McKenna & Cuneo, L.L.P.
Attorneys at Law

Los Angeles
San Francisco
San Diego

1900 K Street, N.W. ■ Washington, D.C. 20006-1108
202-496-7500 ■ Fax: 202-496-7756
www.mckennacuneo.com

Denver
Dallas
Brussels

May 11, 2001

Stuart Kim
202-496-7534
stuart_kim@mckennacuneo.com

VIA FEDERAL EXPRESS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Comments to Docket No. 97N-484P
Proposed Rule: Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement

Dear Sir or Madam:

On January 8, 2001, the Food and Drug Administration ("FDA") published in the *Federal Register* a proposed rule entitled, "Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products."[1] These comments are submitted on behalf of persons who request that the undersigned submit comments and address the content of the preamble as well as the proposed rule itself.

Proposed 21 C.F.R. § 1271.150(b)(2) – Allocation of Regulatory Responsibility

The agency has tentatively concluded that the best approach is to assign ultimate responsibility for the product to the establishment that is responsible for making the product available for distribution. In the preamble, the agency maintains the provision is consistent with the proposed approach document, which states that the:

[1] 66 *Fed. Reg.* 1508 (2001).

97N-484P

C 38

> establishment or person responsible for determining suitability of release of cells or tissues would be responsible for ensuring that required screening and testing had been performed prior to final release of the material.[2]

Thus, the agency would require one company to collect and store exhaustive documentation from all establishments participating in the manufacturing process. This provision would place an undue regulatory burden on a single company, especially one with limited resources. As a result, this provision would provide a strong disincentive for smaller establishments to become distributors of human cellular and tissue-based products.

Alternatively, the agency discussed adopting a "cascading" set of responsibilities, in which every establishment (1) would be responsible for ensuring that its own operations comply with applicable requirements, and (2) would bear the burden of proof that operations performed by other establishments prior to its receipt of cells or tissues were performed in compliance with applicable requirements. The current industry view is that "one company's finished product is another company's raw material." Assigning the responsibility for the product to all establishments participating in the manufacturing process would better ensure the risk of disease transmission is minimized and not increase the regulatory burden on any one establishment. Therefore, the agency should reconsider adopting the "cascading" set of responsibilities as discussed in the preamble to the proposed rule.

Proposed 21 C.F.R. § 1271.160(b)(2) – Sharing and Receiving Information

Under the proposed rule, the agency would require every establishment to establish procedures for sharing and receiving information that could affect the integrity and function of a human cellular or tissue-based product, the possible contamination of the product, or the potential transmission of communicable disease by the product. However, this provision would be impractical if all establishments participating in the manufacturing process were required to share and receive information because a company may have to disclose proprietary information, including manufacturing procedures and customer lists, to actual or

---

[2] *Id.* at 1512.

potential competitors. On the other hand, assigning the responsibility for sharing and receiving information to each vendor would ensure the risk of disease transmission is minimized, reduce the regulatory burden on establishments, and protect proprietary information from disclosure. In light of these concerns, the agency should narrow the scope of this provision.

Proposed 21 C.F.R. § 1271.160(b)(7) – Functions

Under the proposed rule, the agency would require an establishment to investigate and document all product deviations in manufacturing. However, the definition of *product deviation* under proposed 21 C.F.R. § 1271.3(kk) could be broadly interpreted to include documentation of trivial events that would not increase the risk of disease transmission. Therefore, the agency should clarify this provision to include only product deviations in manufacturing that would increase the risk of disease transmission.

Proposed 21 C.F.R. § 1271.160(e) – Computer Software

Under the proposed rule, the agency would require an establishment to validate computer software for its intended use according to an established protocol. On its face, the provision appears to be consistent with the Quality System Regulation.[3] However, the estimated cost for one particular small company to comply with this provision could exceed $1 million, which would create an enormous financial burden and make it difficult for this company to compete.

