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June 12, 2003

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CITIZEN PETITION

The undersigned submits this petition on behalf of Associates of Cape Cod, Inc. ("ACC") pursuant to sections 501, 502, 505, 510, 512 and 515 of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), section 351 of the Public Health Service Act ("PHS Act"), and 21 C.F.R. §§ 3.9(b) and 10.30 to request that the Commissioner of Food and Drugs direct the Food and Drug Administration ("FDA") to regulate recombinant and any other previously unlicensed endotoxin detection tests for validation, in-process and finished product endotoxin testing of drugs, biological products and medical devices in accordance with the same requirements that have been applied to Limulus amebocyte lysate ("LAL") endotoxin detection tests for the past 30 years.

ACC is the manufacturer of Pyrotell® and other brands of FDA-licensed LAL tests. LAL tests are produced from the blood of horseshoe crabs. The tests are used for detection of bacterial endotoxins in human and animal parenteral drugs, biological products, and

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medical devices. When introduced into the body, endotoxins can cause serious pyrogenic reactions including fever, shock, and death. Since 1973, FDA has regulated LAL endotoxin detection tests as biological products requiring premarket approval under section 351 of the PHS Act.[1] LAL tests are the current industry gold standard for endotoxin testing.

On May 8, 2003, Cambrex Bio Science Walkersville, Inc. ("Cambrex") issued a press release announcing the availability of a new PyroGene™ Recombinant Factor C Endotoxin Detection System ("PyroGene™") (Exhibit 1). The press release claimed superiority of PyroGene™ over existing LAL tests, and stated that "[FDA] has determined that PyroGene, when used according to its labeled purpose (for the detection of endotoxin contamination in drug products and medical devices and not for use in man, animals or patient management, or to qualify blood or blood products), does not require premarket approval." A Cambrex promotional piece says that the PyroGene™ test utilizes "a recombinant form of Factor C, the first component in the *Limulus* clotting cascade activated by endotoxin." (Exhibit 2).

On information and belief, the basis for Cambrex's statement concerning the lack of any premarket approval requirement for PyroGene™ is a Letter of Designation issued by the FDA Ombudsman in response to a Request for Designation ("RFD") filed by Cambrex.[2] Such agency pronouncement, unlawfully issued without public notice or opportunity for comment, constitutes a significant, unexplained departure from the

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1 See "Status of Biological Substances Used for Detecting Bacterial Endotoxins," 38 Fed. Reg. 1404 (Jan. 12, 1973).

2 Counsel for ACC has contacted officials in FDA's Office of the Ombudsman and the Center for Biologics Evaluation and Research to investigate the basis of Cambrex's claim. The officials confirmed that FDA has not issued any new public document or policy statement concerning the regulatory status or regulation of endotoxin tests. ACC is aware, however, that Cambrex representatives are showing customers a "letter from FDA" stating that no premarket approval is required for PyroGene™. Counsel for ACC has filed a Freedom of Information Act request to obtain any communications (i.e., the RFD and Letter for Designation) between Cambrex and FDA concerning the regulatory status of PyroGene™. ACC reserves the right to supplement this petition after it has had the opportunity to review FDA's Letter of Designation.

agency's 30-year-old regulatory framework for endotoxin detection tests, and creates an uneven playing field for products properly licensed and regulated under that framework. FDA's action further ignores important public health concerns which the established regulatory framework and premarket approval requirement were intended to address.

A. Action Requested

ACC requests that the Commissioner of Food and Drugs direct FDA to:

(1) Reconsider the response to Cambrex's RFD, revoke the determination that premarket approval is not required, and require premarket approval for any recombinant Factor C or any other endotoxin test for validation, in-process and/or finished product detection of endotoxin in human and animal parenteral drugs, biological products and medical devices.[3]

(2) If FDA refuses to take the above actions:

(a) Clarify that sponsors of new and previously approved human and animal parenteral drugs, biological products and medical devices desiring to use previously unlicensed endotoxin tests for validation, in-process and/or end-product pyrogenicity testing must submit data validating, and obtain prior agency approval for, the use of such tests; and

(b) Promptly deregulate all previously licensed endotoxin tests to restore a level playing field.

