DADE BEHRING

DADE BEHRING INC.
P.O. Box 6101
Newark, DE 19714

January 25, 2001

Food and Drug Administration
Center for Devices and Radiological Health
Regulations Staff (HFZ-215)
1350 Piccard Drive
Rockville, MD 20857

RE: 513 (f) Petition to Reclassify Cyclosporine Diagnostic Test Devices from Class III to Class II

Dade Behring, Incorporated, requests that the Food and Drug Administration, Center for Devices and Radiological Health, consider the enclosed petition seeking reclassification of Cyclosporine Test Devices. Specifically, we request that all *in vitro* diagnostic tests intended for the quantitative determination of Cyclosporine in patient whole blood samples be reclassified from the present class III (premarket approval) category, into class II (special controls). Additionally we request that:

* All currently approved *in vitro* diagnostic Cyclosporine tests, as well as all new tests which FDA determines are substantially equivalent be classified as class II devices;

*All Cyclosporine calibrators used in conjunction with *in vitro* diagnostic Cyclosporine tests be classified as class II devices;

* The Draft Guidance for Industry regarding *In Vitro* Diagnostic Cyclosporine Test Systems, included as part of this petition, be reviewed and issued as a 510(k) Guidance Document that can become the basis for FDA's review of all new and revised Cyclosporine premarket notifications.

This request does not extend to *in vivo* diagnostic tests or reagents.

This petition is being submitted in accordance with the procedures contained within 21CFR860.120. Additionally, we believe that this petition accords with Congress' intent, contained in Section 513(f) as enacted in the Federal Food, Drug, and Cosmetic Act.

While Dade Behring has filed this petition as an individual sponsor, our decision to proceed with this effort was based, in part, on discussions with persons knowledgeable in the field and with FDA staff from CDRH. We respectfully suggest that FDA also seek input from a range of knowledgeable and interested individuals and groups including:

OIP-0119

CCP 1

* American Association for Clinical Chemistry (AACC)
* College of American Pathologists (CAP)
* Advanced Medical Technology Association (AdvaMed)

For your convenience, we have enclosed one original and two copies of this petition. Please feel free to contact me directly if you require further information or assistance.

Sincerely,

Lorraine Piestrak

Lorraine Piestrak
Regulatory Affairs/Compliance Manager

Phone: 302.631.6279
E mail: piestrlh@dadebehring.com
Fax : 302.631.6299

Table of Contents

Section One

Specification of the Type of Device for Which Reclassification is Requested

Cyclosporine immunoassay devices are intended for use in clinical laboratories as *in vitro* diagnostic tests for the quantitative measurement of Cyclosporine in patient whole blood samples.

Section Two

Statement of the Action Requested

It is requested that all *in vitro* diagnostic tests intended for the quantitative determination of Cyclosporine in patient whole blood and associated calibrators, be reclassified from the present class III (premarket approval) category, into class II (special controls). Additionally, we request that:

* All currently approved Cyclosporine tests, as well as all new tests which FDA determines are substantially equivalent, be classified as class II devices; and that

* The document, "Draft Guidance Criteria for Cyclosporine PMAs" be replaced by a 510(k) guidance document for Cyclosporine. An initial draft, included as part of this petition, should be reviewed and issued as a 510(k) Guidance Document that can become the basis for FDA's review of all new or revised Cyclosporine premarket notifications.

The request does not extend to *in vivo* diagnostic tests or reagents.

Section Three

Completed Supplemental Data Sheet

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE — FOOD AND DRUG ADMINISTRATION

SUPPLEMENTAL DATA SHEET

FORM APPROVED: OMB NO. 0910-0138
EXPIRATION DATE: January 1, 2000
(See OMB Statement on Page 2)

1. GENERIC TYPE OF DEVICE
In Vitro diagnostic device to measure Cyclosporine in human whole blood

2. ADVISORY PANEL
Immunology Devices

3. IS DEVICE AN IMPLANT ?
☐ Yes ☒ No

4. INDICATIONS FOR USE PRESCRIBED, RECOMMENDED, OR SUGGESTED IN THE DEVICE'S LABELING THAT WERE CONSIDERED BY THE ADVISORY PANEL

5. IDENTIFICATION OF ANY RISKS TO HEALTH PRESENTED BY DEVICE

General Risks to health are comparable to other Class II devices. Failure of the test to perform as intended may result in erroneous test results and thus mismanagement of the patient and/or delay of appropriate treatment.