The purpose of the proposed rule is to minimize the risk of disease transmission in human cellular and tissue-based products, and this provision should be implemented to the extent that software validation will minimize this risk of disease transmission during the manufacturing process. In addition, the agency included no exemption in this provision for general-purpose software (e.g. spreadsheet, database, and word processing software) intended for broad general use. These software products are currently exempt from most of the general controls under the Federal Food, Drug, and Cosmetic Act ("the Act"). The agency should revise this provision to reflect these concerns.

---

[3] See 21 C.F.R. § 820.

Proposed 21 C.F.R. § 1271.170(c) – Training

Under the proposed rule, the agency would require an establishment to train all personnel to perform their assigned responsibilities adequately. However, it is unclear what criteria a company should use to determine qualifications of laboratory personnel. Therefore, the agency should clarify this provision in order to provide further guidance to the industry.

Proposed 21 C.F.R. § 1271.190(c) – Facility Cleaning and Sanitation

Under the proposed rule, the agency would require an establishment to develop procedures for facility cleaning and sanitation. The wording of the provision appears to take the concept of a clean facility to an extreme. Developing and maintaining procedures for routine cleaning and maintenance – trash removal, cleaning toilets, sweeping floors – would be a waste of valuable time and resources for any company. The agency should consider rewording this provision to address this concern.

Proposed 21 C.F.R. § 1271.220(c) – Pooling

Under the proposed rule, the agency would prohibit an establishment from pooling of human cells or tissues from two or more donors during manufacturing. In the preamble, the agency maintains the provision is consistent with recommendations made by the Transmissible Spongiform Encephalopathy ("TSE") Advisory Committee with respect to the pooling of dura mater. However, this provision is not only contrary to decades of established practice and procedures but also would be impossible to implement. Since all human source material is already tested on an individual donor basis by approved methods, subsequent commingling of human cells or tissues would not increase the risk to recipients of exposure to infectious agents. Furthermore, this provision would require a company to manufacture every lot of product in a small quantity. For example, if a company was purifying an enzyme from human liver, and 10 livers were required, the company would have to perform ten separate preparations with appropriate documentation. It would be impossible for a company to manufacture human-based *in vitro* diagnostic ("IVD") products on any scale that could meet demand.

The provision appears to be an overreaction to the current fears regarding "mad cow" disease and new variant Creutzfeldt-Jakob disease ("nvCJD"). Since the

recommendation of the TSE Advisory Committee was limited to the pooling of dura mater, expanding this recommendation to include all human cells and tissues is premature because not all human cells and tissues have been shown to transmit nvCJD. Furthermore, the industry continues to work with the federal government in developing procedures to minimize the risk of transmitting nvCJD. Therefore, the agency should consider revoking this provision.

Proposed 21 C.F.R. § 1271.230 – Process Validation

Under the proposed rule, the agency would require an establishment to validate and approve a process according to established procedures where the results of the process cannot be fully verified by subsequent inspection and tests. However, the provision is vague as to which process a company should validate and approve, and how the validation and approval of a process should be conducted. Although the intent of the proposed rule is to minimize the actual risks of disease transmission, the broad wording of this regulation attempts to completely eliminate all theoretical risks, which is impossible unless the manufacturing of all human cellular and tissue-based products is stopped. This proposed rule is arbitrary because it fails to take into account the unique biological characteristics of the various human cell and tissue types. For example, musculoskeletal tissue is generally a poor vehicle for viruses, which require proliferating tissue to propagate.

Another example of this arbitrary rule is proposed 21 C.F.R. § 1271.230(c), where a company must process dura mater using a validated procedure that reduces TSE and preserves the clinical utility of the product. However, the agency has not validated methods of decontaminating tissues contaminated with prions, despite industry efforts to refine existing decontamination methods. In effect, the agency could arbitrarily suspend the operations of any establishment that employs methods that do not address every possible risk of disease transmission. In light of these concerns, the agency should reevaluate this provision by considering the actual risk of disease transmission with respect to the human cells and tissues involved.