B. Statement of Grounds

1. Introduction; Regulatory History of Endotoxin Tests

Endotoxins, the most common and potent pyrogens, are produced during the growth and break-down of gram-negative bacteria such as E. coli and Pseudomonas sp. If endotoxins are introduced to the body through, e.g., parenteral drugs or invasive or

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[3] Cambrex's press release says that no premarket approval is required when its test is used to detect endotoxin testing in "drug products and medical devices" but not "to qualify blood or blood products." It is unclear how FDA's decision applies to biological products that are not blood products.

implanted medical devices, they can cause a range of adverse bodily effects including fever, chills, shock, hemorrhagic stroke, even death. For this reason, it is vital that pharmaceutical manufacturers perform validation, in-process and finished product testing to ensure that their products are endotoxin-free. FDA has stressed the importance of endotoxin testing in regulations, guidance documents, and Warning Letters to pharmaceutical manufacturers.[4]

Prior to 1970, pyrogen testing was performed by injecting product samples into rabbits, and waiting several hours to see whether the rabbit developed a fever. In the early 1970s, researchers at the Marine Biological Laboratory, Woods Hole, Massachusetts, accidentally discovered that the blood of horseshoe crabs clotted when exposed to endotoxin pyrogens. The discovery led to the development of a lysate made from amebocyte cells circulating in horseshoe crab blood.

In 1973, the agency issued a Federal Register notice declaring that LAL was a biological product subject to licensure under section 351 of the PHS Act.[5] Instrumental to this determination was FDA's recognition of the "value of such a product when employed for the prevention or treatment of disease in man by the detection of bacterial endotoxins to prevent the administration of unsafe drugs."[6] The notice observed that "[i]t is well known

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4 See, e.g., 21 C.F.R. §§ 211.167(a), 610.13(b); "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (Nov. 1994), at 8; "Guidance Document for the Preparation of Investigational Device Exemptions and Premarket Approval Applications for Intra-Articular Prosthetic Knee Ligament Devices" (Feb. 1993), at 7; "Devices Used for In Vitro Fertilization and Related Assisted Reproduction Procedures," (Draft) (Sept. 1998), at 12; Warning Letter ("WL") CIN-03-13127 to Celsus Laboratories, Inc. (Nov. 12, 2002); WL CIN-WL-02-13061-0 to MPW Industrial Services, Inc. (Sept. 23, 2002); WL 320-99-06 to Long March Pharmaceuticals (Sept. 7, 1999); WL SJN-98-12 to Bristol-Myers Squibb Company (May 28, 1998); WL CIN-WL-97-416 to Pharmacia Hepar, Inc. (Aug. 12, 1997); WL BUF 92-19 to C.R. Bard, Inc. (Apr. 6, 1992); WL WL-30-2 to Cardiosource (Mar. 5, 1992).

5 "Status of Biological Substances Used for Detecting Bacterial Endotoxins," 38 Fed. Reg. 1404 (Jan. 12, 1973).

6 Id.

that the administration of fluids containing bacterial endotoxins can produce shock, fever, and death."[7] Manifesting clear concern for product consistency and quality, FDA's notice said that the agency would develop regulatory standards for the safety, purity and potency of LAL, and that no LAL licenses would be issued until these standards were published. In the meantime, FDA allowed LAL tests to be marketed without a license for in-process testing only; all final product testing was to be performed using the rabbit pyrogen test.[8]

Later that year, FDA published proposed regulatory standards for LAL tests addressing product identity, potency, processing, and labeling.[9] In the preamble to the proposal, FDA explained:

> In view of the critical uses [of LAL], the Commissioner has concluded that rigid production controls are necessary to give maximum assurance that this potent diagnostic product will prevent unexpected and harmful pyrogenic reactions in man. Therefore, the Commissioner finds that the public health requires that the product be marketed only under the strict regulatory controls of section 351 of the [PHS Act] and section 505 of the [FDC Act]. . . . In conjunction with the license requirement for this product, the Commissioner is publishing proposed additional standards . . . to assure the safety, purity, and potency of the licensed product.[10]

In 1977, FDA announced the licensure of the first LAL test. Again manifesting its view that endotoxin contamination posed a serious public health hazard, the agency stated that manufacturers of biological products were required to submit an amendment for each product for which an LAL test would be used as the official pyrogen test. An LAL test

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7 Id.

