Draft Only
S/F IVD

AUG 3 1992

Note from: Ron Johnson, Director
Office of Compliance and Surveillance

As we previously discussed, attached is our DRAFT Compliance Policy Guide entitled, "Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation".

This DRAFT document sets forth FDA's proposed policy and requirements on how unapproved in-vitro products may be distributed for research and investigational purposes. It also identifies a very specific, limited group of products which have become the "standard of medical care", which FDA will allow to remain available for a specified period of time, if properly labeled, while manufacturers conduct studies to firmly establish the product's safety and efficacy.

We have provided a copy of this DRAFT document for your information. Should you have any comments, please submit them by September 1, 1992, to the attention of Mr. James Lucas of our Regulatory Guidance Branch at 1390 Piccard Drive, Rockville, Maryland 20850, HFZ-323.

DRAFT

FOOD AND DRUG ADMINISTRATION
COMPLIANCE POLICY GUIDE

GUIDE _____

CHAPTER 24 - Devices

SUBJECT: Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation.

BACKGROUND:

Numerous unapproved in vitro diagnostic devices (IVD) labeled for investigational or research purposes are being promoted, distributed, and used for purposes other than investigation or research. These IVD products are often Class III products requiring an approved application for Premarket Approval (PMA) before they can be commercially marketed. The commercialization of these unproven diagnostic tests has resulted in the widespread use of test results, from devices whose performance characteristics have not been established, as a basis for patient diagnosis or clinical evaluation. These unproven diagnostic tests, without adequate controls in place, could have potential serious adverse health consequences to unknowing patients.

In the past, attempts to justify the commercialization of these unproven IVD's for human use have been made by selectively interpreting and not adequately applying exemptions found in Part 812 - Investigational Device Exemptions, Section 812.2(c)(3). This section grants an exemption to IVD's if the sponsor of the diagnostic device complies with all applicable requirements identified within this section. One part of these requirements is that if the IVD is to be used in a diagnostic procedure, this procedure must be confirmed by another medically established diagnostic product or procedure. Use of an unproven IVD product in a diagnostic procedure without confirmation by a proven product or procedure, would be a violation of the Federal Food, Drug, and Cosmetic Act (the Act) and subject the unapproved device to regulatory action.

In order to preclude further violations and problems as identified above, the FDA deems it necessary that a Certification Program be implemented. See Attachments B, C, and D. This program is designed to demonstrate compliance with the investigational/research products and establish an audit trail of the use of the product from the manufacturer or importer to the end user.

POLICY:

The exemption granted to IVD's in Part 812 does not in any way relieve the sponsor of the IVD device from the obligation of exercising due diligence by establishing distribution controls to assure that use of the IVD device is consistent with the status of the product, i.e. for investigation or research purposes.

Sponsors have an obligation to exercise due diligence in controlling the distribution of investigational and research IVD products. Attachments B, C, and D provide guidance for the controlled distribution of these investigational and research devices. These guidelines should not be considered as the only way to comply, but they do contain key elements acceptable to the FDA to demonstrate a firm's compliance with IVD test systems in the investigational and research phase of development. A firm may adopt these suggestions or develop its own procedures for assuring that research and investigational IVD products are used as intended. The determining factor in this certification program is that the responsible firm makes a concerted effort to assure that due diligence is exercised over the use of unproven IVD products, in that they are not sold or diverted for an unintended or unapproved use. Manufacturers of unapproved IVD products are required to follow the guidance provided in Attachments B, C, and D, or an equivalent system that will provide a comparable level of product certification.

REGULATORY GUIDANCE:

Exemption: IVD Devices Essential to Public Health

As a result of the widespread commercialization of unapproved products, several have gained recognition in the healthcare community as the standard of care in diagnosing and/or monitoring certain serious disease conditions such as cancer. FDA has determined immediate withdrawal of such products or severe restrictions on their access through limited investigational or research studies would not be in the best interests of public health.

