

**IV. MEDICAL DEVICE PANEL  
RECLASSIFICATION OF HIV DRUG  
SENSITIVITY ASSAYS**

**Andrew Dayton, M.D., Ph.D**  
**Regulatory Scientist, Molecular Virology Branch, DETTD, OBRR**

64<sup>th</sup> Meeting  
September 16, 1999  
Bethesda Ramada Inn  
8400 Wisconsin Avenue  
Bethesda, MD

**BLOOD PRODUCTS ADVISORY COMMITTEE**  
**64th Meeting - September 16-17,1999**  
**Bethesda Ramada Inn**  
**8400 Wisconsin Avenue, Bethesda MD**

**Topic:** HIV Drug Resistance Genotype Assays

**Issue:** Should HIV Drug Resistance Genotype Assays be Reclassified from Class III to Class II?

**Background:**

Successful implementation of HAART (Highly Active Anti-Retroviral Therapy) is heavily dependent upon identification of therapeutic failure, typically heralded by falling levels of circulating CD4+ lymphocytes and rising levels of circulating HIV. Because these two parameters are not always inversely correlated and because they are indirect measurements of therapeutic failure, physicians are increasingly in need of direct measures of therapeutic failure, particularly measures which directly indicate the mechanism of therapeutic failure.

One of the most common, though by no means only, causes of treatment failure is the existence or emergence of virus species resistant to the drugs included in the regimen. HIV Genotype Assays have been developed to identify the genotypes of virus present in the patient. These assays use either amplification and sequencing technology or hybridization technology to identify the nucleic acid sequences in specific portions of the HIV genomes (e.g., the protease – PR - and reverse transcriptase – RT - genes) that make up the viral population in a patient. Identification of certain known genotypes is then used to predict the phenotype of the infecting virus. The predicted phenotypes are then used to guide treatment choices for patients, identifying to which drugs the predominant viral species is resistant. This information, used with information about the patient's previous anti-retroviral regimens can be useful in choosing new regimens in patients experiencing therapeutic failure.

Assays other than genotype assays exist to determine the drug sensitivity of HIV in patients, but they are unsatisfactory for a variety of reasons. Virus can be isolated from patients, titered and replicated *in vitro* to determine the inhibitory concentrations of known drugs. Alternatively, segments of the virus containing protease and reverse transcriptase sequences can be cloned from patients and re-cloned into well characterized, cloned, laboratory strains of HIV for similar *in vitro* replication studies. Unfortunately, such assays are highly specialized (and therefore unsuitable for general use in clinical laboratories) expensive and time-consuming, with results often not available for weeks after specimens are collected.

Genotype assays, on the other hand, are rapid, comparatively inexpensive and eminently suitable for general use in clinical laboratories. With adequate validation of the phenotypic predictions of various genotypes, genotype assays can provide considerable benefit to patients. Although "archived" viral species left over from previous anti-retroviral therapy and other low-titer viruses in the swarm can escape detection by

genotyping assays, genotyping assays can still give valuable information about high titer viral species present in the patient and combined with prior knowledge of patient anti-retroviral exposure, such assays should allow improved accuracy in tailoring anti-retroviral therapies to individual patients. Cross-resistance and dependence of phenotype on multiple simultaneous changes in the viral genome can make phenotype predictions problematic. However, *in vitro* assays are well suited to validating these complicated situations.

Currently there are no FDA approved/cleared assays for the determination of HIV drug resistance. Because FDA is not aware of a predicate product, HIV drug resistance assays, by default, are Class III medical devices requiring premarket approval. An option exists, however, to reclassify such devices into Class II [510(k)] when general controls and special controls exist to ensure the safety and effectiveness of the device. It is FDA's view that special controls, such as 1) a guidance document containing recommendations for non-clinical study designs, reagent characterization and performance characteristics (e.g., reportable range, sensitivity, precision, specificity, stability, etc.) and 2) a post marketing surveillance study conducted to evaluate clinical progression correlated to resistance and the capability of the test to identify resistance in emerging genotypes can be used.

FDA is drafting a guidance document outlining the requirements anticipated for regulation of HIV drug resistance assays as Class II medical devices. This document addresses issues pertaining to assay precision, reproducibility and accuracy, quality control of reagents, laboratory testing and pre- and post market clinical data requirements. FDA's current thinking about the contents of the guidance document is contained in a September, 9, 1999, Concept Paper.

FDA also recognizes that reclassification would allow enhanced patient and physician access to these assays by allowing sponsors to go to market with premarket clinical sensitivity and specificity data. Post market clinical trial data can be used to correlate assay predictions with clinical response. Alternatively, sponsors may be allowed to go to market with traditional pre-market clinical trial data with certain clinical sensitivity studies to be provide post-market.

#### **Questions for the committee:**

1. Does the committee support the reclassification of HIV drug resistance assays from Class III medical devices to Class II medical devices?
2. If the answer to number 1 is yes, what additional special controls or requirements, if any, does the committee recommend?
3. If the answer to number 1 is no, what additional, specific criteria does the committee recommend to allow future reclassification as Class II devices?

# CONCEPT MEMO

(September 9, 1999)

For the Blood Products Advisory Committee  
September 17, 1999 Session

## **Concepts being Considered for a Draft guidance for Industry on Special Controls for HIV Drug Resistance Assay Premarket Notifications [510(k)s] including Postmarket Surveillance Requirements**

HIV Genotype assays are assays that detect the existence, at the viral genome level, of known drug resistance mutations in HIV. The genetic information they acquire is then used to predict the drug resistance/sensitivity profile (the phenotype) of predominant HIV species within individual patients, allowing better tailoring of multi-drug, anti-retroviral regimens to individual patients.