Specific Hazards to Health	Characteristics or Features of Device Associated with Hazard
a.	a.
b.	b.
c.	c.
d.	d.

6. RECOMMENDED ADVISORY PANEL CLASSIFICATION AND PRIORITY

Classification Class II Priority (Class II or III Only) High

7. IF DEVICE IS AN IMPLANT, OR IS LIFE-SUSTAINING OR LIFE-SUPPORTING AND HAS BEEN CLASSIFIED IN A CATEGORY OTHER THAN CLASS III, EXPLAIN FULLY, THE REASONS FOR THE LOWER CLASSIFICATION WITH SUPPORTING DOCUMENTATION AND DATA

Not Applicable

8. SUMMARY OF INFORMATION, INCLUDING CLINICAL EXPERIENCE OR JUDGMENT, UPON WHICH CLASSIFICATION RECOMMENDATION IS BASED

See sections 6 and 9 of the Reclassification Petition

9. IDENTIFICATION OF ANY NEEDED RESTRICTIONS ON THE USE OF THE DEVICE

Prescription Use Device

10. IF DEVICE IS IN CLASS I, RECOMMEND WHETHER FDA SHOULD EXEMPT IT FROM

Justification / Comments

- ☐ a. Registration / Device Listing
- ☐ b. Premarket Notification
- ☐ c. Records and Reports
- ☐ d. Good Manufacturing Practice

11. EXISTING STANDARDS APPLICABLE TO THE DEVICE, DEVICE SUBASSEMBLIES *(Components)* OR DEVICE MATERIALS *(Parts and Accessories)*

DRAFT - "Guidance Criteria for Cyclosporine PMAs" - January 24, 1992

12. COMPLETE THIS FORM PURSUANT TO 21 CFR PART 860 AND SUBMIT TO:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Health and Industry Programs (HFZ-215)
1350 Piccard Drive
Rockville, MD 20850

OMB STATEMENT

Public reporting burden for this collection of information is estimated to average 1-2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer, Paperwork Reduction Project (0910-0138)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

(Please DO NOT RETURN this form to this address.)

An agency may not conduct or sponsor, and a person is not required to respond to , a collection of information unless it displays a currently valid OMB control number.

Section Four

Completed In Vitro Diagnostic Product Classification Questionnaire

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE — FOOD AND DRUG ADMINISTRATION

IN VITRO DIAGNOSTIC PRODUCT CLASSIFICATION QUESTIONNAIRE

FORM APPROVED: OMB NO. 0910-0138
EXPIRATION DATE: January 1, 2000
(See OMB Statement on Page 2)

PANEL MEMBER / PETITIONER: Dade Behring Inc.

DATE: 1/24/01

GENERIC TYPE OF DEVICE: In Vitro diagnostic test to measure cyclosporine in human whole blood

CLASSIFICATION RECOMMENDATION: Class II Special Controls

1. IS THE IN VITRO DIAGNOSTIC PRODUCT OR INFORMATION DERIVED FROM ITS USE POTENTIALLY HAZARDOUS TO LIFE, HEALTH, OR WELL BEING WHEN PUT TO ITS INTENDED USE ?	[X] YES [ ] NO	Go to Item 2.
2. IS THERE SUFFICIENT INFORMATION TO DETERMINE THAT GENERAL CONTROLS ARE SUFFICIENT TO PROVIDE REASONABLE ASSURANCE OF THE SAFETY AND EFFECTIVENESS OF THE DEVICE ?	[ ] YES [X] NO	If "Yes," classify in Class I If "No,", go to Item 3.
3a. CONSIDERING THE NATURE AND COMPLEXITY OF THE PRODUCT AND THE AVAILABLE SCIENTIFIC AND MEDICAL INFORMATION, IS THERE SUFFICIENT INFORMATION TO ESTABLISH A SPECIAL CONTROL OR SET OF SPECIAL CONTROLS TO PROVIDE REASONABLE ASSURANCE OF THE SAFETY AND EFFECTIVENESS OF THE DEVICE ?	[X] YES [ ] NO	If "Yes," Classify in Class II and go to Item 3b. If "No," Classify in Class III and go to Item 4a.
3b. CHECK THE SPECIAL CONTROL(S) NEEDED TO PROVIDE SUCH REASONABLE ASSURANCES *(If "YES" to Item 3a.)* [ ] Postmarket Surveillance [ ] Performance Standard(s) [X] Testing Guidelines [ ] Device Tracking [ ] Other *(Specify)* _____	[X] YES [ ] NO	
4a. IS A REGULATORY PERFORMANCE STANDARD NEEDED TO PROVIDE REASONABLE ASSURANCE OF THE SAFETY AND EFFECTIVENESS OF A CLASS II OR III DEVICE ?	[ ] YES [X] NO	
4b. IF "YES," TO ITEM 4a., IDENTIFY THE PRIORITY FOR ESTABLISHING SUCH A STANDARD. [ ] Low Priority [ ] Medium Priority [ ] High Priority	[X] NOT Applicable	
5. FOR A DEVICE RECOMMENDED FOR RECLASSIFICATION INTO CLASS II, SHOULD THE RECOMMENDED REGULATORY PERFORMANCE STANDARD BE IN PLACE *BEFORE* THE RECLASSIFICATION TAKES EFFECT ?	[ ] YES [ ] NO [X] NOT Applicable	
6. FOR A DEVICE RECOMMENDED FOR CLASSIFICATION / RECLASSIFICATION INTO CLASS III, IDENTIFY THE PRIORITY FOR REQUIRING PREMARKET APPROVAL APPLICATION (PMA) SUBMISSIONS. [ ] Low Priority [ ] Medium Priority [ ] High Priority [X] Not Applicable		