Therefore, after consulting with private and public medical and scientific experts, FDA has determined that availability of these specific products should be assured while they undergo scientific studies to obtain sufficient data in support of an appropriate marketing application. This accommodation will allow the IVD devices identified in Attachment A to remain on the market until appropriate product approval submissions are made by the manufacturers. This accommodation shall not be extended beyond thirty (30) months (, 1995), from the date of the Federal Register notice of availability of this Compliance Policy Guide. During this period manufacturers are expected to gather sufficient validation data to provide the basis for a product approval application. Manufacturers/sponsors of these products must conduct appropriate studies intended to gather safety and efficacy data. Failure to collect sufficient data to support the safety and efficacy of these products by the expiration of this accommodation period, will result in the removal of that product from commerce at that time. Firms are expected to make a good faith effort to conduct studies during this

accommodation period. If it is determined that manufacturers of these devices are not undertaking such studies, this accommodation may be suspended, thereby requiring the sponsor to remove all unapproved products from the marketplace and be subject to other regulatory action.

Physicians and medical professionals will be allowed to use the IVD devices identified in Attachment A, which are considered the current standard of care essential to patient health and the practice of medicine.

It is the responsibility of the manufacturer or importer to assure that these products be labeled appropriately as "Unapproved products being temporarily provided for essential health purposes." Additionally, the manufacturer/importer shall be responsible for assuring that the laboratory informs the physician or other health care professional that the test results being reported were obtained from an unapproved product that is being temporarily provided for essential health purposes. If the device labeling or device test results do not conform to the above requirements, the device may be removed from the accommodation list, thereby stopping all distribution and use of the product, and legal action may be taken against the product and/or responsible party. Consult the Regulatory Guidance Branch, HFZ-323, for guidance when any investigation confirms this situation.

Written procedures shall be in effect which provides for the creation of an audit trail from the manufacturer or importer to the end-user of the IVD device. Additionally, when a product listed in Attachment A is approved for its accommodated use, all additional products on the Accommodation List for that intended use will be removed.

SUBSEQUENT ACCOMMODATIONS:

Attachment A includes unapproved products which are currently considered the "standard of care." Subsequent to the publication of the Federal Register notice of availability of this CPG, no IVD devices will be added to the accommodation list. Such products are subject to the same regulatory requirements as any unapproved medical device not identified in Attachment A.

OTHER CONSIDERATIONS:

It has come to the attention of FDA that laboratories have been manufacturing, "home brew" products, either from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes. These products are subject to the same regulatory requirements as any unapproved medical device not identified in Attachment A.

REGULATORY ACTION GUIDANCE:

If it is determined that a manufacturer or importer of IVD's labeled "for research use only" or "for investigational use only" is not complying with the Certification Program as described, or a comparable certification method or procedure, the district should follow this sequence:

1. Conduct an investigation to determine if violations of the Act exist. The investigation should start at the manufacturer level and move on to the distributor, laboratory, and finally the investigator/researcher level, stopping at the level where any violations are first encountered, If violations are suspected at one particular level, the investigation should start at that level. With respect to the Certification Program Requirements, in brief, the investigation shall determine:

   - whether the device labeling is in compliance
   - whether the device is being used consistent with its intended use (for investigational devices, see also 21 CFR 812.2(c)(3)(iv)), and
   - whether the requirements for Clinical Protocol, Institutional Review Board (IRB) approval, and Informed Consent (as necessary) have been met for investigational use devices only

2. If violations are found, submit a Warning Letter recommendation to CDRH for concurrence. Use Specimen Charges 1,2,3 and/or 4 as appropriate.

3. If the manufacturer provides the district clear assurance that:

   a. it will not commercially market the device prior to receiving an approved PMA or 510(k) determination from FDA or;

b. it will not distribute the device for investigational or research use without complying with the Certification Program and/or* will correct the violation(s) noted in the Warning Letter, and

c. it will voluntarily recall or correct any device(s) in the marketplace,

further action should be held in abeyance pending confirmation of these voluntary corrections.