8 Id.

9 "Limulus Amebocyte Lysate: Additional Standards," 38 Fed. Reg. 26,130 (Sept. 18, 1973). This proposal was revised and reissued in 1978. See 43 Fed. Reg. 35,731 (Aug. 11, 1978).

10 38 Fed. Reg. at 26,131.

could not be used as the official pyrogen test for such products until FDA approved the amendment. In addition, FDA announced that a device would be considered misbranded and/or adulterated with respect to pyrogenicity unless the manufacturer submitted data establishing that the LAL test was equivalent to the rabbit test, and obtained written agency approval to use the test. FDA reserved conditions for use of LAL tests with drugs other than biological products for later publication.[11]

In 1980, the agency issued a final rule promulgating the additional standards for LAL tests.[12] Among other criteria, the standards required manufacturers of LAL tests to submit at least 28 samples of each production lot to the agency for analysis and official release prior to commercial distribution, along with a protocol summarizing the manufacturing history of each filling, the dates of all required testing, and the results of those tests.[13] The standards also required potency testing of at least 20 samples using an official U.S. Standard and an official U.S. Reference Limulus Amebocyte Lysate which were to be obtained by the manufacturer from FDA.[14] In response to a comment suggesting that the number of samples required for official release be reduced once FDA released the first three successive lots produced by a firm, the agency reasoned that it was "still necessary to require manufacturers to submit each filling of each lot of LAL . . . for official release to ensure that the product performs reliably for its intended use," and that "[i]f continued experience and knowledge from use of LAL justifies a reduction in the number of lots that must be submitted . . . , § 660.105 will be amended as appropriate."[15] The agency similarly rejected the suggestion that only 4 samples instead of 20 be required for

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11 "Licensing of Limulus Amebocyte Lysate: Use as an Alternative for Rabbit Pyrogen Test," 42 Fed. Reg. 57,749 (Nov. 4, 1977).

12 "Additional Standards for Limulus Amebocyte Lysate," 45 Fed. Reg. 32,296 (May 16, 1980).

13 Id. at 32,300 (21 C.F.R. § 660.105).

14 Id. at 32,299 (21 C.F.R. §§ 660.101, 660.102).

15 Id. at 32,298 (comment 24).

potency testing. FDA explained: "[T]his amount is necessary to ensure that the procedure is statistically valid for estimating vial-to-vial variability."[16]

From 1979 to 1983, FDA issued a series of guidances and draft guidances outlining procedures for use of the LAL test with FDA-regulated products.[17] In 1987, it published a comprehensive guidance document called "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" ("LAL Guidance").[18] The LAL guidance specifies the regulatory provisions that must be met by pharmaceutical manufacturers before using the LAL test as an end-product test for endotoxin. Significantly, the guidance clarifies that "[m]anufacturers shall use an LAL reagent licensed by [FDA] in all validation, in-process, and end-product LAL tests."[19] In 1991,

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16 Id. at 32,296 (comment 2). Ultimately, in 1987, FDA reduced the minimum number of samples for both potency testing and official release to 8. "Limulus Amebocyte Lysate; Reduction of Samples for Testing," 52 Fed. Reg. 32,636 (Oct. 23, 1987).

17 See FDA, "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" (Dec. 1987), at 1-2.

18 See id.

19 Id. at 6, 11 (emphasis added). More than fifteen years later, most pharmaceutical manufacturers are using LAL tests for endotoxin testing. While the LAL Guidance arguably would not apply to situations where a manufacturer wanted to change to a recombinant endotoxin test such as the PyroGene™ product, FDA has issued several guidance documents to implement sections 506A and 515(d)(6) of the FDC Act, which prescribe requirements for making and reporting manufacturing changes to approved applications. See "Changes to an Approved NDA or ANDA" (Nov. 1999); "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products" (July 1997); "Changes to an Approved Application: Biological Products" (July 1997); "30-Day Notices and 135-Day PMA Supplements for Manufacturing Method or Process Changes, Guidance for Industry and CDRH" (Feb. 1998). Switching from a licensed LAL test to an unlicensed test for endotoxin testing that will be considered in product release determinations certainly appears, under the guidances, to be a type of change requiring supplemental approval, or, at a minimum, prior notice to the agency. See also 21

FDA issued an "Interim Guidance for Human and Veterinary Drug Products and Biologicals" covering the use of new kinetic-turbidimetric chromogenic LAL techniques which were not addressed in the original LAL Guidance.

