Kyper & Associates

Consultants to the Medical Device Industry

August 31, 2001

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

Re: Citizen Petition

Dear Sir/Madam:

Action Requested

The undersigned submits this petition to request that the Commissioner of the Food and Drug Administration take administrative action to revoke Compliance Program 7383.003 [QS/GMP Pre-Clearance Inspection Program for Class III 510(k) Pre-amendment Devices] and to delete the reference to this Compliance Program on page 4 of the "Compliance Program Guidance Manual: Inspection of Medical Devices; Final Guidance for Industry and FDA (CP 7382.845)." The availability of the latter document was announced in the February 7, 2001 *Federal Register*. In the interim, the Commissioner of the Food and Drug Administration is requested to take immediate administrative action to discontinue all further pre-clearance inspections for Class III pre-amendment devices undergoing premarket notification [510(k)] review. Administrative action by the FDA Commissioner is necessary as senior management in the Office of Compliance and the Office of Device Evaluation in the FDA Center for Devices and Radiological Health have informed me that they cannot unilaterally revoke this program or grant exceptions. I have referred this matter to the CDRH Ombudsman and the CDRH Director without any resolution of this matter to date.

Statement of Primary Grounds

The primary reasons for this request are the lack of FDA statutory authority and the lack of legislative intent under the Medical Device Amendments of 1976, Safe Medical Devices Act of 1990, Safe Medical Devices Act of 1992, and FDA Modernization Act of 1997 to withhold 510(k) clearance for a Class III pre-amendment device pending a FDA pre-clearance inspection demonstrating substantial compliance of each involved facility with the Quality System Regulation under 21 CFR Part 820. The legislative intent for the premarket notification requirements under section 510(k) and section 513(i) of the Food,

(919) 960-0049 Fax: (919) 960-0009
103 Nolen Lane • Chapel Hill, NC 27516

Drug, and Cosmetic Act (Act) is to screen out devices that require an approved premarket approval application (PMA) before marketing and to permit the marketing of a medical device that is substantially equivalent to legally marketed devices not required to have an approved premarket approval application (PMA) in effect. Only the device's indication(s) for use and its technological characteristics are to be considered for the purposes of establishing substantial equivalence under section 513(i) of the Act.

Unlike the PMA provisions under section 515 of the Act, the premarket notification provisions do not grant FDA the authority to deny or withdraw marketing clearance for failure to comply with the good manufacturing requirements under section 520(f) of the Act and 21 CFR Part 820. Even the proposed rule published in the January 16, 2001 *Federal Register* for rescinding inappropriate 510(k) clearances does not include non-compliance with the Quality System Regulation among the grounds for rescinding 510(k) clearances.

This pre-clearance inspection program was proposed and drafted in 1992 or 1993 by the Office of Compliance in the FDA Center for Devices and Radiological Health (CDRH) following a congressional committee hearing that was very critical of CDRH approving PMAs despite knowledge of relevant adverse inspectional findings. In particular, the committee cited a 1991 PMA approval of an ophthalmic surgical aid despite FDA knowledge of manufacturing problems that post-approval resulted in temporary blindness and delayed significant increases in intraocular pressure. In June 1990 I requested to be relieved of my position as the Chief of the PMA Section in the CDRH Office of Device Evaluation (ODE) and assume a position elsewhere in CDRH. At the ODE Director's request, I remained in ODE as the Associate Director for Reclassification and Compliance. In that capacity I had a major role in implementing many provisions in the Safe Medical Devices Act of 1990 as well as serving as ODE liaison to the CDRH Office of Compliance on compliance matters involving 510(k)s, PMAs, IDEs, labeling, advertising, and promotion. In this capacity I sent a memo to the Director of the CDRH Office of Compliance (Ronald Johnson) advising that there is a lack of FDA authority and legislative intent for this 510(k) pre-clearance inspection program and that it would unduly delay 510(k) marketing clearances well beyond the 90-day period envisioned in the statute. I recently learned that the Division of Small Manufacturers Assistance within the CDRH Office of Health and Industry Programs sent a similar memo to the CDRH Office of Compliance at the time.