* Note: If a firm corrects the violations, but does not implement a Certification Program, controls will not be in place to preclude further violations. In such case, the firm should be re-inspected, as necessary, to determine if violations exist. If violations are found, the district should consider submitting an injunction recommendation to CDRH, whereby Certification-like controls would be included in any Consent Decree.

4. If the firm fails to provide the district with adequate assurance of conditions a. or b. and c.,

   a. The district should submit a seizure recommendation to Division of Compliance and Operations, HFC-210, (DCMO) if the device(s) in question are Class I and II devices.

   b. For Class III devices, Consult CPG 7124.30 for information on using Direct Reference Authority if the device(s) is Class III.

SPECIMEN CHARGES:

That the article of device is adulterated within the meaning of the Act as follows:

1. 21 U.S.C. 351(f)(1)(B), in that it is classified as Class III device under 21 U.S.C. 360c(f) and it does not have an approved premarket application in effect pursuant to 21 U.S.C. 360e.

That the article of device is misbranded within the meaning of the Act as follows:

2. 21 U.S.C. 352(o) in that a notice or other information respecting the device was not provided to the Food and Drug Administration at least 90 days prior to its introduction into interstate commerce, as required by 21 U.S.C. 360(k), and an order finding the device substantially equivalent did not issue, as required by 21 U.S.C. 360c(i)(1)(A). (use only when a 510(k) was not submitted for a post enactment device)

3. 21 U.S.C. 352(a) in that the labeling for the device contains statements which are false, misleading, or otherwise contrary to fact.*

4. 21 U.S.C. 352(f)(1) in that the labeling for the device fails to bear adequate directions for use for the purposes for which it is intended because adequate directions cannot be written for such purposes.

* Specific labeling and statements are sometimes included in the charge.

ACCOMODATION LIST OF MONOCLONAL ANTIBODIES: FDA APPROVAL STATUS BY ANALYTE AND INTENDED USE				
NO.	ANALYTE	IMMUNOCYTOCHEMISTRY APPROVED USE(S)	FLOW CYTOMETRY APPROVED USE(S)	SERUM MARKER (STAND ALONE) APPROVED USE(S)
1.	Actin			
2.	Alpha-Fetoprotein			Neural tube defects & Tumor marker for testicular cancer (non-seminoma)
3.	B72.3			
4 a.	Breast CA (15-3)			
4 b.	CA 27-29			
5.	CA 19-9			
6.	CA 72-4			
7.	Calcitonin			Parathyroid disease DX & RX
8.	Carcinoembryonic Antigen			Colorectal cancer
9.	CD 2 (T Cells)		CCT11 (SPC 13 Pt 2H9) OKT 11 (OKT11A) Sigma anti-CD2	
10.	CD 3 (T cells)		Leu 4 (clone SK7) CC CD3 (UCHT1) CCT3 (SCFIRW2-8C8) OKT 3 (OKT3) SIGMA anti-CD3	

58.	Vimentin			
59.	UCHL-1			

48.	PgR-ICA Monoclonal			DX & RX of disorders of anterior pituitary gland or hypothalamus of brain
49.	Prolactin			
50.	Progesterone Receptor Antigen			Aid in prediction of patient response to hormonal RX & prognosis & management of breast cancer patients
51.	Prostate Specific Antigen (PSA)			Monitoring prostate cancer (but not for screening)
52.	Prostatic Acid Phosphatase			To measure activity of acid phosphatase
53.	S-100 Protein			
54.	Somatostatin			
55.	Synaptophysin			
56.	Terminal Deoxynucleoidyl Transferase (TdT)			
57.	Thyroglobulin			DX & Rx of thyroid disease