7a. CAN THERE OTHERWISE BE REASONABLE ASSURANCE OF ITS SAFETY AND EFFECTIVENESS WITHOUT RESTRICTIONS ON ITS SALE, DISTRIBUTION OR USE, BECAUSE OF ANY POTENTIALITY FOR HARMFUL EFFECT OR THE COLLATERAL MEASURES NECESSARY FOR THE DEVICE'S USE ?	☐ YES ☒ NO	If "Yes," go to Item 8. If "No," go to Item 7b.
7b. IDENTIFY THE NEEDED RESTRICTION(S) IF ITEM 7a. IS "NO." ☒ Only upon the written or oral authorization of a practitioner licensed by law to administer or use the device. ☐ Use only by persons with specific training or experience in its use. ☐ Use only in certain facilities. ☐ Other *(Specify):* _____		
8. COMPLETE THIS FORM PURSUANT TO 21 CFR PART 860 AND SUBMIT TO: Food and Drug Administration Center for Devices and Radiological Health Office of Health and Industry Programs (HFZ-215) 1350 Piccard Drive Rockville, MD 20850		

OMB STATEMENT

Public reporting burden for this collection of information is estimated to average 1-2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer, Paperwork Reduction Project (0910-0138)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

(Please **DO NOT** RETURN this form to this address.)

An agency may not conduct or sponsor, and a person is not required to respond to , a collection of information unless it displays a currently valid OMB control number.

Section Five

Statement of the Basis of Disagreement with the Present Classification

Following are the fundamental reasons on which our disagreement with the present classification is based. Our full statement of disagreement with the present classification, including supporting data, is included within Section Six of this petition.

1. The immunosuppressive qualities and effectiveness of Cyclosporine as well as its consequences have been very well characterized. Retaining the current class III designation for Cyclosporine assays is unnecessary and inappropriate given the current state of scientific knowledge and clinical practice in its use.

2. Cyclosporine has been used extensively over the last 15 to 20 years and Cyclosporine assays have been marketed since 1989. The physician monitors the concentration of Cyclosporine in whole blood and will adjust the dose of CSA to achieve an "optimal" whole blood concentration. Retaining the class III designation is not supported by any substantiated reasons relating to increased potential for risk or harm to patients.

3. Cyclosporine assays are analogous to other Class II *in vitro* test procedures. Class II is an appropriate regulatory category for Cyclosporine assays to provide for reasonable assurance that they are safe and effective.