Proposed 21 C.F.R. § 1271.290 – Tracking

Under the proposed rule, the agency would require every establishment to track human cellular or tissue-based products in order to set up a *chain-of-custody* from donor to recipient. However, unless all establishments adopt a uniform method of tracking, it would be impossible to comply with this provision.

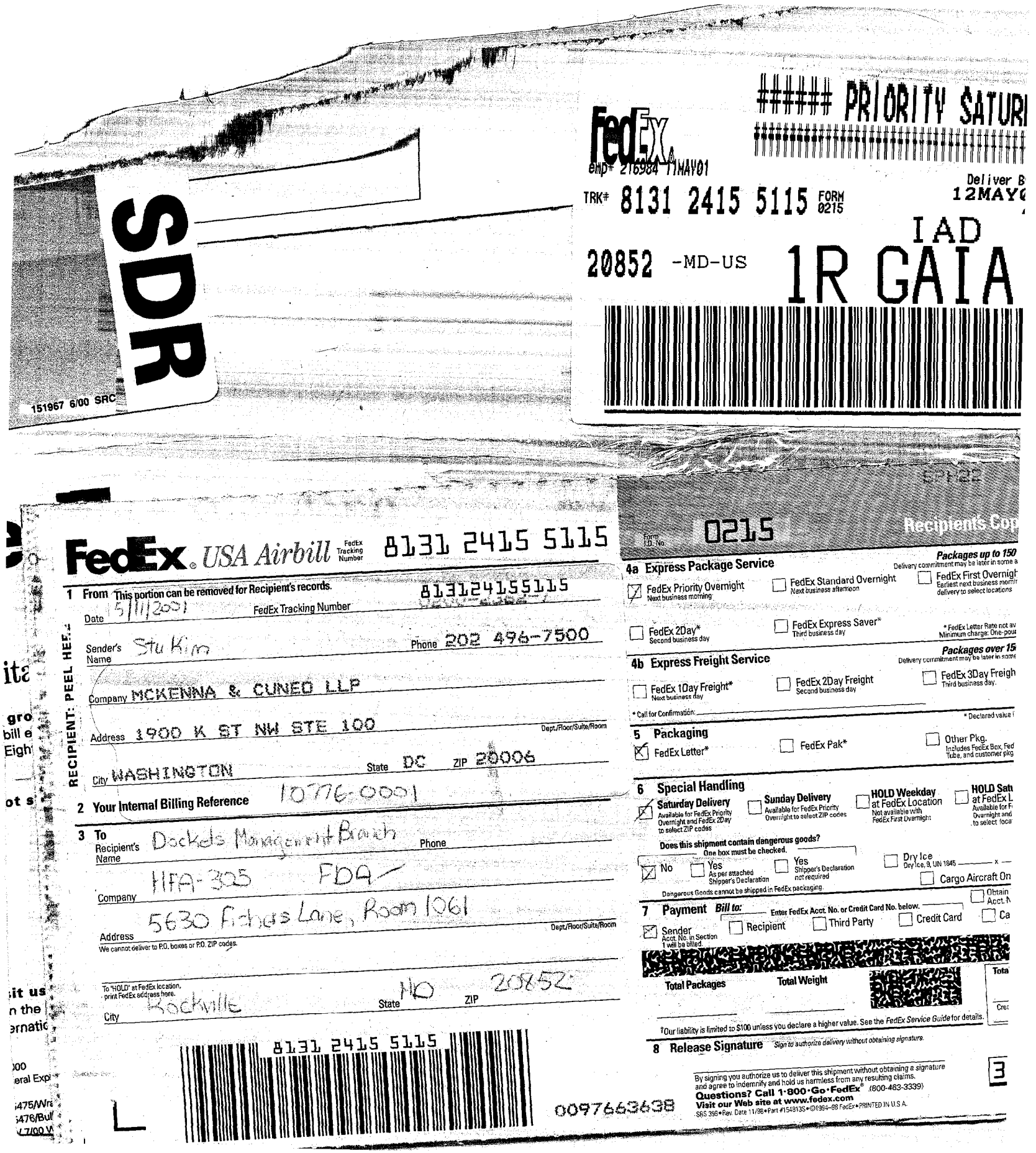
Furthermore, a fewer number of vendors would be available to establishments because many vendors may elect not to participate in tracking due to potential disclosure of proprietary information. All establishments should share in the responsibility of preserving a *chain-of-custody*, but the record keeping requirements should be kept to a minimum. Therefore, the agency should revise this provision to require every company to maintain a uniform set of records in the event the agency must track the *chain-of-custody* from donor to recipient.