FDA is drafting a guidance document concerning the requirements for approval/clearance of HIV Genotype Drug Resistance Assays. This guidance document is currently at the "concept" stage. And the salient data considerations are summarized in this Memo to the Blood Products Advisory Committee.

### **I. Non-clinical laboratory data**

#### **A. Validation of Phenotypes Predicted by Genotyping**

In general, sponsors will be expected to validate claims that certain genotypes predict certain phenotypes. FDA expects that validation studies will include *in vitro* viral replication assays and determination of the effect of the given genotype on IC<sub>50</sub> or IC<sub>90</sub>. FDA is entertaining the concept that when non-clinical validation studies demonstrate an 8-fold or greater increase in IC<sub>50</sub> or IC<sub>90</sub> associated with a given resistance mutation, validation may or may not also include certain types of clinical validation studies of individual mutants. FDA is also entertaining the concept that when non-clinical validation studies demonstrate a less than 8-fold increase in the IC<sub>50</sub> or IC<sub>90</sub> level associated with a given mutation, validation will need to include clinical validation studies.

#### **B. Analytic Sensitivity**

FDA anticipates sponsors will perform sensitivity, precision and reproducibility studies on spiked samples and anticipates that sponsors will submit sensitivity data for all single and multiple mutations for which a claim is sought. The sensitivity studies should determine and validate both the minimum viral level (e.g. copies per ml) and minimum mutant proportions (as a % of total virus) reliably detected by the assay. Current FDA thinking is that the assays will demonstrate sensitivity at viral levels which are clinically relevant.

FDA also anticipates requiring accurate titration of sensitivity through and below minimum detectable viral levels and minimum viral mutant proportions to document how quickly assay performance deteriorates with reductions in analyte input.

## II. Clinical Data

### A. Validation of Phenotypes Predicted by Genotyping

Current FDA thinking is that validation studies should optimally include determinations of the existence/appearance of the given genotype in patients subjected to anti-retroviral therapy, as well as correlation of the disappearance of the given mutation with changes in anti-retroviral therapy. Throughout these studies, FDA will probably want to see data on overall viral burden. FDA is considering the possibility that viral burden may be an adequate indicator of response to therapy with particular drugs. FDA may variably recommend or require clinical studies to validate the phenotypes of individual mutations according to the changes in IC<sub>50</sub> or IC<sub>90</sub> (50% or 90% inhibitory concentrations) determined by *in vitro* viral replication studies.

### B. Clinical sensitivity

FDA is considering requiring sensitivity and reproducibility studies on a panel of unspiked specimens whose genetic makeup is known. Further discussions will determine whether or not the panel must include representatives of all genotypes for which a claim is sought.

FDA is also considering requiring traditional clinical trials in which assay phenotype predictions based on genotype correlate with changes in viral burden and/or mutant representation in response to anti-retroviral therapy. FDA may allow these studies to be prospective or retrospective, on archived specimens.

FDA is giving serious consideration to the concept of requiring either the panel-type clinical studies or the traditional clinical trials, but not both, to be submitted premarket. In this case, FDA would anticipate requiring the alternative studies to be submitted postmarket. (e.g. panel studies premarket and clinical trials post market or clinical trials premarket and panel studies postmarket).

Furthermore, FDA is seriously entertaining the possibility of relying on extensive post-market studies to further support claims made during approval/clearance as well as additional efficacy claims (e.g., new correlations between phenotype and genotype).

9/09/99

## PENDING OBRR WORKSHOPS FOR 1999

### 1- Bacterial Contamination of Platelets

Date and Place: September 24, 1999. Jack Masur Auditorium, Bldg. 10, NIH Clinical Center  
Chairperson: Dr. Chiang Syin  
Purpose: The workshop will focus on three main issues: an update on the epidemiology of platelet contamination, advances in detection methodology of contamination, and current efforts on bacterial inactivation methods

### 2- Workshop on Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics and Red Cell Substitutes

Dates and Place: September 27-28, 1999, Natcher Conference Center, Auditorium Balconies A,B and C  
Chairperson: Dr. Abdu Alayash  
Purpose: To discuss recent advances in the use of hemoglobin based oxygen carriers

### 3-Plasticizers: Safety Issues in Blood Collection and Storage

Dates and Place: October 18, 1999, Jack Masur Auditorium, Bldg. 10, NIH Clinical Center  
Chairpersons: Dr. Jaroslav Vostal  
Purpose: OBRR plans to hold a workshop on plasticizers in blood bags to review the scientific data concerning the safety of plasticizers used in blood bags and their effectiveness in use.

### 4 -Standards for Inactivation and Clearance of Infectious Agents in the Manufacture of Plasma Derivatives from Non-Human Sources for Human Injectable Use

Date and Place: October 25, 1999, Jack Masur Auditorium, Bldg. 10, NIH Clinical Center  
Chairperson: Dr. Mark Heintzelman  
Purpose: Currently, plasma derivatives manufactured from non-human sources are not inactivated. FDA has identified this practice as an area subject to standards setting that will require inactivation procedures of these products.

## **5- Public Meeting**

Dates and Place: November 22, 1999, Jack Masur Auditorium, Building 10, NIH Clinical Center

Chairperson: Martin Ruta, Ph.D.

Purpose: To receive public comments on three recent Federal Register proposed rules and one direct final rule that addresses various issues dealing with the safety and efficacy of the nation's blood supply.