In 1995, as part of the "Reinventing Government" initiative instituted by the Clinton administration to streamline government and reduce the burden on regulated industry, FDA proposed to revoke a number of regulations, among them, the additional standards for LAL and certain other biological products. The agency reasoned that such "additional standards regulations" were "duplicative and unnecessary" and that the codification of standards by regulation did not always allow enough flexibility to accommodate technological advances.[20] Moreover, FDA noted that for several years, it had deliberately not codified additional standards for licensed biological products, choosing instead to place the required standards within the product licenses themselves.[21] In 1996, FDA issued a final rule revoking the additional standard for LAL tests.[22] At no time, however, did the agency revoke the requirement for premarket approval, exempt LAL manufacturers from other regulatory controls such as annual reporting and compliance with current good manufacturing practices ("CGMPs"), or disavow the significant public health concerns underlying these controls.

C.F.R. §§ 314.70(c)(1), 610.9, 601.12(c), and 814.39(f).

20 Proposed Rule, "Revocation of Certain Regulations; Opportunity for Public Comment," 60 Fed. Reg. 53,480, 53,482 (Oct. 13, 1995).

21 Id.

22 Final Rule, "Revocation of Certain Regulations; Biological Products," 61 Fed. Reg. 40,153 (Aug. 1, 1996).

2. FDA's Pronouncement that the PyroGene™ Endotoxin Test Does Not Require Premarket Approval is Arbitrary and Capricious and Contrary to Law

a. FDA's Action Creates an Uneven Playing Field

Under the APA, courts review and hold unlawful agency action that is arbitrary and capricious and contrary to law.[23] It is well-established that disparate agency treatment of similarly situated entities constitutes "arbitrary and capricious" action.[24]

PyroGene™ is intended for the same uses as approved LAL tests. According to Cambrex's product insert (Exhibit 3), PyroGene™ is intended "as an *in vitro* end-product endotoxin test for human and animal parenteral drugs, biological products, and medical devices."[25] For nearly 30 years, FDA has required manufacturers of LAL-based tests for pyrogenicity testing of drugs and medical devices to obtain FDA premarket approval prior to marketing these tests, and to comply with other regulatory controls such as registration and listing[26] and CGMPs.[27] That PyroGene™ is a recombinant product should not, from an FDA regulatory standpoint, distinguish it from LAL tests; nor does it justify disparate

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23 5 U.S.C. § 706(2)(A) ("The reviewing court shall . . . (2) hold unlawful and set aside agency action, findings, and conclusions found to be (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law . . . .").

24 See, e.g., United States v. Diapulse Corp. of America, 748 F.2d 56, 62 (2d Cir. 1994) (FDA must act "evenhandedly" and may "not 'grant to one person the right to do that which it denies to another similarly situated'"); Federal Election Comm'n v. Rose, 806 F.2d 1081, 1089 (D.C. Cir. 1986) ("an agency's unjustifiably disparate treatment of two similarly situated parties works a violation of the arbitrary-and-capricious standard").

25 As of the date of this petition, the product insert attached as Exhibit 3 was posted at http://www.cambrex.com/catalognews/PryoG_insert_final_Mar18.pdf. It is curious that the intended uses of PyroGene™ in the product insert include end-product testing of biological products while Cambrex's press release limits the uses to "detection of endotoxin contamination in drug products and medical devices."

26 21 C.F.R. Part 607.

27 21 C.F.R. Parts 210 and 211.

agency treatment. Both PyroGene™ and ACC's Pyrotell® are biological products.[28] FDA has historically regulated recombinant products according to the same standards, requirements and policies as their original, non-recombinant counterparts. Examples include recombinant insulin and recombinant growth hormone.