Section Six

Full Statement of Reasons, Including Supporting Data Satisfying the Requirements of 21CFR 860.7 (Determination of Safety and Effectiveness), Why the Device should not be in its Present Class and How the Proposed Classification will Provide Reasonable Assurance of Safety and Effectiveness

Background

Cyclosporine A (CSA) is a cyclic undecapeptide of fungal origin that has potent immunosuppressive activity. It has a narrow therapeutic range and variable pharmacokinetics in humans, which makes monitoring of CSA mandatory[1]. It is widely used, often in conjunction with steroids and other drugs, to help prevent immunologic rejection of a number of different types of organ transplants. Therapeutic ranges have been established, primarily for heart, kidney, and liver allografts. CSA is also used for lung, bone marrow, and other allografts. The immunosuppressive qualities and effectiveness of CSA as well as its consequences have been very well characterized. Toxic levels and the effects of toxicity are well understood and there have been many reports in the literature on these effects. A host of studies have been undertaken, articles written, and scenarios investigated regarding the use of CSA. In general, the benefits of using CSA and its potential toxicity outweigh the consequences of not using CSA in the field of transplantation medicine.

The following is a quote from Jon Kobashigawa, MD, Medical Director, University of California/Los Angeles (UCLA) Heart Transplant Program, UCLA Medical Center: "Cyclosporine has been used extensively over the past 20 years and has been demonstrated to improve survival in all solid organ transplants. Most transplant physicians are experienced with this medication and are aware of side effects and drug-drug interactions."[2]

Rationale for Reclassification

We believe that a reclassification from class III (PMA) to Class II (510(k)) status by the Food and Drug Administration (FDA) should be considered for CSA assays. This belief is based on the following factors:

1. There are a number of assays available and in wide use for the quantitative measurement of CSA. These include High Pressure Liquid Chromatography (HPLC), Radioimmunoassay (RIA), Fluorescent Polarization Immuno Assay (FPIA, both monoclonal and polyclonal), and Enzyme multiplied Immunoassay Technique (EMIT) technologies. HPLC and FPIA are the two most widely used methods. The advantages and disadvantages of these methods will be discussed in the "assays currently in use" section of this report.
2. CSA has been in wide use since approximately 1980, and the pharmacokinetics, therapeutic ranges and toxic effects of CSA are well known. A strong case has been made for the safety and efficacy of this drug. Cyclosporine A has remained the primary immunosuppressant drug of choice

for human allografts despite the development and use of newer immunosuppressants such as tacrolimus (FK (506)), sirolimus, and mycophenolate mofetil (MMF).

3. Quality assurance and quality control programs for CSA assays have been developed and are readily available. Whole blood QC products are available to monitor cyclosporine A performance. The College of American Pathologists offers a survey of immunosuppressant drugs including CSA (series CS) that consists of two samples, 3 times per year. In 2000, 471 labs participated in this program.

A vast body of literature has been written over the last 15-20 years that deals with studies related to cyclosporine and its use. These studies have included a variety of topics such as: appropriate dose based on the organ type, appropriate dose to prevent renal toxicity yet maintain immunosuppression, concomitant administration with steroids and other immunosuppressive drugs, case studies focused on age, race and sex demographics, dose versus whole blood levels, monoclonal versus polyclonal assays, and many more topics. Based upon the size of the knowledge base on CSA as well as the other factors stated above, we believe that detailed clinical studies (required in a PMA submission) are no longer necessary and that proof of analytical performance in comparison to a predicate device (510(k)) is now appropriate for CSA assays.

Assays Currently in Use

A number of assays for the quantitation of CSA are available, however, a definitive method or a reference method according to the International Federation of Clinical Chemistry criteria is not yet available.[3] A carefully validated high-performance liquid chromatography (HPLC) assay that specifically measures the parent drug has been suggested as a reference procedure for CSA measurement[4] by a consensus panel of experts. Abbott Laboratories FPIA assays are available, both in polyclonal (pFPIA, nonspecific for the parent compound CSA) and monoclonal (mFPIA, specific for the parent compound CSA) formats. The DiaSorin CYCLO-Trac SP radioimmunoassay (m ^{125}I-RIA) is also in use, as well as the Syva enzyme multiplied immunoassay technique (EMIT).