## **6- Donor Suitability Workshop**

Dates and Place: December 9, 1999, 5630 Fishers Lane, conference room # 1066, Rockville, MD

Chairperson: Captain Mary Gustafson

Purpose: To bring additional issues related to donor suitability for scientific and public discussion

## **7- Workshop on Leukoreduction**

Dates and Place: December 10, 1999, Natcher Auditorium, National Institutes of Health

Chairperson: Captain Mary Gustafson

Purpose: To resolve implementation and practical issues concerning pre-storage leukoreduction of transfusable blood products

## **8- NAT Implementation Workshop**

Dates and Place: December 14, 1999, Jack Masur Auditorium, Building 10, NIH Clinical Center

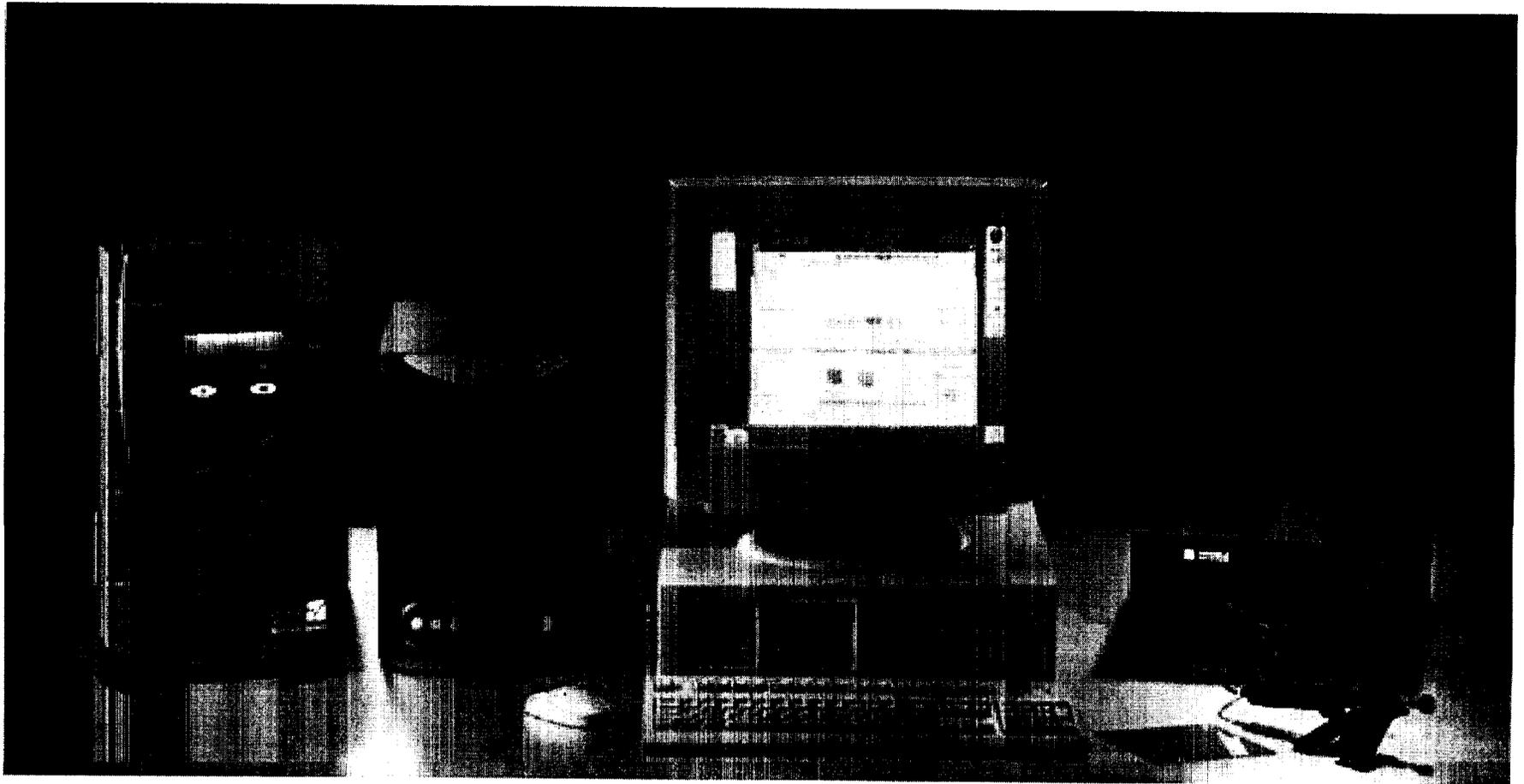
Chairperson: Dr. Indira Hewlett

Purpose: To assess and evaluate the status of nucleic acid testing, and to discuss regulatory issues regarding implementation of NAT testing procedures

Note: Additional information about these workshops, including registration, agendas, hotel accommodations etc. will be placed on the FDA website as soon as it is available under [www.FDA.GOV/CBER/WHATSNEW.HTM](http://www.FDA.GOV/CBER/WHATSNEW.HTM). Federal Register announcements concerning the workshops will also be published.