In Bracco Diagnostics, Inc. v. Shalala,[29] the manufacturer of an injectable contrast imaging agent successfully challenged FDA's determination that its product should be regulated as a drug, while a competitor's similar product was subjected to more lenient regulatory controls as a device. The court, in enjoining FDA from taking any action on the products until it had settled on a uniform regulatory regime, explained that "[t]he disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious."[30]

Like the contrast imaging agents at issue in Bracco, Cambrex's recombinant PyroGene™ test is "functionally indistinguishable" from LAL-based endotoxin tests. However, whereas LAL tests like those manufactured by ACC have long been subject to premarket approval, CGMP requirements, and FDA inspections, FDA's pronouncement permits Cambrex to market its recombinant product without prior approval and, presumably, without adherence to CGMPs or other regulatory controls. Consequently, FDA's pronouncement is arbitrary and capricious in violation of the APA.

b. FDA's Pronouncement is an Unexplained Departure from Long-Standing Agency Precedent

"It is an elementary tenet of administrative law that an agency must either conform to its own precedents or explain its departure from them."[31] "[W]hen an agency decides to

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28 It is ACC's understanding that the starting material for Cambrex's PyroGene™ recombinant Factor C is DNA from an Asian species of horseshoe crab, Carcinoscorpius rotundicauda, instead of Limulus polyphemus. That difference should not affect the regulatory status of Cambrex's biological product.

29 963 F. Supp. 20 (D.D.C. 1997).

30 Id. at 28.

31 International Union, United Auto Workers v. NLRB, 459 F.2d 1329, 1341 (D.C. Cir. 1972).

reverse its course, it must provide an opinion or analysis indicating that the standard is being changed and not ignored, and assuring that it is faithful and not indifferent to the rule of law."[32]

LAL tests have been subject to premarket approval for nearly 30 years. LAL tests have also been subject to "additional standards" codified in FDA's regulations. Moreover, to use LAL tests for validation, in-process and end-product testing, manufacturers of approved human and animal parenteral drugs, biological products and medical devices have been required to submit amendments, supplements, or other types of submissions containing data that validate such use for FDA review and approval.

As evidenced by the regulatory history summarized above, FDA imposed these controls because it believed they were necessary to protect the public health. Because endotoxin contamination of drugs, biological products and medical devices poses serious health risks, the agency took measures to ensure that the products used to detect endotoxins, and to make end-product release determinations, are effective, validated, and consistently manufactured.

FDA's determination that the PyroGene™ recombinant endotoxin test is exempt from premarket review when used for the same purpose as LAL tests is an unexplained, unjustified departure from long-standing agency precedent. As such, it is arbitrary and capricious under the APA.

c. FDA's Pronouncement, Contrary to a 30-Year Regulatory Framework, Was Improperly Issued Without Notice or Opportunity for Public Comment

To issue, revoke, or amend any substantive rule having the force of law, an agency is required to conduct notice-and-comment rulemaking.[33] The APA defines the term "rule" as "an agency statement of general or particular applicability and future effect designed to

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32 Greyhound Corp. v. ICC, 551 F.2d 414, 416 (D.C. Cir. 1977) (citation omitted). See also Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 42 (1983); National Ass'n for Better Broadcasting v. FCC, 849 F.2d 665, 669 (D.C. Cir. 1988).

33 5 U.S.C. § 553(b).

implement, interpret, or prescribe law or policy . . . includ[ing] practices bearing on any of the foregoing."[34] As recently articulated by the Court of Appeals for the District of Columbia in CropLife America v. EPA, "the case law reflects two related formulations for determining whether a challenged action constitutes a [substantive rule subject to notice and comment] or merely a statement of policy" exempt from APA rulemaking requirements.[35] In both analyses, the critical question is "whether the agency action binds private parties or the agency itself with the 'force of law.'"[36] As expressed in an earlier, much-cited opinion by the same court, "[s]ubstantive rules are ones which 'grant rights, impose obligations, or produce other significant effects on private interests.'"[37]

According to Cambrex's May 8, 2003 press release, FDA told Cambrex that the PyroGene™ endotoxin test does not require premarket approval when used according to its labeled uses. These uses are the same uses for which FDA has consistently required premarket approval of LAL endotoxin tests since 1973. FDA announced the premarket approval requirement for LAL tests as well as its public health reasons for regulating such products in the Federal Register.[38] These public health concerns, reiterated by the agency

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34 Id. § 551(4).