HPLC is highly specific for the parent drug while RIA and pFPIA assays are nonspecific, with metabolites contributing to reported CSA values to varying degrees. A major active metabolite of CSA, M17, demonstrates 45% and 75% cross-reactivity, with the RIA and pFPIA assays[5], respectively. The mean overestimation of CSA concentrations compared with HPLC due to the presence of cross-reactivity with CSA metabolites ranged from 8 to 30% with EMIT, 24 to 48% with mFPIA, and 22 to 30% with m ^{125}I-RIA. Because CSA metabolites do not significantly contribute to overall immunosuppression, the use of less specific assays in such patients may result in the physician underdosing the patient.[4]

A study performed at the University of Cincinnati Medical Center examined the clinical correlation of CSA-specific and nonspecific assays in stable renal transplants, acute rejection and CSA nephrotoxicity. They concluded that the mean CSA levels determined by HPLC were significantly different in patients with acute CSA toxicity and patients with acute rejection when compared to those with stable renal function. The

mean CSA levels as measured by FPIA were not significantly different between the three groups. However, a larger percentage of patients with rejection were sub-therapeutic when measured by HPLC, while a higher proportion of patients with nephrotoxicity were above the therapeutic range measured by FPIA.[6] This suggests that co-measurement of metabolites as well as parent drug can be misleading when attempting to determine toxic levels or monitor for adequate immunosuppressive levels.

Therapeutic Ranges and Pharmacokinetics

The most frequently quoted general dose for CSA is 4 mg/kg/day. This dose, however, is varied for a number of reasons. Co-administration with other drugs such as steroids, Micophenolate Mofetil, (MMF), (also known as micophenolic acid, MPA), and a host of other non-immunosuppression related drugs could cause a need for higher or lower doses of CSA to maintain immunosuppression or prevent toxicity.

A major laboratory medical textbook, "Clinical Guide to Laboratory Tests" by Tietz, references several studies that were performed in 1986 to establish therapeutic ranges for whole blood CSA determinations performed by HPLC. For HPLC assays, Tietz suggests that a range of 100-200 ng/mL drawn 24 hours after dose is effective for renal transplant. For cardiac transplant, a range of 250-500 ng/mL is therapeutic, and for hepatic transplant, a range of 100-400 ng/mL is suggested. These ranges are for samples drawn 12 hours after dose.[7, 8] These ranges are remarkably similar to current suggested ranges published 10 years later[4], which have undergone only minor adjustments. This supports the suggestion that the therapeutic ranges are well understood.

A more recent publication, The Lake Louise Consensus Conference on Cyclosporin Monitoring in Organ Transplantation: Report of the Consensus Panel[4], lists the suggested therapeutic ranges from 35 transplant centers. Table 2 from this publication lists therapeutic ranges for cyclosporine stratified according to transplanted organ, immunosuppressive regimen, and induction/maintenance therapy and immunoassay technique (Table 2 is reproduced at the end of Section 6). Almost all institutions recommend twice daily (b.i.d) dosage patterns, with blood samples drawn at 12 hours post-dose (trough). The Lake Louise ranges agree with the general nature of the earlier published ranges. These are well established in the literature and in practice, and new assays that show equivalence to HPLC in this range of values can be used interchangeably.

Adverse Side Effects and Dose Related Issues

Of basic consideration with the use of cyclosporine A are adverse side effects. The main adverse reaction is dose-related nephrotoxicity. This is not a minor issue as the majority of transplants are renal. Other adverse effects include hirsutism, gingival hyperplasia, hepatotoxicity, hypertension, anaphylaxis, neurotoxicity, diabetes and lymphoproliferative disorders[5]. Enterohepatic recycling has been reported for CSA use.[5] Higher doses and whole blood values are maintained for heart and liver allografts, potentially putting renal function at risk. Low whole blood concentrations of cyclosporine are ineffective in providing adequate immunosuppression. Low values might be caused by an individual's capacity to metabolize CSA, non-compliance, co-administration with other drugs or inadequate dosage. Based on the consequences of whole blood concentrations of CSA that are either too high or too low, the physician monitors the

concentration of CSA and will adjust the dose of CSA to achieve an "optimal" whole blood concentration.

There are a number of studies that support the safety and effectiveness of using CSA versus the consequences of not using it. Despite the described consequences of nephrotoxicity, one study shows that the majority of renal-transplant patients tolerate long-term cyclosporine therapy without evidence of progressive toxic nephropathies. Graft failure is most often due to rejection rather than CSA toxicity.[9] Another study concludes that in pediatric renal transplant patients, CSA doses are routinely decreased following renal transplantation, and that lower doses are associated with rejection episodes, particularly late rejections. They conclude that CSA doses of pediatric recipients of renal transplants should not be tapered.[10] A study performed on cardiac allograft recipients in the UK concludes that CSA trough levels above 200 ng/mL in the first 2 years after heart transplantation are associated with reduced cellular rejection without deleterious effects on renal function.[11]