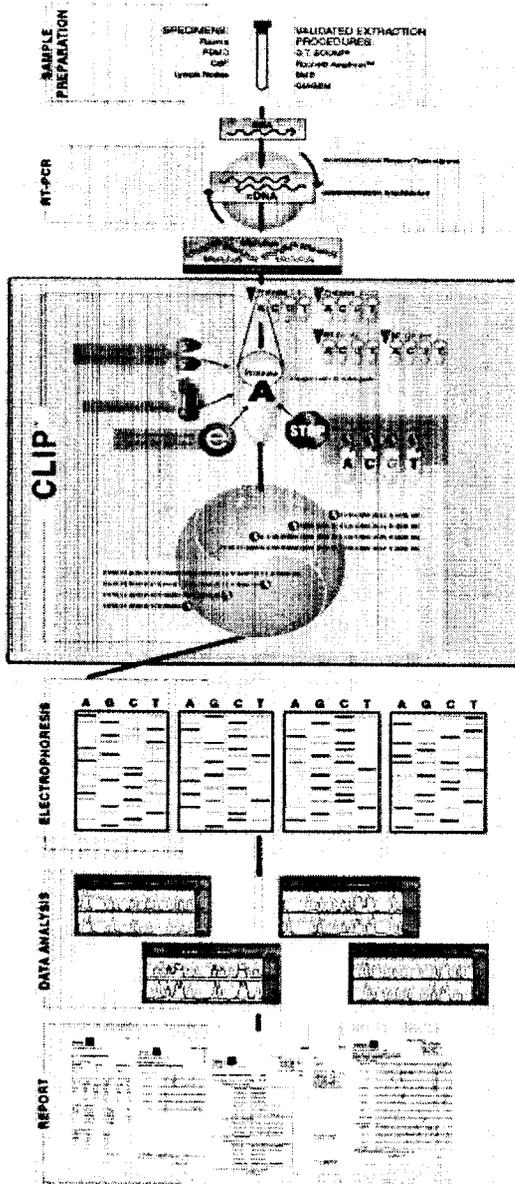
# The OpenGene™ System

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# The TruGene™ HIV-1 Procedure



Extraction

Reverse transcription

Amplification

CLIP™ bi-directional sequencing

Separation by gel electrophoresis

Analysis by GeneObjects™ CMS

TruGene HIV-1 Resistance Report (based on GuideLines™)



# The TruGene™ Resistance Reports

- Based on the GuideLines™ rules

## TruGene™ HIV-1 Resistance Report

Patient ID: 1200-00  
 Sample ID: 99-07-01-1234  
 Date Drawn: Aug 30, 1999  
 Physician: Dr. Smith

Report Date: Aug 31, 1999

Reverse Transcriptase mutations: M41L\* V75M\* M184V\* H208Y\* L210W\* T215Y\*

### Nucleoside RT Inhibitors

	Resistance
Zidovudine	Partial Resistance
Didanosine	Partial Resistance
Zalcitabine	Partial Resistance
Lamivudine	Resistance
Stavudine	No evidence of Resistance
Abacavir	Resistance
Adefovir	No evidence of Resistance

### Nonnucleoside RT Inhibitors

Nevirapine	No evidence of Resistance
Delavirdine	No evidence of Resistance
Efavirenz	No evidence of Resistance

\* See TruGene HIV-1 Resistance Details page for a Comment pertaining to this mutation.

Protease mutations: L10I M36I M46I L63P V77I I84V L90M

### Protease Inhibitors

Indinavir	Resistance
Ritonavir	Resistance
Saquinavir	Resistance
Nelfinavir	Resistance
Ampranavir	Resistance

Authorized reviewer: \_\_\_\_\_ Signature: \_\_\_\_\_ Date: \_\_\_\_\_  
 Title: \_\_\_\_\_ Name: \_\_\_\_\_



The TruGene HIV-1 Resistance Report uses GuideLines™ rules developed by expert peer review consensus.  
 For Internal Use Only

HIV-1v2: 1.0 Beta (1/16/99) SDC/CK (Rev. 1.0 (1.0) © Visible Genetics Inc.

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## TruGene™ HIV-1 Resistance Details

Patient ID: 1200-00  
 Sample ID: 99-07-01-1234  
 Date Drawn: Aug 30, 1999  
 Physician: Dr. Smith

Report Date: Aug 31, 1999

(6) Saquinavir L90M indicates Resistance to Saquinavir.

If M36I L63P L10I indicates Partial Resistance to Saquinavir.  
 ce to Nelfinavir.  
 If M36I L63P L10I indicates Partial Resistance to Nelfinavir,  
 resistance to Ampranavir.  
 If M46I indicates Resistance to Ampranavir.  
 If M36I L63P L10I indicates Partial Resistance to Ampranavir.

## TruGene™ HIV-1 Resistance Details

Patient ID: 1200-00  
 Sample ID: 99-07-01-1234  
 Date Drawn: Aug 30, 1999  
 Physician: Dr. Smith

Report Date: Aug 31, 1999

Nucleoside RT (13 data)

Inhibitors:

- (1) Zidovudine T215Y indicates Resistance to Zidovudine.
- (2) Zidovudine Any of M41L L210W indicates Partial Resistance to Zidovudine
- (3) Zidovudine Comment: 184 may reduce the level of Zidovudine resistance measured in vitro for an uncertain duration.
- (4) Zidovudine Comment: 208 may reduce the level of Zidovudine resistance measured in vitro for an uncertain duration.
- (5) Didanosine M184V indicates Partial Resistance to Didanosine.
- (6) Zalcitabine M184V indicates Partial Resistance to Zalcitabine.
- (7) Lamivudine M184V indicates Resistance to Lamivudine.
- (8) Stavudine Comment: Preliminary data suggest 3 or more Zidovudine mutations may result in reduced sensitivity to Stavudine (M41L L210W T215Y in this sample).
- (9) Stavudine Comment: Preliminary data suggest V75M/S/A may result in Stavudine resistance (V75M in this sample).
- (10) Abacavir T215Y M184V and M41L L210W indicates Resistance to Abacavir.
- (11) Abacavir Any two of L210W T215Y M41L indicate Partial Resistance to Abacavir.
- (12) Adefovir Comment: 184 may increase susceptibility to Adefovir.
- (13) Foscarnet Comment: H208Y has been associated with Foscarnet-resistant HIV.

