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September 25, 2003

'03 SEP 26 P1:17

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket Nos. 2003P-0278, 2003P-0280; Reply of Associates of Cape Cod, Inc. to Comments of Cambrex Bio Science Walkersville, Inc.

On behalf of Associates of Cape Cod, Inc. ("ACC"), the undersigned submits the following reply to the comments of Cambrex Bio Science Walkersville, Inc. ("Cambrex"). ACC's petition challenges the Food and Drug Administration's ("FDA's") decision not to require premarket approval for recombinant endotoxin tests. Cambrex's comments would effectively overturn FDA's regulation of recombinant products because, under Cambrex's novel statutory interpretation, recombinant products are not biologics. ACC will address this statutory issue first and then respond to the various procedural arguments raised by Cambrex.

I. Both Limulus Amebocyte Lysate ("LAL") And Recombinant Endotoxin Detection Tests Originate From Horseshoe Crab Blood, And, Consistent With Existing FDA Precedent, Both Are Biologics And Should Be Subject To The Same Regulatory Requirements

Cambrex asserts that because LAL-based tests and PyroGene™ "are not derived in the same manner," they "must be regulated differently" under the Public Health Service Act ("PHS Act"). The entire premise for this argument is Cambrex's claim that "rFC

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[recombinant Factor C] is not derived from blood," and therefore, "is properly classified as a product other than a regulated biological product."

The PHS Act defines the term "biological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i) (emphasis added). Cambrex does not disagree that its PyroGene™ product and LAL tests have the same intended use. Cambrex argues, however, that its product is not derived from blood and therefore is not a biologic.

PyroGene™ is a biologic both because it is a "blood derivative" and because it is an "analogous" product. Although the statute does not define "analogous product," FDA's regulations reveal how the agency interprets this term. Specifically, a product is "analogous" to a virus "if prepared from or with a virus or agent actually or potentially infectious." 21 C.F.R. § 600.3(h)(5)(i) (emphasis added). A product is "analogous" to a therapeutic serum "if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum." Id. § 600.3(h)(5)(ii) (emphasis added). A product is "analogous" to a toxin or antitoxin "if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process." Id. § 600.3(h)(5)(iii) (emphasis added).

In its Petition, ACC asserted its understanding that the starting material for PyroGene™ is DNA from an Asian species of horseshoe crab. Cambrex has not denied this in its comments. A "Technical Sheet" on PyroGene™ accessible through the Cambrex website states that PyroGene™ is covered by two patents. One of these patents, U.S. Patent No. 5,712,144, reveals that the Factor C starting material for this recombinant product is obtained from lysing amebocytes – i.e., the predominant type of cell circulating in the blood of horseshoe crabs. Given that PyroGene™ is "prepared from or with" horseshoe crab blood, and "contain[s] some organic constituent or product . . . derived from . . . blood," it is clear that PyroGene™ is both a "blood derivative" and an "analogous" biological product.

Moreover, as ACC also noted in its Petition, FDA has historically regulated recombinant products in the same manner as their original, non-recombinant counterparts. Two examples cited in the Petition were recombinant insulin and recombinant growth hormone. Another instructive example is the recent BLA approval of Baxter Healthcare Corporation's ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin Free Method (rAHF-PFM). According to FDA Talk Paper T03-55 (July 25, 2003), like

previously approved recombinant antihemophilic factor products, ADVATE is produced using genetically engineered Chinese hamster ovary cells. However, unlike previously-approved antihemophilic products which require use of blood-derived additives of human or animal origin to maintain the viability of factor VIII-making cells, ADVATE is the first recombinant factor VIII product whose manufacturing process does not use any additives derived from human or animal blood. Nevertheless, ADVATE was reviewed and approved by FDA as a biologic. Given these precedents, ACC fails to comprehend how PyroGene's™ recombinant status justifies different regulatory treatment from LAL-based tests.

