlled trials evaluating [redacted] thiopental sodium for use as part of a lethal injection or, for that matter, any other use. FDA therefore tentatively concluded that the detained thiopental sodium is not GRAS/E for use in lethal injection. In its submissions, ADC does not claim that any adequate and well-controlled trials evaluating [redacted] thiopental sodium have been published in the scientific literature. Nor does ADC appear to argue that the detained drugs are actually GRAS/E under any conditions of use. *See* Ref. 9 at 8. Instead, ADC contends that the Agency should not have limited its search of the published scientific literature to studies involving [redacted] thiopental product. *Id.* We disagree, but, as discussed below, the point is moot both because there are no published adequate and well-controlled trials evaluating any manufacturer's sodium thiopental for use in lethal injection and because there is no evidence in the record that [redacted] has marketed [redacted] (thiopental sodium USP) to a material extent or for a material time.

1. It Was Proper to Focus the "General Recognition" Analysis on the Detained Drug Product Rather Than Just Its Active Ingredient

As noted, ADC contends that "the Tentative Decision has no basis for concluding that the detained drugs are not generally accepted [sic] as safe and effective for any use simply because FDA could not find scientific literature documenting studies with this particular distributor's product." Ref. 9 at 8 (emphasis added). Instead, ADC argues, "FDA often establishes general acceptance [sic] of safety and effectiveness with respect to active ingredients (whose finished dosage forms have specific required labeling) – and not with respect to finished dosage forms manufactured or distributed by a particular company. *See generally* 21 C.F.R. §§ 331-358." *Id.* We disagree.

It is well settled that the FD&C Act's definitions of "drug" and "new drug" apply to the drug product,[14] not just its active ingredient. *United States v. Generix Drug Corp.*, 460 U.S. 453, 459 (1983). In the *Generix* case, Generix Drug Corporation argued that it was not required to have approved new drug applications to market generic drug products, because those drug products contained the same active ingredients as FDA-approved pioneer drug products. The Supreme Court determined that a generic drug product – that is, one that contains the "same active ingredients as a previously approved pioneer drug" but different inactive ingredients – is a "new drug" subject to the FD&C Act's premarket approval requirement. *Id.* at 455. In reaching that conclusion, the Court held that the "statutory phrase 'any drug'" in the new drug definition

[14] "Drug product" means "a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients." 21 C.F.R. § 314.3.

("any drug . . . [which] is not generally recognized as safe and effective . . . or . . . which has not, otherwise than in [safety and effectiveness] investigations, been used to a material extent or for a material time . . . .") applies to the "complete drug product," not just its active ingredient. *Id.* at 457; *see also id.* at 459 ("The term 'drug' is plainly intended throughout the [FD&C] Act to include entire drug products, complete with active and inactive ingredients."). Thus, every drug product remains subject to the premarket approval requirement in section 355(a), "until the product (and not merely its active ingredient) no longer falls within the terms of [section 321(p)]." *Id.* at 461.

Because the *Generix* Court held that the word "drug" in the "new drug" definition refers to an entire finished drug product, including excipients, and not just to the active ingredient, courts generally have held that studies of one drug product are insufficient to support a claim that a similar drug product is GRAS/E. *See Premo Pharm.*, 629 F.2d at 803 (2d Cir. 1980) ("later developed 'me-too' products such as Insulase are required to apply for FDA approval for the undisputed reason that a difference in inactive ingredients, as exists here, when combined with the active ingredient, can affect the safety and effectiveness of the drug product. . . . [T]he purpose of the [FD&C] Act is to subject all such drug products not generally recognized as safe and effective (whether or not labelled 'me-too' products) to the premarket clearance requirements of the Act."); *United States v. Baxter Healthcare Corp.*, 712 F. Supp. 1352, 1356 (N.D. Ill. 1989) ("When examining a product to determine whether it is a drug, new or otherwise, the court must look at the product as a whole, 'complete with active and inactive ingredients.'") (quoting *Generix*, 460 U.S. at 459); *Undetermined Quantities of an Article of Drug (Anucort)*, 709 F. Supp. at 515-16 ("the 'substantial evidence' requirement" can be satisfied "only by (1) adequate and well-controlled studies of the product Anucort itself or by (2)(a) adequate and well-controlled studies of another drug with the same active ingredients as Anucort and (b) adequate and well-controlled studies demonstrating that the other drug and Anucort are bioequivalent.").[15]