Nonnucleoside RT Inhibitors:

No evidence of resistance.

Protease Inhibitors: (11 data)

- (1) Indinavir I84V indicates Partial Resistance to Indinavir.
- (2) Indinavir M46I I84V and any two of M36I L63P L10I indicates Resistance to Indinavir.
- (3) Ritonavir I84V indicates Partial Resistance to Ritonavir.
- (4) Ritonavir M46I I84V and any two of M36I L63P L10I indicates Resistance to Ritonavir.

Other resistance reports are omitted.

See GuideLines™ rules developed by expert peer review consensus.  
 in International AIDS Code  
 HIV-1 SEARCH: Rules 1.0 (1.0) © Visible Genetics Inc.

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Pages 2 & 3

Note: This document refers to the report on the preceding page. If different resistance levels are detected.



The TruGene HIV-1 Resistance Report uses GuideLines™ rules developed by expert peer review consensus.  
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HIV-1v2: 1.0 Beta (1/16/99) SDC/CK (Rev. 1.0 (1.0) © Visible Genetics Inc.

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## PMA / PMN Submission

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- Device Characteristics
  - > 400 assays will be performed and analyzed at 8 sites
- Clinical Utility
  - > 400 assays will be performed at 2-3 sites on plasma samples that have been banked from prospective clinical studies and are correlated with clinical outcomes data



# Performance Characteristics of the Device

- **Collection of Plasma** ( $N = 9$  with Viral Loads from 1,300 to 300,000 copies/mL to make testing panels)
- **Multi-center study** ( $N = 6$ ) for reproducibility and accuracy of device - different sites, days, technicians and kit lots
- **Freeze-thaw study** - 2 samples - VLs ~ 1,200 and ~ 43,000 copies/mL - up to 10 cycles

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# Performance Characteristics of the Device

- **Interfering substances study** - *pathogens; biochemicals; ARVs*
- **Mutant-wild-type mixture study**- *ratios from 100% WT to 100% mutant*
- **Plasma extraction study** - *3 common manual methods*
- **Anticoagulant study** - *3 common blood collection tubes*

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# PMA / PMN Submission

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- Clinical Utility
  - GART baseline sample re-analysis (153 plasma samples with documented clinical outcomes)
  - Viradapt samples re-analysis (108 subjects with up to 5 genotypes in a 12 month period).



FDA Blood Products Advisory Committee Meeting of Sept. 17, 1999

## FDA CBER Device Reclassification of HIV Drug Resistance Tests to Class II

### PRESENTATION & COMMENTS BY PE BIOSYSTEMS ON THE PROPOSED CBER REGULATORY REVIEW PROCESS FOR HIV-1 GENOTYPING AND PHENOTYPING ASSAYS

Presented By:

**Eric Shulse**, Director, Molecular Diagnostics  
**Tony Lam**, Senior Manager of RA and QA, Molecular Diagnostics

PE Biosystems supports the proposal of the Center for Biologics Evaluation and Research (CBER) to down-grade sequencing resistance testing devices from Class III, which would require a PMA, to Class II, which would require a 510(k). There are compelling reasons for genotyping and phenotyping assays used to type Human Immunodeficiency Virus Type 1 (HIV-1) to be marketed under section 510(k), of the Federal Food, Drug, and Cosmetic Act. The molecular diagnostic technology used in these assays has become common place in laboratory tools and analytical procedures employed by research and clinical laboratories.

In clinical situations, genotyping and phenotyping of HIV-1 viruses would be used to provide guidance to physicians on the drug resistance of the viruses infecting the patient, not as a blood banking diagnostic for donations. The intended clinical diagnostic use of these assays clearly fall under the statutory purview of the Federal Food, Drug, and Cosmetic Act medical device amendments, not under the Public Health Service Act.

The continued classification of these HIV-1 drug resistance in vitro diagnostic assays into Class III, subject to marketing through the Pre-Market Approval (PMA) application process, would raise regulatory hurdles that do not serve the public health interests. By contrast, reclassification into the Class II category and regulation of market entry of these assays via the more flexible 510(k) process would permit the rapid addition of information describing new HIV-1 drug resistance genomic markers, as well as increases in assay performance. Such regulatory flexibility has already been indicated by CBER in its policies

There is an analogous situation with HIV-1 drug resistance markers, where there are continuous mutations of HIV-1 viruses and also public database compendia to provide notice of these rapidly evolving drug resistance markers to physicians. PE Biosystems encourages CBER to adopt the same 510(k) regulatory approach with these genotyping and phenotyping HIV-1 assays.

Second, the 510(k) process should focus on companies providing class evidence of the analytical performance of the genotyping and phenotyping HIV-1 assays, and not require of device companies large scale clinical studies for each new drug and viral isolate, which would delay clinical access to useful knowledge. The ongoing clinical research in the HIV area by both academic and commercial entities now provides useful drug resistance data which are incorporated into database compendia. Furthermore, pharmaceutical companies are now routinely including genotyping and phenotyping of HIV-1 in their clinical protocols to assess the effectiveness of new antiretroviral drugs. The rapid availability of 510(k)-cleared HIV-1 drug resistance diagnostic devices would encourage their use by pharmaceutical companies and eliminate any inherent variability from the use of "home brew" assays.

Third, the HIV Resistance Collaborative Group's proposal of a Guideline in The Validation of Genotyping and Phenotyping Assays Used in Human Immunodeficiency Virus Type 1 Diagnosis provides a clear technical consensus on what analytical performance data would be necessary to validate these assays. PE Biosystems supports the adoption by FDA of this Guidance as the basis for 510(k) clearance of HIV-1 Genotyping and

Phenotyping Diagnostic kits. FDA's focus on the analytical performance of these kits, i.e., sensitivity, specificity, reproductibility, and precisions along with the use of public database results in product labeling, will protect the public health. PE Biosystems also believes that FDA's recognition of the HIV Resistance Collaborative Group's proposed guidance is consistent with the Congressional mandate articulated in the 1997 FDA Modernization Act.