Singling out Class III pre-amendment devices for this 510(k) pre-clearance inspection program reflects a significant misunderstanding on the part of the FDA staff involved in this program regarding the risks presented by these devices and the relevance of the quality system requirements in addressing these risks compared to Class II and many Class I devices. The Safe Medical Devices Act of 1990 expanded the controls applicable to Class II devices. It mandated FDA to reconsider the classification of Class III pre-amendment devices in the light of this revised definition of Class II devices. At that time there was a belief by many congressional committee members overseeing FDA activities that Class III pre-amendment devices were inherently dangerous.

In 1991 I was assigned the responsibility to determine the current state of FDA knowledge of the safety and effectiveness of these devices and to identify those that could be readily reclassified into Class II as well as to identify the lingering safety or effectiveness issues to be addressed in PMAs for those that remained in Class III. Questionable effectiveness for one or more of their intended uses was the primary reason for retaining pre-amendment devices in Class III. The congressional committee staffs reviewed this information and agreed that these devices are not inherently dangerous and that FDA had developed a reasonable strategy for issuing rulemaking to require PMA approval for those that may need to remain in Class III. Many actively marketed pre-amendment Class III devices were subsequently reclassified as a result. A substantial number are still awaiting reclassification into Class II or rulemaking to require PMA approval.

Statement of Secondary Grounds

Secondary, but no less significant, reasons for discontinuing these pre-clearance inspections are that they are nonproductive and wasteful of limited FDA inspection resources and have unnecessarily delayed the marketing clearance of pre-amendment Class III devices well beyond the determination of substantial equivalence by the CDRH Office of Device Evaluation. FDA has a statutory mandate to inspect manufacturers of Class II and Class III devices at least once every two years. Fiscal year 2000 FDA data show that there are more than 9000 such manufactures but that slightly more than 1300 inspections were conducted. At this rate FDA will inspect these manufacturers once every seven years on average. FDA acknowledges that it lacks the resources to meet this biannual inspection requirement. This is despite significant streamlining of inspectional procedures in recent years to concentrate on a limited number of quality system requirements as well as adverse experience reporting and device tracking requirements.

The case history that follows is atypical but illustrates the unnecessary delay and financial loss that can result from this ill-conceived and non-mandated pre-clearance inspection program.

Device: Endosseous implant recommended for high priority for reclassification into Class II by the FDA Dental Products Advisory Panel during a January 13, 1997 public meeting; no FDA rulemaking to date to effect this reclassification

510(k) Applicant: U.S.-based firm that utilizes contract manufacturers in South Africa and Switzerland and a U.S.-based contract packager/sterilizer

Manufacturing Facilities:

1. South Africa: manufactures and markets endosseous outside of the U.S. for more than 10 years; will manufacture and bulk ship the same endosseous implants for packaging and sterilization by the 510(k) applicant's U.S.-based contract packager/sterilizer; no previous FDA inspection of this South African manufacturer

2. Switzerland: manufactures and markets tools to firms in the U.S. and elsewhere for use with their endosseous implants; tools were reclassified into Class II in a October 7, 1998 final order; will ship tools in bulk for packaging and sterilization by the 510(k) applicant's U.S.-based contract packager/sterilizer; satisfactory FDA inspectional history

3. U.S.-based contract packager/sterilizer: satisfactory FDA inspectional history

510(k) Chronology:

November 22, 2000: CDRH Office of Device Evaluation receives 510(k)

January 17, 2001: CDRH Office of Device Evaluation notifies the 510(k) applicant that FDA has found its device to be substantially equivalent to legally marketed endosseous implants but cannot issue the 510(k) order until the CDRH Office of Compliance determines that the firm's manufacturing facilities comply with the Quality System Regulation

March 27, 2001: On behalf of the 510(k) applicant I contacted the Division of Compliance Programs (DCP) in the CDRH Office of Compliance re the delay in conducting the pre-clearance inspections; after searching its records DCP informed me that no inspection assignments have been issued as the Office of Device Evaluation has yet to provide DCP a copy of the 510(k) and should have done this within 5 days of ODE receipt of the 510(k); DCP acknowledged that it had received a copy of the January 17, 2001 letter to the 510(k) applicant at the time it was issued but was still awaiting a copy of the 510(k)