To determine GRAS/E status for the detained thiopental, the specific drug product (including its active ingredients, excipients, and dosage) would have to be shown to be safe and effective in adequate and well-controlled clinical investigations. Because the relevant question is whether the detained drug products, not just their active ingredients, are GRAS/E for use under the conditions suggested in their labeling, it was appropriate for FDA to search for adequate and well-controlled clinical trials of [redacted] thiopental sodium in

[15] Likewise, passage of the Hatch-Waxman Amendments to the FD&C Act in 1984, The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. Law 98-417), provides evidence of congressional intent to subject drugs that share very similar characteristics to the application requirement. Under the Hatch-Waxman Amendments, drugs that are bioequivalent to drugs with approved new drug applications still need approved abbreviated new drug applications. This requirement enables FDA to evaluate active ingredients, inactive ingredients, labeling, chemistry, manufacturing, and controls, and other factors, in addition to bioequivalence, that combine to determine the safety and effectiveness of a finished drug product.

the published scientific literature. FDA's searches identified no such studies, nor have any been cited by ADC. And, as discussed above, in the absence of such studies, it is not possible for the detained drugs to meet the "general recognition" standard.

We do not agree that FDA "often establishes general acceptance [sic] of safety and effectiveness with respect to active ingredients (whose finished dosage forms have specific required labeling) — and not with respect to finished dosage forms manufactured or distributed by a particular company. See generally 21 C.F.R. §§ 331-358." Ref. 9 at 8. ADC cites a portion, but not the entirety, of the regulations established as part of the over-the counter (OTC) Drug Review, a regulatory system specific to nonprescription drugs. Thus, ADC presents an incomplete picture. In order to be GRAS/E and not misbranded, each individual nonprescription drug product regulated under the OTC Drug Review must comply with the general conditions set forth in 21 C.F.R. Part 330 (and other applicable regulations), as well as with the specific conditions set forth in the applicable OTC drug monograph (the regulations to which ADC refers, i.e., 21 C.F.R. §§ 331-358), which include specific OTC uses of active ingredients, along with other parameters, such as dosage forms, dosage strengths, route of administration, and the associated directions and warnings that must be included in labeling. *See generally* 21 C.F.R. § 330.14(a); 21 C.F.R. §§ 331-358. As a result, it is the drug product – not its active ingredient(s) alone – which complies with all of these requirements that is GRAS/E for its intended use.

FDA has not promulgated any drug monographs that apply to prescription drugs, such as sodium thiopental.[16] Moreover, as discussed, FDA has not identified sufficient evidence to show that the detained thiopental sodium drug products are, themselves, GRAS/E for use in lethal injection (or under any other conditions of use).

In sum, the GRAS/E status of the detained drugs is not and cannot be established simply by claiming similarity to, or based on data regarding, another drug product, even one with the same active ingredient. It must independently be shown to be safe and effective in adequate and well-controlled clinical investigations, and no such studies have been published regarding the detained sodium thiopental.

In any event, even if ADC were correct that the detained sodium thiopental's GRAS/E status can be determined based on published adequate and well-controlled studies of its active ingredient, the result would be the same. We have searched for published adequate and well-controlled studies evaluating the use of the active ingredient sodium thiopental for use in lethal injection, either as a sole agent or in combination with other agents, and no such studies were identified. Thus, it is not possible for sodium thiopental from [redacted] or any other firm to qualify as GRAS/E for use under the conditions suggested by the detained drugs' labeling.