Under the aforementioned recommendations, PE Biosystems believes that FDA will still be able to exercise appropriate regulatory oversight over the commercialization of these genotyping and phenotyping HIV-1 assays. Failure to pursue this reasonable regulatory policy could have some dire consequences, in that it would:

- delay of adoption and use of FDA-cleared products in clinical studies of new antiretroviral therapies,
- encourage the development by reference laboratories of unregulated "home brew" assays of unknown variation, performance, and clinical utility, and
- create a public misconception that FDA was creating high regulatory hurdles for a proven diagnostic technology, thereby delaying patient access to more effective use of existing antiretroviral therapies and to more effective new antiretroviral therapies.

*FDA CBER Blood Products Advisory Committee  
Meeting: September 17, 1999*

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***Device Reclassification of HIV  
Drug Resistance Tests to Class II***

**Eric Shulse**  
Director, Molecular Diagnostics

**Tony Lam**  
Senior Manager, Regulatory Affairs & QA  
Molecular Diagnostics

**Applied Biosystems**

***PE Biosystems***

# *PE Biosystems*

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- Leader in molecular genetics instrumentation and reagents
- PE Biosystems HIV Genotyping System:
  - Utilizes PCR, sequencing and software technology
  - Qualitative RNA assay providing genotype nucleotide sequences of the protease and reverse transcriptase genes in HIV virus to identify HIV antiviral drug resistance mutations

## ***Reclassification from Class III to Class II Compelling Reasons:***

- Molecular Biology/Genetics techniques have become common place in research & clinical labs
- INTENDED USE of clinical diagnosis should fall under statutory purview of sec. 510(k) of FDC Act, NOT Public Health Service Act
  - REASON: HIV genotyping provides viral drug resistance guidance to physicians, NOT as blood banking diagnostic for donation

# *Regulatory Flexibility Better Serves Public Health Interest*

- Class III: IDE / PMA
  - Needlessly raises regulatory hurdles in absence of technology risk
  - Does not serve public health interest
- Class II: 510(k)
  - More flexible 510(k) process
  - Permits more rapid availability of FDA cleared tests for new HIV antiviral drug resistance
  - Easier to update 510(k) for improvements & changes

# *Focus on Evidence of Analytical Performance*

- 510(k) proof of performance using statistically representative small panel per mutation should be acceptable for detecting new mutations as well
- Should not require additional clinical studies for each new drug and viral isolate by diagnostic manufacturers
- **Benefit:**
  - Avoid delay in clinical access to useful knowledge
  - Avoid expensive, impractical & large scale clinical studies

## *Focus on Evidence of Analytical Performance (Cont.)*

- On-going academic research in HIV provides and enables incorporation of new drug resistance data into public database compendia
  - **Benefit:** Continuous update & improvement by independent peer review; not only based on one manufacturer's limited resources

## *Focus on Evidence of Analytical Performance (Cont.)*

- Rapidly available 510(k) cleared HIV drug resistance diagnostic for use by pharmaceutical companies in assessing effectiveness of new antiviral drugs
  - **Benefit:** Reduces inherent variability and unknown performance of “home brew”

# ***ADOPT Consensus HIV Resistance Collaborative Group's Proposed Guidelines for Validation as Basis for 510(k) Clearance***

- Provides clear technical consensus on analytical performance necessary to validate assays
- Consistent with congressional mandate as in 1997 FDA Modernization Act favoring industry consensus guidance
- Together with the use of public database compendia in product labeling will protect public health

# *Consequences if Not Class II*

- Delay FDA cleared products in clinical studies of new antiviral therapies
- Encourage reference lab development of unregulated “home brew” assays of unknown variation & performance
- Create public misconception that FDA raises high hurdles for proven diagnostic technology
- Delay patients’ access to more effective existing and new antiviral therapies

# *Conclusion*

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- FDA still can exercise appropriate regulatory oversight through class II: Tier III 510(k)

### Proposed Clinical Uses of HIV Resistance Testing

- Monitor prevalence/transmission of resistance
- Post-Exposure Prophylaxis
  - therapy cannot be delayed for test results
- Adult Naïve: high risk area/group for resistance
  - wild type may have outgrown resistant virus
- Pregnancy: in naïve patients in high risk area/group for resistance or in treatment experienced patients (controversial)

### Proposed Clinical Uses of HIV Resistance Testing (cont'd)

- First virologic failure
  - not when to change therapy
  - guide in selection of second line treatment
- Subsequent virologic failure
  - latent viruses
  - fewer treatment options

### DAVDP's Interest in HIV Resistance Testing

- Monitor prevalence of resistance
- Provide useful clinical information in label
- Stimulate further research into defining clinical resistance and assay development
- Level playing field for drug sponsors
- To aid in negotiation of fair and balanced promotional ads

### DAVDP's Interest Promotional Claims

- Hypothetical Example
- Use Drug "X" First: There is less drug class cross resistance after failure on drug X compared to drugs W, Y or Z.
- Supporting data from a retrospective analysis of patients pooled from several studies.
- Less than 50 patients.