38.	Human Chorionic Gonadotropin (HCG)			Early detection of pregnancy. Not approved for dx & prognosis of tumors (cancers)
39.	IMx SCC			
40.	Ki-67			
41.	L26			
42.	Leu 22			
43.	Luteinizing Hormone (LH)			DX & RX of gonadal dysfunction
44.	Myelin Basic Protein			
45.	Ovarian CA (CA 125)			(second look) Ovarian cancer
46.	Placental Alkaline Phosphatase			
47.	Placental Lacto			

28.	CD 38 (Thymocytes; activated T; plasma cells)			
29.	CD 45 (Pan leukocytes; LCA)		anti-leukocyte (H Le-1); (clone 2D1)	
30.	Chromogranin			
31.	Cytokeratins	MAK 6 CAM 5.0		
32.	Cytomegalovirus (About 70 or more tests for CMV have been cleared by FDA)	Tissue specimens		Viral identification on patient samples and from viral culture
33.	Desmin			
34.	Epithelial Membrane Antigen			
35.	Factor VIII			
36.	Glial Fibrillar			
37.	HMB45 (Melanoma)			

20.	CD 19 (Pan B cell, pre-B ALL)		anti-Leu 12 (4G7) CCB4(89B) Sigma anti-CD19	
21.	CD 20 (Pan B cell)		CCB1(H299)	
22.	CD 21 (Resting B Cells (C3d, EBV receptor)			
23.	CD 22 (Resting B cells, hairy cell leukemia cells)			
24.	CD 23 (IgE Fc receptor 11; altereded B)			
25.	CD 30 (activated T & B cells, Reed-Sternberg cells)			
26.	CD 33 (Early myeloid progenitors; myeloid cells; AML)			
27.	CD 34 (Myeloid progenitors)			

11.	CD4 (T subset)		anti-Leu 3a (clone SK3) CCT4 (SFC112T4D11) OKT 4 (OKT4)	
12.	CD 5 (T, B subset)		CCT1 (SCF124T6G12) Sigma anti-CD5	
13.	CD 7 (T cell)			
14.	CD 8 (T subset)		anti-Leu 2 a (clone SK1) CCT8 (SFC121thy2D3) OKT8 (OKT8A)	
15.	CD 10 (Granulocyte and CALLA, Common Acute Lymphoblastic Leukemia only)			
16.	CD11b (Granulocytes, monocytes, LCL (NK), C3b, receptor			
17.	CD 13 (Monocytes, granulocytes, CFU-C)			
	CD 14 (Monocytes, few granulocytes)		anti-LeuM3 (clone M0p9) CC My 4 (322A-1) CCM02	
18.	CD 15 (granulocytes, some monocytes)			
19.	CD 16 IgG, Fc receptor III, NK cells, granulocytes CD16 & CD 56)		anti-Leu 11c (B73.1) + Leu19 (My31)	

DRAFT

DRAFT

ATTACHMENT B

Certification Program For In Vitro Diagnostic Devices Labeled "For Investigational Use Only"

Manufacturers and importers must establish in writing, prior to distribution, a certification program as identified below for all in vitro diagnostic devices, labeled "For Investigational Use Only", that are being distributed under the in vitro diagnostic device exemption provision, 21 CFR 812.2(c)(3), of the IDE regulation. For purposes of this program, "For Investigational Use Only" is defined as all uses intended to determine the safety or effectiveness of the device. The manufacturer or importer is responsible for making or assuring this determination. The program should be designed to demonstrate compliance with the IDE Regulation (21 CFR 812.2(c)(3)) and applicable requirements of the Federal Food, Drug, and Cosmetic Act (Act) and associated regulations. The program should provide at all levels of use in the distribution chain, that the devices are appropriately labeled, and used consistent with their intended use, distributed in accordance with the provisions of an established clinical protocol, and used only after Institutional Review Board (IRB) approval and Informed Consent (as necessary) have been obtained. Test results are to be provided to the sponsor in accordance with the clinical protocol for Manufacturer or Importer-Sponsored Studies. Such test results need not necessarily be provided to the manufacturer or importer for independent Investigator-Sponsored Studies, which studies are discussed under Attachment D.