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[16] As previously noted, there is no dispute that the detained drugs, which are labeled "Rx only," are prescription drugs. *See* Ref. 1, Ex. 2; Ref. 3 at 19-22 (showing "Rx only" on the label); Ref. 1 at 5 n.5 (thiopental sodium "easily satisfies the definition of a prescription drug").

2. [redacted]

Although the detained drugs are not GRAS/E, there are pathways for a manufacturer to distribute a sodium thiopental product by obtaining FDA approval of a new drug application (NDA). For example, a manufacturer could file either a stand-alone NDA under 21 U.S.C. § 355(b)(1), or use the abbreviated pathway in 21 U.S.C. § 355(b)(2) by relying in part on the FDA finding that a previously approved sodium thiopental product it references (e.g., Abbott's Pentothal Sodium (thiopental sodium) Suspension NDA 11-679) is safe and effective as evidence in support of its own safety and effectiveness. Such an application would need to support any differences from the listed drug (such as a new dosage form, indication, or new formulation) with appropriate safety and effectiveness information. Likewise, a section 355(b)(2) applicant could submit published literature to FDA for the Agency's review to help establish safety or efficacy for its requested indication. [redacted]. For example, if a manufacturer avails itself of the section 355(b)(2) abbreviated pathway and receives approval for its sodium thiopental product, the drug would not be an unapproved new drug in violation of 21 U.S.C. § 355.

3. The Detained Drugs Have Not Been Used to a Material Extent or for a Material Time

As noted, to bypass the FD&C Act's premarket approval requirement, a drug must also satisfy the "material extent" or "material time" requirement. 21 U.S.C. § 321(p)(2). *See Hynson*, 412 U.S. at 631; *Articles of Drug . . . HORMONIN*, 498 F. Supp. at 432. Like the "general recognition" requirement in subsection 321(p)(1), the material extent/time requirement in subsection 321(p)(2) is specific to the drug product, "not merely its active ingredient." *See Generix*, 460 U.S. at 461.

According to FDA's registration and listing database, the "marketing start date" for the detained drugs was [redacted]. Ref. 12. And, we are aware of only one previous shipment of [redacted] thiopental drug product to the United States.[17] The detained drugs have not been used to a material extent or a material time, and thus are new drugs within the meaning of 21 U.S.C. § 321(p)(2). *See Premo*, 629 F.2d at 804 ("although Premo has produced and sold at wholesale some 16,500,000 Insulase tablets (some of which have been seized in Government actions under 21 U.S.C. § 334), there is no evidence that Insulase has been used to a material extent or for any substantial period of time.").

In short, the detained drugs appear to be new drugs for two independent reasons. They are not GRAS/E for use under the conditions suggested in their labeling. And, even if they were

[17] That shipment was received before the *Beaty/Cook* order was issued.

GRAS/E under such conditions, they are new drugs because they have not been marketed to a material extent or for a material time.

E. The Detained Drugs Appear to Violate Section 355(a) of the FD&C Act

The FD&C Act mandates that all new drugs distributed in interstate commerce be approved by FDA or be the subject of an investigational new drug application. 21 U.S.C. §§ 331(d), 355(a). As noted, ADC does not dispute that the detained drugs are not the subject of an approved new drug application, an approved abbreviated new drug application [redacted] they appear to be unapproved new drugs.

IV. The Detained Drugs Appear to Be Misbranded Under 21 U.S.C. § 352(f)(1)

In addition to appearing to be an unapproved new drug, the detained sodium thiopental appears to be misbranded because its labeling does not bear adequate directions for use, as required by section 21 U.S.C. § 352(f)(1).[18]

In our April 15 letter, the Agency noted that the thiopental sodium that ADC is attempting to import includes no directions for those who would administer the drug or receive it. *See* Ref. 8 at 9. Specifically, it lists no recommended dose and offers no instructions for reconstituting the powder inside the vials. Its labeling includes no precautions, contraindications, or warnings, or other information required in prescribing information for health professionals. Instead, it bears little text beyond "[f]or law enforcement purpose only," "Rx only," "CIII," "1 gm," and manufacturer information. FDA therefore asserted that the labeling provides inadequate directions for a prescription-drug barbiturate that will be administered to humans to produce anesthesia as part of a lethal injection procedure, or, possibly, to be used as the sole drug for lethal injection.