Further support for the benefit of higher doses of CSA verses the consequences of renal nephrotoxicity is reported in a study done by the North American Pediatric Renal Transplant Cooperative[12]. They concluded that a higher maintenance CSA dose decreases the risk of graft failure in North American children. The maintenance 12-month dose in living donor graft recipients increased from 6.4 mg/kg/day for patients who had transplants done in 1987 to 7.9 mg/kg/day for patients who had transplants done in 1992. Among cadaver donor graft recipients, the mean 12-month maintenance dose increased from 6.4 mg/kg/day in 1987 to 7.8 mg/kg/day in 1992. They reported that the hazard of graft failure was reduced by 5 to 6% for each incremental increase of 1 mg/kg/day in the maintenance dose of CSA for both living and cadaver donor source transplants.[12]

A study performed at Tokyo Metropolitan Children's Hospital concluded that the mean blood trough levels of CSA were significantly lower in patients who developed an acute rejection during the first week following transplantation as compared to those without rejection episodes during the same period[13]. They report that since the introduction of CSA has made it difficult to detect acute rejections by clinical findings alone, such as blood chemistry or urinalysis, the role of routine allograft biopsies is very important in renal transplantation. It seems likely that low blood levels and/or acute decline of cyclosporine during early post transplant period could increase the possibility of episodes of acute rejection. Since it is well documented that CSA induces less renal parenchymal damages in children, the blood trough levels of the drug should be kept at between 200 and 300 ng/mL within 5 weeks of transplantation in order to reduce the risk of acute rejections and to improve the chance of long-term allograft survival.[10]

It is difficult to separate issues of adverse effects from discussions of dose and therapeutic ranges, and most discussions include aspects of both, as evidenced by some of the previously cited references.

Quality Assurance and Proficiency Testing

Several consensus documents on CSA monitoring have recommended that laboratories should participate in external quality assessment programs.[14, 15] It is also mandatory that laboratories offering a service for measurement of cyclosporine have a system in place to verify the day-to-day consistency of their results using at least one measure of internal quality control.[4] A commercial, whole blood quality control product

is manufactured by Bio-Rad Diagnostics Laboratory Group, Irvine, California.[16] This is a three level whole blood control that contains cyclosporine and tacrolimus. Ranges are published for pFPIA, mFPIA, HPLC, cloned enzyme donor immunotechnique (CEDIA®), EMIT, and RIA. There is a low, mid and high level control. The product is provided in lyophilized form, and is stable for 14 days once reconstituted and stored at 2-8° C, or 30 days if frozen. This control is now in fairly wide use by those choosing to run CSA in their laboratories.

The College of American Pathologists (CAP) has included in their inventory a survey series (CS) that includes both cyclosporine A and tacrolimus. As mentioned earlier in this report, there are two challenges per set, 3 sets per year issued. The latest survey had 471 laboratories reporting for CSA, and instruments reporting included pFPIA, mFPIA, Cyclo-Trac RIA, HPLC, and EMIT.[17]

These programs being in place can add a measure of assurance that when new assays are developed, they can provide several points of comparison to the assays currently in use in the laboratory, as well as demonstrate the differences in the measurement of metabolites, if present, in the various QC and Survey samples.

Conclusions

We believe that, given the length of time CSA has been in use, the overwhelming number of studies that have been done on CSA, the fact that safety and efficacy of the drug are well established, quality assurance and proficiency systems are in place, and that thorough studies of the therapeutic ranges required for CSA therapy have been conducted, a justification for reclassification to 510(k) status for Cyclosporine A assays is warranted. Comparison of analytical performance to a predicate device is appropriate to validate the performance of a new CSA assay.