### DAVDP Advisory Committee Meeting- Nov 2 & 3, 1999

- Session 1: Performance Characteristics and Limitations of Currently Available Genotypic and Phenotypic Assays
- Session 2: Evaluation of Relationships between HIV Resistance Testing and Treatment Outcome
- Session 3: Practical Considerations for the Use of Resistance Testing in Clinical Trials and Drug Development
- Session 4: Potential Roles of Resistance Testing in Drug Development

### Conclusions

- Knowledge of genotypic data appeared to affect treatment outcome in 2 randomized prospective studies
- The effect was of the magnitude that would potentially support a drug approval
- Retrospective studies show gross associations between baseline gt or susceptibility and treatment outcome
- But., sometimes only for number of mutations and not specific mutations

### Conclusions (2)

- Although, clinicians are desperate for guidance in selecting second-line regimens,
- Currently, limitations in assay analytical sensitivity, specificity, reproducibility, and lack of clinical correlations for many drugs prohibit recommendations for routine monitoring of individual patients
- Monitoring prevalence of resistance and transmission is crucial

### Conclusions (3)

- Compared to HIV RNA testing, HIV resistance testing is drug-dependent much like therapeutic monitoring of drug concentrations
- Mutational algorithms and breakpoints will need to be revised for each new drug approval
- An efficient use of resources would be for drug sponsors to characterize clinical relevance of gt and pt susceptibility in the context of drug development

**Current Strengths and Weaknesses of HIV Resistance Testing and Its Potential Role in Clinical Drug Development**

CDER Perspective

Jeff Murray M.D., M.P.H.  
Division of Antiviral Drug Products

**Available Assays**

(not a comprehensive list)

**Genotypic**

- VircoGEN
- Genotyp PLUS
- VisGen
- Affymetrix
- PE Biosystems
- Stanford
- "Home brews"
- Line Probe (hybridization)

**Phenotypic**

- Antivirogram (Virco)
- PhenoSense (Virologic)
- RVA's
  - recombinant viral assays
  - RT and P inserted
  - no cleavage sites

**Genotypic vs. Phenotypic Assays Relative Advantages**

Modified from Ehrlich et al. JAMA 1998

**Genotyping**

- Availability
- Quicker results (cheaper)
- Technically less demanding
- Mutations may precede phenotypic changes

**Phenotyping**

- Direct measure of susceptibility
- Clinically familiar results: "breakpoints"
- Takes into account increases and decreases in susceptibility in combination therapy

**Genotypic vs. Phenotypic Assays Relative Limitations**

Modified from Ehrlich et al. JAMA 1998

**Genotyping**

- Indirect measurement of susceptibility
- May not correlate with phenotype
- Expert opinion required
- Insensitive for minor species
- Effect of "Sensitizing" mutations

**Phenotyping**

- Restricted Availability
- Processing time longer
- Technically more demanding
- Clinically significant cutoffs not defined
- Insensitive for minor species

**Current Analytical Limitations GT and PT Assays**

- Amplification Sensitivity
  - > 1,000 copies (some quote less)
- Analytical Sensitivity
  - detects minor (quasi) species 20-25% or greater
- Reproducibility/quality control
  - poorer for viral mixtures (ENVA-2 panel)
- Interpretation of results
  - complex mutational patterns
  - no breakpoints
- Technically demanding
  - processing time and cost (PT > GT)

**Other Considerations/Limitations**

- Clonal vs. population sequencing
  - are resistant mutations on same genome?
  - clonal methods are technically demanding
  - Limited data suggest linkage, Martinez- Picado et al.
- Other viral reservoirs, lymph nodes, gut, etc.
- Timing of Samples in relation to drug exposure
  - reversion to WT
- Clinical Correlations-Defining Resistance

### Limitations: Reproducibility

#### ENVA-2 - genotyping panel

Schuurman et al. Antiviral Therapy 1999, Absrt 58

- 5 Samples sent to 60 labs (results received from 33)
- 0-100% mixtures of two HIV strains
- RESULTS % CORRECT CALLS
- 100% WT: RT-100%, P-94%
- 100% Mut: RT-66%, P-71%
- 50/50 Mix: RT-37%, P-49%
- Results improved since ENVA-1

### Evidence Supporting Clinical Relevance

- Two prospective studies for Genotyping
  - VIRADAPT and GART (Europe and U.S.)
- No completed prospective study for phenotyping
- Several Retrospective Studies
  - some show predictive value of certain mutations at baseline
  - others show relationship between number of mutations and outcome but not specific mutations
  - relationship between pt susceptibility and outcome

### Prospective Studies

#### Genotyping and Treatment Outcome

- Similar Design
- Similar outcome
  - VIRADAPT: -0.67 log difference (6 mos.)
  - GAART: -0.44 log difference (3 mos.)
  - GAART: each sensitive drug added 0.28 log reduction
- Criticisms
  - GAART “expert opinion”, but not a factor for VIRADAPT
  - Short term follow-up for GART
  - VIRADAPT more ZDV mutations

### Retrospective Studies

- Zolopa et al. # of PI mutations and virologic response to RTV/SQV (51 patients failing at least one PI.
  - Number of mutations correlated with response
  - GT independently predictive above Rx history
- Deeks et al. PT susceptibility testing was predictive of virologic response to regimens after IDV failure
  - Outcome greater for patients sensitive to 2 or 3 drugs compared to those sensitive to 0 or 1 drug

### Correlation of GT and PT

- Virco data base (7000 samples) show “good” correlations between gt and pt for 3TC 184 mutation, multiple ZDV mutations and multiple PI mutation (NLF)
- Harrigan et al. 59 patients who had failed at least 2 regimens: strong correlation between gt and pt for antiretrovirals except for ABC and d4T (mod); ddI and ddC (low)

### Algorithms for Defining GT Resistance

- Based on Consensus Opinion of Expert
  - Literature/Abstracts
  - Data from industry and academia
  - Drugs added on a case-by-case basis
- IDSA Consensus Hirsch et al. JAMA
- GART protocol team
- VIRADAPT protocol team
- Resistance Collaborative Group

# **Procedures for Class II Device Exemptions from Premarket Notification, Guidance for Industry and CDRH Staff**

## **I. Purpose**

The purpose of this guidance<sup>1</sup> is to establish standard operating procedures for the Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA) to carry out Section 510(m)(2) of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by Section 206 of the FDA Modernization Act of 1997 (FDAMA). This FDAMA amendment provides that interested persons may petition FDA to exempt class II device types, as defined in 21 CFR 860.3(i), from the premarket notification requirements of section 510(k) of the Act.