ADC contends that the detained thiopental sodium is not misbranded under 21 U.S.C. § 352(f)(1) because it "falls within the exemption established by 21 C.F.R. § 201.125." Ref. 1 at 4.[19] Section 201.125's "law enforcement" exemption, however, occurs in the context where

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[18] The Agency tentatively concluded that the detained sodium thiopental also appears to be misbranded because its labeling fails to bear adequate warnings, as required by 21 U.S.C. § 352(f)(2). Because the Agency concludes that the detained drugs appear to be unapproved new drugs and misbranded within the meaning of section 352(f)(1) and because ADC indicated a willingness to add warnings to the detained product, it is not necessary to reach a final determination regarding whether the detained drugs are misbranded within the meaning of section 352(f)(2). *See* Ref. 1 at 7 n.6 (regarding section 352(f)(2), ADC stated "Under FFDCA section 801(b), we further request the opportunity to relabel the detained drug to include the warnings FDA deems adequate.").

[19] ADC interpreted our tentative decision as a contention that a drug needs to meet all of the requirements of section 201.100 (which governs prescription drugs for human use) "to fit within section 201.125" (which includes the law enforcement exemption). Ref. 9 at 2 n.4. Instead, our

otherwise misbranded drugs are not administered to humans. Thus, applying this exception to excuse the absence of adequate directions for use in the labeling of drugs for lethal injection is not supported by the text and the history of the exemption.

Section 201.125 states:

> A drug subject to § 201.100 or § 201.105, shall be exempt from [21 U.S.C. § 352(f)(1) requiring adequate directions for use] if [1] shipped or sold to, or in the possession of, persons regularly and lawfully engaged in instruction in pharmacy, chemistry, or medicine not involving clinical use, or engaged in law enforcement, or in research not involving clinical use, or in chemical analysis, or physical testing, and is to be used only for such instruction, law enforcement, research, analysis, or testing.

21 C.F.R. § 201.125 (emphases added). Thus, the law enforcement exemption resides within a regulation with a two-part test for each exemption: the drug must be shipped, sold to, or in the possession of people engaged in particular activities, and it must be to be used only for the specific exempted purpose.

As an initial matter, as noted in our tentative decision, the law enforcement exemption could not have been intended to apply to lethal injection, because FDA issued the regulation adding the exemption to section 201.125 in 1956, well before any State used lethal injection as a method of execution. *See* Regulations for the Enforcement of the Federal Food, Drug, and Cosmetic Act; Exemption of Certain Drugs and Devices from Labeling Requirements, 21 Fed. Reg. 2309, 2327 (Apr. 11, 1956) (final rule); *Baze*, 553 U.S. at 42 (describing the first State use of lethal injection).

ADC argues that the absence of the phrase "not involving clinical use" following "law enforcement" reflects a "conscious decision not to apply the qualifier to the law enforcement exemption." Ref. 9 at 3. Based on this, ADC contends that the "law enforcement" exception extends to use of drugs in lethal injection. Nevertheless, in context, FDA inserted the law enforcement exemption into an existing regulation addressing six other possible uses of drugs, not one of which involves administration to humans: instruction in pharmacy, instruction in

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view is that that the detained thiopental sodium fits within neither exemption from the requirement to bear adequate directions for use. ADC does not dispute the Agency's tentative conclusion that the detained drugs do not meet the conditions for the exemption from the requirement to bear adequate directions for use in 21 C.F.R. § 201.100. For example, as discussed in FDA's tentative decision, the label of the drug lacks a "recommended or usual dosage," and the labeling on or within the drug's package lacks "adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended . . . ." *See* 21 C.F.R. 201.100(c)(1).

chemistry, and instruction in medicine not involving clinical use, research not involving clinical use, chemical analysis, and physical testing. In each category that was likely to have implicated administration of the drug to humans – "instruction in medicine" and "research" – FDA explicitly provided that such use is outside the exemption. In the other categories – including law enforcement – no explicit limitation was specified, but it is implied by the context and the time period when FDA issued these regulations. Thus, FDA believes "law enforcement" should be interpreted in the context of "chemical analysis" and "physical testing": the Agency did not attach the "not involving clinical use" modifier because "law enforcement" was understood to refer to activities similar to chemical analysis and physical testing.