Bibliography

1. Yee GC, Salomon DR. Cyclosporine. In: Evans WE, Schentag JJ, Jusko WJ, Eds. Applied Pharmacokinetics, Principles of therapeutic drug monitoring. 3rd ed. Vancouver, WA: Applied Therapeutics Inc., 1992; 28:1-40.
2. Jon Kobashigawa, MD, Medscape.com, immunosuppression in Heart Transplantation, Ask the Experts, 11-30-00.
3. Buttner J, Borth R, Boutwell JH, Broughton PMG, Bowyer RC. Recommendation on quality control in clinical chemistry, Part 2. Assessment of analytical methods for routine use. J Clin Chem Clin Biochem 1980;18:78-88
4. Oellerich M, Armstrong VW, Kahan B, Shaw L, Holt DW, Yatscoff R, Lindholm A, Halloran P, Gallicano K, Wonigeit K, Schutz E, Schran H, Annesley T, Lake Louise Consensus Conference on Cyclosporin Monitoring in organ transplantation, Report of the Consensus Panel. Therapeutic Drug Monitoring, 17:642-654 1995
5. Tietz, Norbert W, Clinical Guide to Laboratory Tests, 2nd. Edition, pp 704-706, 1990.
6. Schroeder TJ; Sridhar N; Pesce AJ; Alexander JW; First MR; University of Cincinnati Medical Center, Ohio. Ther Drug Monit 1993 June; 15(3): 190-4.
7. Evans, W.E., Schentag, J.J., and Jusko, W.J. (Eds.): Applied Pharmacokinetics – Principles of Therapeutic Drug Monitoring, 2nd ed. San Francisco, Applied Therapeutics, Inc., 1986
8. Ptachcinski, R.J., Venkataramanan, R., and Burckart, G.J.: Clinical Pharmacokinetics of cyclosporin. Clin. Pharmacokinet. *11*:107-132, 1986.
9. Burke JF Jr; Pirsch JD; Ramos EL; Salomon DR; Stablein DM; Van Buren DH; West JC, N.Engl J Med 1994 Aug 11; 331 (6): 358-63.
10. Harmon, WE; Sullivan EK; Affiliation: Division of Pediatric Nephrology, Harvard Medical School, Children's Hospital, Boston, Mass. Kidney Int Suppl 1993 Oct; 43:S50-5.
11. El Gamel A; Keevil B; Rahman A; Campbell C; Deiraniya A; Yonan N, Wythenshawe Hospital, Manchester, UK, J Heart Lung Transplant 1997 Mar; 16(3): 268-74.
12. Tejani A; Sullivan EK; Department of Pediatrics, State University of New York, Brooklyn, NY, J Am Soc Nephrol 1996, Apr;7(4) ;550-5
13. Sakuma T; Ogawa O; Kawamura T; Hasegawa A; Kamidono S; Tokyo Metropolitan Children's Hospital, Nippon Hinyokika Gakkai Zasshi 1995 Sep;86 (9) ;1450-9
14. Morris RG, Tett SE, Ray JE. Cyclosporine A monitoring in Australia: consensus recommendations. Therapeutic Drug Monitoring 1994: 16:570-6.
15. Shaw LM, Yatscoff RW, Bowers LD, et al. Canadian consensus meeting on cyclosporine monitoring: report of the consensus panel. Clin Chem 1990; 36:1841-6.
16. BioRad Lyhpochek® Whole Blood Control, Levels 1,2,and 3. Package insert, printed August 1998.
17. College of American Pathologist, Series (CS 01, 02) survey summary report, 2000.

TABLE 2. *Therapeutic ranges for cyclosporin stratified according to Transplanted organ, immunosuppressive regimen, induction/maintenance therapy and immunoassay technique*

Method	Kidney Triple therapy	Heart Triple therapy	Liver Triple therapy	Liver Double therapy
Induction[a]				
HPLC	150-225 (5)	250-325 (1)	225-300 (4)	
mFPIA	250-375 (6)	300-400 (3)	250-313 (8)	300-375 (2)
m^{125}I-RIA	160-200 (5)	250-325 (2)	250-300 (3)	
EMIT	125-200 (2)	275-375 (2)		125-200 (2)
Maintenance				
HPLC	100-150 (5)	125-175 (2)	100-150 (6)	100-150 (1)
mFPIA	100-250 (8)	150-250 (5)	135-200 (8)	150-250 (3)
m^{125}I-RIA	75-150 (5)	90-160 (2)	150-238 (4)	
EMIT	75-150 (2)			75-150 (2)

The ranges are the median values (μg/L) for the minimum and maximum trough cyclosporin concentrations (whole blood) calculated from the data of those centers listed in Table 1 that fitted the particular category. The number of contributing centers is given in parentheses.

HPLC, high-performance liquid chromatography; mFPIA, monoclonal antibody fluorescence polarization immunoassay; m^{125}I-RIA, monoclonal antibody INCSTAR radioimmunoassay; EMIT, enzyme multiplied immunoassay technique.

[a]In some centers, anti-lymphocyte antibodies were also included as part of induction therapy.