Respectfully submitted,

Stuart Kim

Stuart Kim

SK/sk



SDR

151967 6/00 SRC

FedEx

emp# 216984 11MAY01

PRIORITY SATURI

TRK# 8131 2415 5115 FORM 0215

Deliver B
12MAY(

20852 -MD-US

IAD
1R GAIA

FedEx USA Airbill FedEx Tracking Number 8131 2415 5115

RECIPIENT: PEEL HERE

1 From This portion can be removed for Recipient's records. 813124155115

Date 5/11/2001 FedEx Tracking Number

Sender's Name Stu Kim Phone 202 496-7500

Company MCKENNA & CUNEO LLP

Address 1900 K ST NW STE 100 Dept./Floor/Suite/Room

City WASHINGTON State DC ZIP 20006

2 Your Internal Billing Reference 10776-0001

3 To Recipient's Name Dockets Management Branch Phone

Company HFA-305 FDA

Address 5630 Fishers Lane, Room 1061 Dept./Floor/Suite/Room

We cannot deliver to P.O. boxes or P.O. ZIP codes.

To "HOLD" at FedEx location, print FedEx address here.

City Rockville State MD ZIP 20852

8131 2415 5115

0097663638

Form I.D. No. 0215 Recipients Cop

4a Express Package Service — Packages up to 150

Delivery commitment may be later in some a

☒ FedEx Priority Overnight — Next business morning

☐ FedEx Standard Overnight — Next business afternoon

☐ FedEx First Overnigh — Earliest next business mornin delivery to select locations

☐ FedEx 2Day* — Second business day

☐ FedEx Express Saver* — Third business day

* FedEx Letter Rate not av Minimum charge: One-pou

4b Express Freight Service — Packages over 15

Delivery commitment may be later in some

☐ FedEx 1Day Freight* — Next business day

☐ FedEx 2Day Freight — Second business day

☐ FedEx 3Day Freigh — Third business day.

* Call for Confirmation:

* Declared value

5 Packaging

☒ FedEx Letter*

☐ FedEx Pak*

☐ Other Pkg. Includes FedEx Box, Fed Tube, and customer pkg

6 Special Handling

☒ Saturday Delivery — Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes

☐ Sunday Delivery — Available for FedEx Priority Overnight to select ZIP codes

☐ HOLD Weekday at FedEx Location — Not available with FedEx First Overnight

☐ HOLD Satu at FedEx L — Available for F Overnight and to select loca

Does this shipment contain dangerous goods? One box must be checked.

☒ No ☐ Yes As per attached Shipper's Declaration ☐ Yes Shipper's Declaration not required ☐ Dry Ice Dry Ice, 9, UN 1845 — x —

Dangerous Goods cannot be shipped in FedEx packaging.

☐ Cargo Aircraft On

☐ Obtain Acct. N

7 Payment Bill to: Enter FedEx Acct. No. or Credit Card No. below.

☒ Sender Acct. No. in Section 1 will be billed. ☐ Recipient ☐ Third Party ☐ Credit Card ☐ Ca

Total Packages Total Weight Tota

†Our liability is limited to $100 unless you declare a higher value. See the FedEx Service Guide for details. Cre

8 Release Signature Sign to authorize delivery without obtaining signature.

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

Questions? Call 1-800-Go-FedEx® (800-463-3339)

Visit our Web site at www.fedex.com

SRS 398 • Rev. Date 11/98 • Part #154813S • ©1994–98 FedEx • PRINTED IN U.S.A.

3