35 2003 U.S. App. LEXIS 10944, at *17. One test asks whether the agency action "(1) 'imposes any rights and obligations,' or (2) 'genuinely leaves the agency and its decisionmakers free to exercise discretion.'" Id. (quoting Community Nutrition Inst. v. Young, 818 F.2d 943, 946 (D.C. Cir. 1987)). The other considers "'(1) the Agency's own characterization of the action; (2) whether the action was published in the Federal Register or the Code of Federal Regulations; and (3) whether the action has binding effects on private parties or on the agency.'" Id. at *18 (quoting Molycorp, Inc. v. EPA, 197 F.3d 543, 545 (D.C. Cir. 1999).

36 CropLife at *18 (quoting General Electric Co. v. EPA, 290 F.3d 377, 382 (D.C. Cir. 2002)). See also Chamber of Commerce v. OSHA, 174 F.3d 206, 209 (D.C. Cir. 1999) ("Our concern . . . is with the practical effect (the 'basic function') of the rule, not its formal characteristics").

37 American Hosp. Ass'n v. Bowen, 834 F.2d 1037, 1045 (D.C. Cir. 1987) (citation omitted).

38 See supra, notes 5, 9.

in subsequent Federal Register notices and guidance documents, are as relevant to the PyroGene™ test as they are to LAL tests.

In practical effect, and to the detriment of properly licensed endotoxin test manufacturers, FDA's pronouncement grants a legal right to Cambrex which the company would not otherwise have had under the existing, 30-year-old regulatory framework, i.e., the right to market PyroGene™ without premarket approval. The pronouncement is binding on the agency in that FDA seemingly could not, without revoking or amending the determination, take enforcement action against PyroGene™ or Cambrex for failure to obtain premarket approval. Moreover, even though the pronouncement appears to have been specific to PyroGene™, it is not unreasonable to anticipate that other endotoxin test manufacturers will attempt to rely on it, and that FDA will apply the same approach to other currently unlicensed endotoxin tests. Given these characteristics, FDA's determination that PyroGene™ does not require premarket approval constitutes a substantive rule requiring notice-and-comment rulemaking.[39]

3. FDA Should Regulate Recombinant and Other Types of Endotoxin Tests in the Same Manner as It Currently Regulates LAL Tests

The existing regulatory framework for LAL endotoxin tests was established to protect the public health. Whether endotoxin testing is performed using a licensed LAL test, a test based on recombinant technology, or a test derived from some yet-to-be-discovered source, the same public health concerns are relevant: If the test is not effective, is not consistently manufactured to specifications, or is not appropriately validated for use with the product being tested, there is a danger that contaminated products will be administered to patients causing adverse, even life-threatening reactions. The assurances afforded by premarket approval and other regulatory requirements (e.g., CGMPs) applied to licensed LAL tests are necessary to address these concerns. Failure to require the same assurances of recombinant and other endotoxin tests would compromise public safety.

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[39] See, e.g., CropLife at *22 (EPA press release reflecting a "dramatic change in the agency's established regulatory regime" was a rule subject to notice and comment procedures); Shell Offshore Inc. v. Babbitt, 238 F.3d 622, 630 (5th Cir. 2001) ("If a new agency policy represents a significant departure from long established and consistent practice that substantially affects the regulated industry, the new policy is a substantive rule and the agency is obliged, under the APA, to submit the change for notice and comment.")

In the event that FDA declines to apply the same regulatory controls to recombinant and other types of endotoxin tests, the agency should promptly deregulate previously approved LAL tests to ensure a level playing field which does not favor or discriminate against functionally indistinguishable products. In doing so, however, FDA should take care to protect the public health by clarifying and reinforcing the requirement that pharmaceutical manufacturers obtain agency approval to use any previously unlicensed endotoxin test for end-product testing.

C. Environmental Impact

A claim for categorical exclusion from the requirements for an Environmental Assessment is made under 21 C.F.R. §§ 25.30(h), 25.31(h).

D. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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RAD/JBD/tee