ADC's reading of the regulation is also counterintuitive. As we noted in our tentative decision, if the "not involving clinical use" limitation were to be applied only to categories where it was specifically attached, as ADC advocates, the regulation would require "adequate directions" in the labeling for medical school professors administering drugs to humans, but not law enforcement personnel administering drugs to humans. This result cannot be what the Agency intended when adding the "law enforcement" language to section 201.125.

ADC also cites to a 2001 dictionary definition to argue that "even if the qualifier ['not involving clinical use'] could be read into the law enforcement exemption," the term "clinical use" should be understood to refer to use involving medical treatment of a patient, and thus the law enforcement exemption could still encompass lethal injection. Ref. 9 at 3. As in other FDA regulations, though, "clinical use" in § 201.125 refers to a use involving administration of drugs to humans. *See, e.g.*, 21 C.F.R. § 312.3 (defining "clinical investigation" to mean "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects").

Interpreting the law enforcement exemption as not extending to administration of drugs to humans is supported by the historical context of the regulation's promulgation. At the time the exemption was added to section 201.125, the Agency was extremely active in investigative law enforcement work related to drug safety. More precisely, FDA promulgated the law enforcement exemption four years after the rest of § 201.125, *see* 21 Fed. Reg. 2327 (Apr. 11, 1956); Regulations for the Enforcement of the Federal Food, Drug, and Cosmetic Act; Drugs and Devices; Directions For Use; Exemption From Prescription Requirements, 17 Fed. Reg. 6807, 6819-6820 (July 25, 1952) (final rule), and just five months after testifying before Congress about FDA and State efforts on trafficking and misuse of amphetamines and barbiturates, *see* 21 Fed. Reg. 2327; *Traffic In, and Control of, Narcotics, Barbiturates, and Amphetamines, Hearings Before the H. Subcomm. on Ways and Means*, 84th Congress 1119-1120, 1123 (1955) (statement of John L. Harvey, FDA Deputy Commissioner, Nov. 17, 1955). ADC dismisses the Agency's discussion of these historical facts as a "post-hoc rationalization." Ref. 9 at 3-4. But these sources indicate that the law enforcement exemption was aimed at facilitating the investigative work that the Agency and Congress were focused on at the time, instead of being specifically intended for facilitating shipment of unlabeled drugs to law enforcement officers to administer to people.

FDA's statements in the preamble to the regulation also support the Agency's interpretation. If FDA had intended the law enforcement exemption as extending to drugs to be administered to humans, it seems implausible that the Agency would have stated that, in the cases where the exemption applied, "the [adequate-directions] labeling requirements are not necessary for the protection of the public health." 21 Fed. Reg. 2309, 2327. By contrast, the Agency's preamble statements are entirely consistent with the exempted uses being investigative activities like officer training and undercover buys. There are uses of drugs that could be characterized as part of law enforcement (e.g., court-mandated antipsychotic medication as a condition of supervised release). Interpreting the law enforcement exemption as broadly as ADC advocates would exempt those uses.

Likewise, ADC mischaracterizes FDA's past statements. ADC alleges that the Agency's 2010 press message document "confirms that the detained drugs fit squarely within the Agency's 1956 statements regarding the exemption." Ref. 9 at 4. However, when FDA spoke of deferring to law enforcement in its 2010 press message document, the Agency was not interpreting the "law enforcement" provision of section 201.125. Ref. 1, Ex. 11. Instead, the Agency noted that it was "exercising enforcement discretion" in the context of drugs being imported for lethal injection, in light of flexibility under *Heckler v. Chaney* to "prioritiz[e] . . . enforcement resources to most effectively achieve [its] statutory mission." *Id.* The two concepts are distinct.