Section Seven

Representative Data and Information Which are Unfavorable to the Petitioner's Request

As described and supported by this petition, cyclosporine assays present the same type and level of risk to health as other class II *in vitro* diagnostic assays. The failure of a test to perform as intended may result in erroneous test results, and in either patient mis-management or delay of appropriate treatment. Because class II IVDs are intrinsically safe and because they are seldom used as the sole basis for medical decision making, events such as patient mismanagement or delay of appropriate treatment are rare.

An online search of CDRH's Medical Device Reporting (MDR) database was conducted to obtain information on Cyclosporine devices that may have malfunctioned or caused a death or serious injury during the years 1992 through 1996. Twenty-one entries were found. Six were related to Cyclosporine assays. Two of the six, were operator injuries (finger cuts from vials). The remaining four were related to incorrect patient results and in all four instances there was no report of injury to the patients.

An online search of CDRH's Manufacturer and User Facility Device Experience Database (MAUDE) was conducted to obtain information on adverse events involving Cyclosporine. This database consists of all voluntary reports since June, 1993, user facility reports since 1991, distributor reports since 1993, and manufacturer reports since August, 1996. Twenty-two entries were found. None were related to Cyclosporine assays.

Section Eight

If the Petition is Based on New Information, Provide a Summary of the Information

As described in Section Six of this petition, there is significant empirical scientific data and clinical experience accumulated over the last 15 to 20 years regarding Cyclosporine safety and efficacy. The accumulated body of research on the use and measurement of Cyclosporine provides a multitude of published peer reviewed articles.

See Section Nine for Supporting Articles, References.

Section Nine

Supporting Articles, References

A vast number of articles covering CSA and aspects of its use are available to an investigator of this immunosuppressive agent. We have selected several articles that are examples of the knowledge base on this drug. They cover topics relevant to the critical issues around CSA, such as specificity of the various assays and differences between the assays and the implications of those differences. The consensus documents summarize the shared body of knowledge on CSA. Over 530 references are cited in these seven articles which span a period from 1987 to present. The articles fall into two general categories: Consensus documents and methodological comparisons. The articles are included in Appendix I.

Consensus Documents

1. Shaw LM, Bowers L, Freeman D, Moyer T, Sanghiv A, Seltman H, Venkataramanan R. Critical Issues in Cyclosporine Monitoring: Report of the Task Force on Cyclosporine Monitoring. *Clinical Chemistry* 33/7, 1269-1288 (1987)
2. Shaw LM, Yatscoff RW, Bowers LD, Freeman DJ, Jeffery JR, Keown PA, McGilveray IJ, Rosano TG, Wong PY. Canadian Consensus Meeting on Cyclosporine Monitoring: Report of the Consensus Panel. *Clinical Chemistry* 36/10, 1841-1846 (1990).
3. Holt DW, Johnston A, Roberts NB, Tredger JM, Trull AK. Methodological and clinical aspects of cyclosporin monitoring: report of the Association of Clinical Biochemists task force. *Ann Clin Biochem* 1994; **31**: 420-446.
4. Oellerich M, Armstrong VW, Kahan B, Shaw L, Holt DW, Yatscoff R, Lindholm A, Halloran P, Gallicano K, Wonigeit K, Schütz E, Schran H, Annesley T. Lake Louise Consensus Conference on Cyclosporin Monitoring in Organ Transplantation: Report of the Consensus Panel *Therapeutic Drug Monitoring* 17:642-654 1995.

Methodological Comparisons

5. Schütz E, Svinarov D, Shipkova M, Niedmann PD, Armstrong VW, Wieland E, Oellerich M. Cyclosporin whole blood immunoassays (AxSYM, CEDIA, and Emit): a critical overview of performance characteristics and comparison with HPLC. *Clinical Chemistry* 44/10, 2158-2164 (1998).
6. Murthy JN, Yatscoff RW, Soldin SJ. Cyclosporine Metabolite Cross-Reactivity in Different Cyclosporine Assays *Clinical Biochemistry*, Vol. 31, No. 3, 159-163, 1998
7. Steimer W. Performance and Specificity of Monoclonal Immunoassays for Cyclosporine Monitoring: How Specific Is Specific? *Clinical Chemistry* 45/3, 371-381 (1999).

Section Ten

Financial certification/disclosure

No clinical investigators were contracted to supply data for this petition, therefore this section is not applicable.