II. A Stay Is Appropriate And Justified

FDA's regulations state that "[t]he Commissioner may at any time stay or extend the effective date of an action pending or following a decision on any matter." 21 C.F.R. § 10.35(a) (emphasis added). The plain meaning of the phrase "any matter" clearly encompasses a "product jurisdiction" decision issued in response to a Request for Designation. The regulations further state that "[t]he Commissioner shall grant a stay in any proceeding" if the petitioner will suffer irreparable injury; the petitioner's case is not frivolous and pursued in good faith; sound public policy grounds support the stay; and the stay is not outweighed by public health or other public interests. Id. § 10.35(e) (emphasis added). "The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice." Id. (emphasis added).

Cambrex essentially argues that ACC's Petition does not meet the requirements for a stay because: (1) the injury to ACC is not irreparable, but rather, "measurable and compensable," and (2) the harm to ACC and to the FDA-proclaimed public health interest in regulating endotoxin detection tests is outweighed by "other public health interests."

While it may be possible to quantify ACC's economic loss resulting from lost market share, and from unrecouped resources spent on the design and construction of a new GMP-compliant manufacturing facility, what is not apparent is where Cambrex believes adequate compensation for these losses would come from. Surely Cambrex is not suggesting that the agency could be held accountable for these sums. Nor does ACC imagine that Cambrex expects the compensation would come from its own pockets (e.g., PyroGene™ profits). In fact, there is no source of adequate compensation, and that is precisely why the loss to ACC is irreparable.

Cambrex suggests that ACC's financial outlay for a new facility is not "irreparable" because ACC will reap "associated benefits" such as a research and development tax credit, and the portrayal of a positive image to current and prospective customers. This argument, however, misses the point. ACC acted upon a belief, rationally based on FDA's established regulatory framework for endotoxin detection tests, that its recombinant product – which originates, like LAL-based tests and like Cambrex's recombinant product, from the horseshoe crab – would be subject to licensure and GMPs. Absent this belief, ACC would not have expended the resources to construct a new facility specifically designed to meet FDA licensing requirements. Moreover, Cambrex is marketing its recombinant product in direct competition with ACC's LAL product. Because Cambrex does not have to bear the costs of FDA licensure and on-going GMP compliance, it will be able to produce product at a lower cost than ACC. Two products intended for the same uses and both of biological origin cannot be subject to such unequal and unfair regulation.

Cambrex further contends that there are "other public health interests" that outweigh the harm to ACC and to the FDA-proclaimed public health interest in regulation and oversight of endotoxin tests. This claim is also meritless. First, Cambrex asserts that U.S. manufacturers "may be required" to use non-animal-derived products, whenever available, in order to market products in the European Union. Whether FDA currently or ultimately requires or does not require licensure of Cambrex's recombinant product, however, there is nothing that precludes Cambrex from shipping its product to Europe in accordance with the applicable export requirements. This is simply not an interest that bears on whether FDA should grant a stay.

Cambrex also claims there is an important public environmental interest in using non-animal-derived products. ACC acknowledges and shares the public concern about horseshoe crab populations and water supply contamination issues.[1] However, neither of these environmental concerns is likely to be affected by a stay so that FDA can fully consider ACC's petition. Similarly, a brief delay in the "advancement of technology"

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[1] ACC's LAL licenses require that horseshoe crabs caught for LAL use be returned to their habitats after blood collection. FDA has also approved changes to ACC's LAL licenses to allow for collection of blood from horseshoe crabs that are caught for bait, thereby reducing the number of crabs that would otherwise be caught and released.

which Cambrex argues would result from a stay is not likely to have any adverse impact on the supply of therapeutic products or cost savings to consumers.[2]

Finally, Cambrex claims a public interest in preventing the citizen petition process from being abused. As discussed below, the public petition process is the appropriate forum for raising issues concerning agency departure from an established course of regulation.

III. The Request-For-Designation Process Is Not An Appropriate Mechanism For Challenging The Agency's Departure From An Established Regulatory Framework

Cambrex argues that ACC should have submitted a request for designation ("RFD") instead of its Citizen Petition asking FDA to reconsider the response to Cambrex's RFD, and to revoke the determination that premarket approval is not required for recombinant endotoxin tests. As Cambrex notes, the RFD process is a method for sponsors to obtain agency determinations about particular products for which the sponsor believes agency "jurisdiction is unclear or in dispute."[3] It is a non-public process, the outcome of which the sponsor may challenge directly by submitting a formal "Request for Reconsideration." The RFD process is not an appropriate vehicle for interested parties to challenge agency action which departs from an established regulatory framework – even if that action happens to take the form of a response to an RFD.