April to July 2001: DCP informed me in April that no field office investigator has yet to volunteer to inspect the South African manufacturer of the endosseous implants and that no inspection of the U.S.-based contract packager/sterilizer is necessary based upon its FDA inspectional history; I made repeated calls to several senior staff in the Office of Compliance and Office of Device Evaluation to request a waiver of these inspections based upon a lack of FDA authority and a lack of legislative intent; my requests for waivers were rejected; I rejected the ODE 510(k) Section request that my client withdraw and resubmit the 510(k) because of the expected long delay in conducting the pre-clearance inspections; in late July a volunteer is found to inspect the South African firm but the inspection cannot be initiated until mid-September; at the same

time DCP informed me that a pre-clearance inspection of 510(k) applicant is required and that the Swiss manufacturer of the tools must be inspected because more than two years have now elapsed since the last FDA inspection; DCP Director reportedly cancelled the inspection of the Swiss manufacturer after I informed her that these devices were reclassified into Class II in 1998 and that FDA for many years has been unable to meet the biannual inspection mandate for Class II and Class III devices; a DCP consumer safety officer erroneously informed my client that a 1993 law requires these pre-clearance inspections for Class III devices undergoing 510(k) review; in late July I requested the assistance of the CDRH Ombudsman in obtaining waivers for these inspections; the CDRH Deputy Director directed the Ombudsman to forward this matter to the Office of Compliance (OC) Acting Director for resolution

August 2001: The OC Acting Director did not contact me as promised re his decision in this matter before he left for vacation; I continued to press this matter with the Ombudsman upon his mid-August return from vacation; OC Acting Director informed me that his office cannot waive these inspections; no FDA Form 483 issued during mid-August FDA inspection of the 510(k) applicant; on August 30th a MIN-DO field office investigator notified the 510(k) applicant that he will conduct a pre-clearance inspection of the Swiss manufacturer of the tools in mid-September; on August 30th the CDRH Ombudsman informed me that, in response to my August 10th e-mail to the CDRH Director, there will be a September 14th internal CDRH meeting to discuss this pre-clearance inspection program; on August 31st the DCP Director informed me that steps have been taken to not make the mid-September inspection of the Swiss manufacturer of the tools a routine inspection and not part of the decision process for granting 510(k) clearance for my client's device

All of these pre-clearance inspections should have been scheduled last December. The CDRH Office of Compliance waited until August to schedule inspections of the 510(k) applicant and the Swiss manufacturer of the Class II tools despite previous assurances that no pre-clearance inspection of this Swiss firm was needed. More than eight months will transpire from the time the Office of Device Evaluation notified my client of its finding of substantial equivalence until FDA issues the 510(k) order permitting the marketing of this device.

In my discussions with CDRH senior staff during the past five months I have reminded them that endosseous implants are slated for reclassification into Class II and, subsequent to my leaving the position of Director of the PMA Staff in June 1990, a number of PMAs

have been approved without a pre-approval inspection or a reinspection following a violative inspection. I also reminded them that several PMAs for needle destruction devices were approved in recent years with internal CDRH agreement that pre-approval inspections would not be conducted. Despite this knowledge they continue to indicate that they cannot waive the pre-clearance inspections relative to my client's 510(k) submission. At the present time three inspections will be conducted as part of the clearance of this 510(k) submission whereas slightly more than 1300 FDA inspections were conducted in fiscal year 2000 for the more than 9000 device firms subject to the biannual inspection requirement.

Significantly more resources would be required for this pre-clearance inspection program if it applied to all known and potential Class III devices undergoing 510(k) review. Based upon 510(k) records obtained during discovery in litigation procedures, I have personal knowledge of situations where the 510(k) applicant claimed that its device is a Class II device but the ODE 510(k) order correctly cites it as being a Class III device. Several of these 510(k)s involved firms with a violative FDA inspection history. No FDA pre-clearance inspections were conducted prior to the issuance of the 510(k) orders or the previous FDA inspection occurred several years before then.

Even more significant are the many 510(k) clearances for pre-amendment devices that were overlooked during the device classification review concluded in 1977. One version of a device (i.e., a porous coated temperomandibular joint prosthesis) received considerable public and congressional committee attention starting in the late 1980's because of the serious pain and injuries that resulted from its use. The FDA Dental Devices Classification Panel recommended that the generic type of this device be classified in Class III. FDA neglected to include this device in the dental device classification regulations published in the August 12, 1987 *Federal Register*. A final order placing it in Class III was published in the December 20, 1994 *Federal Register*. As a result of this oversight, I was assigned the responsibility in the early 1990's to identify potentially Class III pre-amendment devices that were unclassified and for which 510(k)s were being received. The ODE divisions identified more than 100 such devices. A program was established for reviewing these devices at applicable FDA advisory panel meetings and then classifying them through rulemaking. To date only a limited number of these devices have been reviewed and classified. Because most are unclassified, they are not subject to the present pre-clearance inspection program.