In short, the 1956 placement of the law enforcement exemption into section 201.125, a regulation with six other categories of uses that do not involve clinical use of drugs, indicates that when the Agency added the language, it was not intended to extend the exemption to drugs to be administered to humans.[20] Today, FDA continues to believe that the law enforcement exemption was not intended to extend to drugs to be administered to humans.[21] Due to the textual and historical context of this exception, the detained drugs at issue appear to be misbranded.

V. FDA's Conclusions Are Not in Conflict with Congressional Intent and Do Not Lead to Absurd Results

ADC offers two additional challenges to FDA's interpretation of the FD&C Act, based on ADC's interpretation of 18 U.S.C. § 3596 and a 1937 predecessor, and its contention that FDA's decision produces "absurd results." We address these issues in turn.

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[20] ADC notes (Ref. 9 at 3) that FDA could have changed the text of the regulation when separating the drug and device exemptions, but it is not surprising that FDA did not add or subtract modifiers in a revision that was simply a recodification into new sections. Subchapter H—Medical Devices: Reorganization and Republication, 41 Fed. Reg. 6896, 6896 (Feb. 13, 1976).

[21] Thus, we do not dispute the idea that regulations can sometimes accommodate changing technology, *see* Ref. 9 at 3, but disagree on the basic scope of the exemption.

A. FDA's Interpretations of the New Drug and Misbranding Provisions Are Not in Conflict with Congressional Intent

ADC argues that the Agency's interpretations of the new drug and misbranding provisions of the FD&C Act, as applied to the detained drugs, "conflict with congressional intent by restricting State options in implementing capital sentences." Ref. 9 at 10. In particular, citing two statutes that address federal death sentences, ADC claims that "Congress has made clear" that States are to be permitted to devise their own procedures for executions "free of any federal interference." *Id.* Because, in ADC's view, FDA's interpretations of the FD&C Act amount to a "federal ban" on the use of sodium thiopental for lethal injections, they impermissibly restrict State options in implementing capital sentences. *Id.* at 10-11. This argument both misreads the cited statutes and overstates the effect of FDA's determination regarding the detained drugs.

Congress enacted the first statute that ADC cites, 18 U.S.C. § 3596,[22] in 1994. Violent Crime Control and Law Enforcement Act, Pub. L. No. 103-322, § 60002, 108 Stat. 1796. This 1994 statute states, among other things, that U.S. Marshals shall supervise a federal death sentence "in the manner prescribed by the law of the State in which the sentence is imposed." *Id.* The law uses language similar to its 1937 predecessor, in which Congress specified that the federal death penalty would be implemented in a manner "prescribed by the laws of the State within which the sentence is imposed." The Capital Punishment Method Act of 1937, Pub. L. No. 156, 50 Stat. 304 (1937) (codified at 18 U.S.C. § 542 (1937) and subsequently repealed). By contrast, previous federal statutes required execution by hanging. *See* Crimes Act of 1790, 1 Stat. 112-119 (1790) ("The manner of inflicting the punishment of death, shall be by hanging the person convicted by the neck until dead."); An Act To Codify, Revise, and Amend the Penal Laws of the United States, Pub. L. No. 350, § 323, 35 Stat. 1151 (1909) ("The manner of inflicting the punishment of death shall be by hanging."). Thus, the statutes discussed by ADC address whether the federal government will apply a state-specific method of execution for

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[22] The statute states in relevant part:

> In general. A person who has been sentenced to death pursuant to this chapter [18 U.S.C. §§ 3591 et seq.] shall be committed to the custody of the Attorney General until exhaustion of the procedures for appeal of the judgment of conviction and for review of the sentence. When the sentence is to be implemented, the Attorney General shall release the person sentenced to death to the custody of a United States marshal, who shall supervise implementation of the sentence in the manner prescribed by the law of the State in which the sentence is imposed. If the law of the State does not provide for implementation of a sentence of death, the court shall designate another State, the law of which does provide for the implementation of a sentence of death, and the sentence shall be implemented in the latter State in the manner prescribed by such law.