Level	Certification Program Items
Manufacturer or Importer	- Devices will only be distributed to or utilized by those individuals/laboratories/health care facilities who have provided written certification of compliance with this program. - Discontinue distribution to those who have failed to comply with the certification program. - Provide all certified distributors and laboratories with an updated list of certified distributors, laboratories, and investigators, as necessary, to keep the list current. - All written, printed, or graphic matter used to identify or promote the device shall comply with 21 CFR 809.10(c)(2)(ii), and shall state "For use only by distributors, laboratories, and investigators who are certified by (insert manufacturer's or importer's name and address)."

- Manufacturers or importers shall maintain copies of all written and signed certification documents, i.e., manufacturer or importer, distributor, laboratory, and investigator certifications.

- Manufacturers or importers must use "due diligence" to assure compliance with the certification program. For example, toward the end of any scientific study, the manufacturer or importer should determine whether the study will be completed within the time specified, and, if so, discontinue distribution at that time.

- Written procedures shall be in effect which provides for the creation of an audit trail from the manufacturer to the end-user.

Distributor

- Devices will only be distributed to or utilized by other distributors, laboratories, and investigators certified by the manufacturer or importer.

- Discontinue distribution to those who the manufacturer or importer have identified as having failed to comply with the certification program, i.e., no longer certified.

- All written, printed, or graphic matter used to identify or promote the devices shall comply with 21 CFR 809.10(c)(2)(ii), and shall state "For use only by distributors, laboratories, and investigators who are certified by (insert manufacturer's or importer's name and address)."

Laboratory

- Device will only be used to conduct tests for other laboratories and for investigators, certified by the manufacturer or importer.

- Testing shall be discontinued for any other laboratory or investigator who the manufacturer or importer has identified as having failed to comply with the certification program, i.e., no longer certified.

- All written, printed, or graphic matter used to identify or promote the devices, including laboratory services price lists and laboratory test results, shall comply with 21 CFR 809.10(c)(2)(ii), and all but the latter shall also state: "For use only by distributors, laboratories, and investigators who are certified by (insert manufacturer's or importer's name and address)."

Investigator

- The device and/or its test results will be used for investigational purposes only, and only to determine the safety and effectiveness of the device.

- The device and/or its test results will not be used for diagnostic purposes without confirmation of the diagnosis under another, medically established diagnostic device or procedure.

- All investigations shall be conducted under IRB approval, subject to Informed Consent, and under an IRB approved protocol, with evidence of each, as well as the actual protocol, to be maintained by the manufacturer or importer for Manufacturer or Importer-Sponsored Studies, or to be provided to the manufacturer or importer for independent Investigator-Sponsored Studies.

- Any data/studies published shall comply with 21 CFR 809.10(c)(2)(ii).

ATTACHMENT C

Certification Program For In Vitro Diagnostic Devices Labeled "For Research Use Only"

Manufacturers and importers must establish in writing, prior to distribution, a certification program as identified below for all in vitro diagnostic devices labeled "For Research Use Only." For purposes of this program, "For Research Use Only' is defined as uses not intended to determine the safety or effectiveness of the device. The manufacturer or importer is responsible for making or assuring this determination. The program should be designed to demonstrate compliance with the applicable requirements of the Federal Food, Drug, and Cosmetic Act and associated regulations. The program covers Manufacturer of Importer-Sponsored Studies and independent Researcher-Sponsored Studies, the latter which is discussed under Attachment D. The IDE regulation, 21 CFR Part 812, and the diagnostic device exemption provision, 21 CFR 812.2(c)(3), do not apply for these products, for purposes of this program.