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[2] Cambrex makes much of the fact that PyroGene™ will reduce the incidence of false positive test results through the elimination of possible interference from glucan contamination. Glucans may be present in FDA-regulated products derived from fungi and in products which have contacted cellulose material, such as hemodialysis filters and depth filters. Like endotoxins, glucans can trigger a positive LAL test response. However, as glucans are biologically active, immunomodulatory substances, ACC does not share Cambrex's view that glucan contamination should be ignored.

[3] Given the established regulatory framework for endotoxin tests, ACC had no reason to believe there was any dispute or lack of clarity regarding FDA's authority to regulate recombinant endotoxin tests.

Moreover, the RFD process is not the only means by which FDA asserts or determines product jurisdiction. More often, in fact, the agency engages in a public process such as notice-and-comment rulemaking, publication of Federal Register notices, or the issuance of interpretive guidance. Notable examples include tobacco products, human cellular/tissue-based products, and, of course, the 30-year regulation of endotoxin detection tests.

As voiced in its Petition, ACC's concern is that when FDA issued its determination that Cambrex's recombinant endotoxin detection test is exempt from premarket approval, it did so without public notice, in direct contravention of an established regulatory framework designed to protect the public health, and in a manner that establishes an unlevel playing field for similarly situated products. FDA regulations clearly state that any interested party "may petition the Commissioner to issue, amend or revoke a regulation or order, or to take or refrain from taking any other form of administrative action." 21 C.F.R. § 10.25(a) (emphasis added). Any interested person may then submit written comments on the petition. Id. § 10.30(d). FDA may also publish its decision on the petition in the Federal Register. Id. § 10.30(e)(3). This public process, as distinguished from the confidential RFD process, is the appropriate forum in which to raise the issues discussed in ACC's Petition.

FDA's procedural obligation to an RFD sponsor, in the event that the agency decides to alter an RFD response based on arguments presented in a Citizen Petition, is a separate matter which has no bearing on whether an RFD decision can be challenged by an interested party in a Citizen Petition. Nevertheless, Cambrex uses a considerable portion of its comments attempting to articulate why it believes revocation or alteration of the determination would not meet the RFD non-consensual reconsideration standard of "necessary to protect the public health or for other compelling reasons." ACC submits that the need for FDA to follow proper procedures when making changes to an established regulatory framework is a "compelling reason" for suspending or altering the RFD determination issued to Cambrex. Moreover, each of the "sufficient regulatory oversight" arguments cited by Cambrex to defend the determination that PyroGene™ is exempt from regulation applies equally well to Limulus Amebocyte Lysate (LAL)-based endotoxin

tests.[4] If FDA does not consider "existing regulatory oversight" to be adequate for LAL tests, ACC fails to see how the agency could find "existing regulatory oversight" to be adequate for recombinant endotoxin tests, which have not been proven safe and effective.

IV. Conclusion

In sum, Cambrex does not dispute the central proposition of ACC's petition – that FDA has treated recombinant endotoxin tests and traditional LAL tests in a disparate manner. Rather, Cambrex argues that this unequal treatment is justified because its recombinant product does not meet the definition of a biologic. This novel statutory interpretation, if accepted by FDA, would have dramatic and far-reaching implications for the regulation – or more accurately the deregulation – of all recombinant products. ACC urges FDA to reject Cambrex's statutory interpretation and to rule that recombinant and non-recombinant endotoxin tests are both subject to the same regulatory controls. FDA should either require licensure of recombinant endotoxin tests or promptly withdraw the requirement for licensing of traditional LAL-based tests.

Respectfully submitted,

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[4] One of the "adequate regulatory controls" cited by Cambrex is the "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Detection Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices." However, this guidance, which states that "[m]anufacturers shall use an LAL reagent licensed by CBER in all validation, in process, and end-product LAL tests," applies only to LAL-based tests. It does not address recombinant endotoxin tests like PyroGene™.