18 U.S.C. § 3596(a).

federal sentences, rather than a uniform federal method. The statutes do not address methods of execution for state-imposed death sentences.

ADC has not cited anything in the text or legislative history of either of these statutes to support its contention that Congress aimed to provide unrestricted State options in implementing a death sentence. Likewise, we have not identified any evidence indicating that Congress even considered the 1937 statute when enacting the FD&C Act in 1938. Instead, Congressional statements at the time the Capital Punishment Method Act of 1937 was enacted reflect a desire to move away from hanging to newer methods of execution employed by states.[23] But this does not equate to Congress intending States to develop procedures for implementing capital sentences "free of any federal interference." Ref. 9 at 10.[24]

In any event, there is no conflict because ADC overstates the scope and consequence of FDA's decision regarding the detained drugs. ADC claims that FDA's "interpretations amount to a federal ban on use of thiopental sodium for lethal injection," Ref. 9 at 10-11, but FDA has not made any determination, one way or the other, about which drugs may be used for lethal injection.[25] Instead, FDA has applied the FD&C Act to conclude that the particular drugs ADC seeks to import cannot be imported under the *Beaty/Cook* order. Moreover, the supposed result about which ADC complains follows directly from the *Beaty/Cook* order. To the extent ADC objects to that result, the proper course is to seek approval by FDA, relief from Congress or the court that issued the *Beaty/Cook* order – or use a drug that has been lawfully imported. FDA cannot flout a court order at ADC's request.

For all of these reasons, we do not agree that FDA's interpretations of the FD&C Act conflict with congressional intent.

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[23] *See, e.g.,* H. Rep. No. 164, at 1 (1937); S. Rep. No. 690, at 1 (1937).

[24] ADC also points to Department of Justice regulations, which were promulgated in an interim period prior to the enactment of 18 U.S.C. § 3596. *See* Ref. 9 at 11 n.15. Those regulations, 28 C.F.R. § 26.2 and § 26.3, require lethal injection in federal death penalty executions. There is no evidence that the Department of Justice intended this regulation to have any effect on the implementation of state executions. Furthermore, many states have altered their procedures to provide for the use of different drugs. *See* Deborah W. Denno, *Lethal Injection Chaos Post-Baze*, 102 Geo. L.J. 1331, 1362-66 (2014).

[25] We also note that FDA's determination that the detained drugs cannot be imported under the *Beaty/Cook* order because they are unapproved new drugs and misbranded drugs has no effect on importation of foreign-manufactured sodium thiopental that is not in violation of the FD&C Act, for example if a foreign manufacturer obtains FDA approval of a new drug application or abbreviated new drug application. Nor does it require FDA to take action against domestic distribution of sodium thiopental, whether or not it is unapproved or misbranded. *See Heckler*, 470 U.S. at 838.

B. FDA's Interpretations Do Not Lead to Absurd Results

ADC also contends that FDA's interpretations should be rejected because they lead to absurd results. Ref. 9 at 12. In particular, ADC points to FDA's tentative conclusions that GRAS/E status, including for use in lethal injection, must be based on adequate and well-controlled clinical trials, and that the detained drugs cannot qualify for the law enforcement exemption. *Id.*

In statutory interpretation, "absurdity is a high bar." *Stovic v. R.R. Ret. Bd.*, 826 F.3d 500, 505 (D.C. Cir. 2016). As the Supreme Court has stated, it applies where the plain language of a statute "would produce an absurd and unjust result which Congress could not have intended." *Griffin v. Oceanic Contractors, Inc.*, 458 U.S. 564, 574 (1982). Thus, an outcome is not absurd merely because it might be unlikely, surprising, or difficult to achieve.