Level	Certification Program Items
Manufacturer or Importer	- Devices will only be distributed to or utilized by those identified below who have provided written certification of compliance with the program. - Discontinue distribution to those who have failed to comply with the certification program. - Provide all certified distributors and laboratories with an updated list of certified distributors, laboratories, and researchers, as necessary, to keep the list current. - Manufacturer or importer studies are not for determining the safety or effectiveness of the device. - All written, printed, or graphic matter used to identify or promote the device shall comply with 21 CFR 809.10(c)(2)(i), and shall state "For use only by distributors, laboratories, and researchers who are certified by (insert manufacturer's or importer's name and address)."

DRAFT

- Manufacturers or importers shall maintain copies of all written and signed certification documents, i.e., manufacturer or importer, distributor, laboratory, and research certifications.

- Manufacturers or importers must use "due diligence" to assure compliance with the certification program. For example, toward the end of any study, the manufacturer or importer should determine if the study will be completed within the time specified, and, if so, discontinue distribution at that time.

- Written procedures shall be in effect which provides for the creation of an audit trail from the manufacturer to the end-user.

Distributor

- Devices will only be distributed to or utilized by distributors, laboratories, and researchers certified by the manufacturer or importer.

- Discontinue distribution to those who the manufacturer or importer have identified as having failed to comply with the certification program i.e., no longer certified.

- All written, printed, or graphic matter used to identify the product shall comply with 21 CFR 809.10(c)(2)(i), and shall state "For use only by other distributors, laboratories, and researchers who are certified by (insert manufacturer's or importer's name and address."

Laboratory

- Device will only be used to conduct tests for other laboratories or for researchers certified by the manufacturer or importer.

- Testing shall be discontinued for any other laboratory or researcher who the manufacturer or importer has identified as having failed to comply with the certification program, i.e., no longer certified.

DRAFT

- All written, printed, or graphic matter use to identify the devices, including laboratory services price lists and laboratory test results, shall comply with 21 CFR 809.10(c)(2)(i), and all but the latter shall also state: "For use only by laboratories and researchers certified by (insert manufacturer's or importer's name and address)."

Researcher

- The device and/or its test results will be used for research purposes only, and not to determine the safety or effectiveness of the device.

- The device and/or its test results will not be used for diagnostic purposes.

DRAFT

ATTACHMENT D

Manufacturer or Importer Distributor to Independent Investigator/Researcher

A manufacturer or importer may make devices available to persons outside its own studies, who want to conduct their own independent investigation or research on the product, e.g., for purposes of developing scientific publications. These would be considered "Investigator or Researcher-Sponsored Studies." However, the manufacturer or importer must be responsible for assuring the exemption requirements under 21 CFR 812.2(c)(3) are met, and must institute the same certification programs identified under Attachments B and C, as for its own sponsored studies. The only difference between Manufacturer/Importer and Investigator Sponsored Studies is that the latter must establish its own protocol, obtain its own IRB approval, and be responsible for its own Informed Consent. The manufacturer or importer must maintain a copy of all the necessary documentation. Also the manufacturer or importer is not required to collect the study results from the independent investigator or researcher for the Investigator or Researcher-Sponsored Studies unless the results are to be used by a manufacturer or importer for future PMA submissions.

There must be predetermined limits on the number of independent investigators and researchers, on the number of patients or patient samples utilized by each investigator or researcher, and on the time period for the studies. Product distribution must be discontinued at the completion of each study. These programs will be monitored carefully during inspections of manufacturers and importers to assure that they are not being used to commercialize these devices. The Agency will limit such distribution on an ad hoc basis, as it deems necessary, to preclude violations of the Act.

The submissions of individual IDE's by the investigators for Investigator-Sponsored Studies would not be acceptable, as it would be too burdensome on the Agency. Only studies under the IDE in vitro diagnostic product exemption (21 CFR 812.2(c)(3)) for these other investigations would be acceptable.