Concluding Remarks

During the past several months I have received support from several CDRH senior staff for my petitioning of the agency to abolish this pre-clearance inspection program. Others who are steadfast in continuing this program are unable to respond to my following questions or requests:

- Compared to Class II devices, what's different about Class III pre-amendment devices undergoing 510(k) review that necessitates pre-clearance inspections?

- What relevance do the quality system requirements under 21 CFR Part 820 have to the determination of substantial equivalence under section 513(i) of the Act?

- Cite the statutory authority for these pre-clearance inspections as part of the premarket notification review process.

- Cite the legislative intent for these pre-clearance inspections as part of the premarket notification review process.

FDA needs to establish more appropriate priorities for the use of its limited resources for inspecting device manufacturers. Significant inspection resources are being unnecessarily expended in the case of my client's 510(k) submission and those submitted for other pre-amendment Class III devices. A step in the right direction should be the revocation of Compliance Program 7383.003 [QS/GMP Pre-Clearance Inspection Program for Class III 510(k) Pre-Amendment Devices] and the deletion of all references to this Compliance Program in "Compliance Program Guidance Manual: Inspection of Medical Devices; Final Guidance for Industry and FDA (CP 7382.845)." CDRH re-engineering efforts during past years apparently failed to recognize that this program lacks statutory authority and legislative intent and is non-productive and wasteful of FDA resources.

Environmental Impact

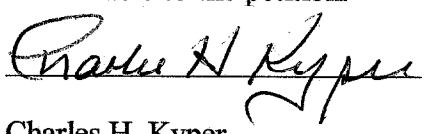
Although this requested FDA administrative action does not involve environmental considerations, a claim for categorical exclusion is made in accordance with 21 CFR 25.30 of FDA's implementing regulations for the National Environmental Policy Act (NEPA).

Economic Impact

This information is to be submitted only when requested by FDA.

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.



Charles H. Kyper
Kyper & Associates LLC
103 Nolen Lane
Chapel Hill, NC 27516
(919) 960-0049

DOMESTIC USE ONLY

SOBRE DE TARIFA ÚNICA

TARIFA DE FRANQUEO DE 2 LIBRAS SIN CONSIDERAR PESO
USO NACIONAL ÚNICAMENTE

Para recolección o localización, llame al 1-800-222-1811

PRIORITY MAIL
UNITED STATES POSTAL SERVICE®

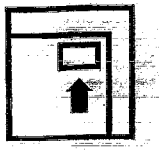
www.usps.com

"PRIORITY MAIL" DE 2 L
USO NACIONAL ÚNICAM

HOW TO USE:
ÓMO USAR:

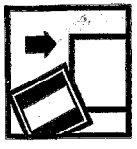
1. COMPLETE ADDRESS LABEL AREA
Type or print required return address and addressee information.

ESCRIBA LA DIRECCION EN EL AREA INDICADA
Escriba en letras de imprenta la dirección del remitente y la del destinatario.



2. PAYMENT METHOD
Affix postage, meter strip or PC postage label to area indicated in upper right hand corner.

FORMA DE PAGO
En el área superior del lado derecho, coloque sello postal, franja de máquina franqueadora o etiqueta de franqueo impreso por computadora.



3. ATTACH LABEL (If provided)
Remove label backing and adhere where indicated.

ADHIERA ETIQUETA (Si le fue provista)
Remueva la parte posterior y adhiera sobre la zona de dirección indicada.

PRIORITY MAIL
UNITED STATES POSTA

From: Kyper & Associates
103 Nolen Lane
Chapel Hill, NC 27516

From:

To:

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

Label 228, Jan 1999

www.usps.gov

The efficient FLAT RATE ENVELOPE. You don't have to weigh the envelope... just pack all your correspondence and documents inside and pay only the 2 lb. Priority Mail postage rate. ***We Deliver.***

El eficiente SOBRE DE TARIFA ÚNICA. No tiene que pesar este sobre...simplemente coloque toda su correspondencia y documentos adentro y pague sólo la tarifa de fraqueo por correo Priority Mail de 2 libras. ***Le Servimos.***