Here, it is not absurd to suggest that the FD&C Act requires a drug to be shown to be safe and effective for use under the conditions suggested in its labeling. There are numerous situations where it is difficult to design appropriate clinical trials, such as testing a treatment for anthrax infection or plague. In such cases, FDA regulations may allow flexibility, or trials may differ from what scientists generally envision, but FDA's statutory mandate remains the same. ADC's absurdity point also fails to grapple with the total absence of scientific research evaluating the safety or efficacy of the detained drugs for any use. In short, ADC has not shown that FDA's position leads to absurd results.

At one time, FDA exercised enforcement discretion with respect to thiopental imports, thus avoiding questions about how to assess the safety and effectiveness of thiopental for lethal injection, or whether the thiopental was or was not approved. FDA is now subject to the Court's order in *Beaty/Cook* with respect to importation of foreign-manufactured sodium thiopental that is unapproved or misbranded. As a result, FDA has conducted its established inquiry to determine whether the detained sodium thiopental is GRAS/E for use under the conditions suggested in its labeling, leading to the conclusion that the drug is not GRAS/E for use in lethal injection – and to determine whether the manufacturer of the detained drugs holds an FDA approval of such drugs, which it does not.

As discussed in greater detail above, we also reject ADC's contention that requiring a drug to comply with section 352(f)(1) produces absurd results when it is being shipped to law enforcement for use in lethal injection. We fail to see how requiring a drug to bear labeling explaining, for example, how it should be reconstituted, the appropriate dose, or descriptions of proper methods of administration is inconsistent with the FD&C Act.

VI. Conclusion

For the reasons set forth above, we have determined that the thiopental sodium appears to be an unapproved new drug and misbranded. Based on the order issued in the *Beaty/Cook* case, FDA must refuse admission to the detained drugs. *Beaty*, 853 F. Supp. 2d 30, *aff'd in part, rev'd in part sub nom. Cook*, 733 F.3d 1.

ADC has requested that FDA "retain custody of the detained drugs under conditions that preserve their integrity pending completion of any judicial review," or "confirm that ADC will be given 90 days to export the drugs to the original foreign distributor," to hold ready for re-importation if a court rules in ADC's favor. Ref. 9, Attch. C ¶ 6. We confirm that, because we are refusing admission, ADC has ninety days from the date of notice of refusal to export or destroy the drugs, consistent with applicable regulations. *See, e.g.*, 21 U.S.C. § 381(a).

Sincerely,

CDR Steven Porter
Director, Los Angeles District Office

References:

Reference 1: Release Request for Thiopental Sodium on Behalf of the Arizona Dept. of Corrections, October 23, 2015

Exhibit 1: FDA Notice of Action

Exhibit 2: Label

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Exhibit 8: CBP Detention Notice

Exhibit 9: Request for Delivery of Goods

Exhibit 10: FDA Response to Request for Delivery of Goods

Exhibit 11: FDA Statement regarding Sodium Thiopental

Exhibit 12: Declaration

Exhibit 13: Goodman & Gilman's, The Pharmacological Basis of Therapeutics

Exhibit 14: History of Barbiturates

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Reference 2: Entry Documentation, [redacted]

Reference 3: Photos of Detained Thiopental Sodium

Reference 4: Order issued in *Beaty v. FDA*, March 27, 2012

Reference 5: Order issued in *Beaty v. FDA*, June 22, 2012

Reference 6: Letter from FDA to Arizona Dept. of Corrections, April 9, 2012

Reference 7: Letter from FDA to [redacted] June 23, 2015

Reference 8: Tentative Decision to Arizona Dept. of Corrections, April 15, 2016

Reference 9: Response to April 15, 2016 Tentative Decision on Behalf of the Arizona Dept. of Corrections, May 20, 2016

Attachment A: Documents Pertaining to Federal Execution Protocol

Attachment B: Labeling for *Beaty/Cook* Drugs

Attachment C: Affidavit

Attachment D: Affidavit

Attachment E: Affidavit

Reference 10: Email from FDA to [redacted] April 28, 2016

Reference 11: Webster's New International Dictionary Second Edition Unabridged (G&C Merriam Co. 1940)

Reference 12: Registration and Listing Information