## **II. Background**

As provided by FDAMA, FDA exempted through a FEDERAL REGISTER (FR) notice, 62 class II device types from premarket notification (section 510(k)) requirements on January 21, 1998 (63 FR 3142). Beginning on January 22, 1998, (1 day after the date of the publication in the FR of the list of class II devices exempt from premarket notice), FDA, upon its own initiative or upon a petition of an interested person, may exempt a class II device from premarket notification requirements under section 510(m)(2). This may be done if FDA finds that a premarket notification for the class II device type is not necessary to assure the safety and effectiveness of the device. Before granting an exemption, FDA must publish a notice in the FR of the petitioner's request or of FDA's intent to exempt the class II device type. The FR notice will provide a 30-day period for public comment. In addition, within 120 days of this FR notice requesting comment, FDA will publish an order in the FR of its final determination regarding the exemption of the device type. If FDA receives a petition requesting exemption from premarket notification for a class II device type and does not respond within 180 days of receipt of such a petition, the exemption will be deemed effective by operation of the statute.

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<sup>1</sup> This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

### **III. Factors FDA May Consider for Exemption**

In its January 21, 1998 FR notice (63 FR 3142), FDA described the criteria the agency had used to determine which class II device types should be exempt from the premarket notification (510(k)) requirements. The FR notice stated:

"In considering whether to exempt class II devices from premarket notification, FDA focused on whether premarket notification for the type of device is necessary to provide reasonable assurance of safety and effectiveness of the device. FDA considered the following factors: (1) The device does not have a significant history of false or misleading claims or of risks associated with inherent characteristics of the device, such as device design or materials (when making these determinations, FDA has considered the risks associated with false or misleading claims, and the frequency, persistence, cause or seriousness of the inherent risks of the device); (2) characteristics of the device necessary for its safe and effective performance are well established; (3) changes in the device that could affect safety and effectiveness will either: (a) be readily detectable by users by visual examination or other means such as routine testing, before causing harm, e.g., testing of a clinical laboratory reagent with positive and negative controls; or (b) not materially increase the risk of injury, incorrect diagnosis, or ineffective treatment; and (4) any changes to the device would not be likely to result in a change in the device's classification. FDA also considered that even when exempting devices, these devices would still be subject to the limitations on exemptions, as described in section III of this document."

The agency believes these factors should also be considered when determining if any additional class II device type(s) should be exempted from 510(k) requirements. Among these factors the agency believes are important for special consideration are the "Limitations on Exemptions," a copy of which is found in the Attachment with this document. Likewise, a petition by an interested person for exemption for a class II device type should clearly address the factors described above so the agency and respondents can expeditiously consider whether to concur in the request.

### **IV. Standard Operating Procedures (SOPs)**

A petition requesting that a class II device type be exempt from section 510(k) under 21 CFR 10.30 must be submitted to Dockets Management Branch, HFA-305, Food and Drug Administration, Dept. of Health and Human Services, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857. We also request that the petitioner send a copy to CDRH's Document Mail Center (HFZ-401), 9200 Corporate Blvd., Rockville, MD 20850. The petitioner should state prominently on the outside of the envelope, the inside cover, if any, and the cover sheet "Class II 510(k) exemption petition". The

petition must include information described in 10.30(b). The petitioner should identify the device classification name, regulation number, the petitioner's name, address, telephone and fax number, and clearly address why the petitioner believes premarket notification requirements are not necessary to assure safety and effectiveness for the device type. The petitioner is requested to specifically address the factors enumerated under Section III of this document.

Upon receipt of a petition, the Dockets Management Branch will date stamp the petition. This stamped FDA receipt date will serve to start the 180-day time period for FDA to respond to the petition.

FDA will publish an **FR** notice announcing the petition, or of FDA's intent to exempt a device type on its own initiative, and provide a 30-day comment period. FDA will review any Medical Device Reports (MDRs) and recalls for the device type, obtain advisory panel input, as needed, and review any comments received in response to the **FR** notice. Once the agency determination regarding the exemption of the device type has been made, FDA will publish an order in the **FR** announcing the final determination. This should publish within 180 days of receipt of any such petition.

### **Special Notes**

1. At any time during the review of a petition to request exemption from 510(k), FDA may request clarification from the petitioner. However, if the petitioner wishes to amend the petition by submission of additional information, FDA will generally consider it to be a new petition and it will restart the 180-day clock.

2. The exemptions from the premarket notification requirements may be subject to certain limitations. For example, FDA may exempt a device provided that it bear certain labeling statements, or provided that it meet certain testing requirements. Devices that do not meet these requirements would not be considered exempt from premarket notification requirements and would be required to submit premarket notifications and obtain FDA clearance prior to marketing.

Attachment

### Limitations on Exemptions

The exemption from the requirement of premarket notification for a generic type of device listed in this document applies only to those devices that have existing or reasonably foreseeable characteristics of commercially distributed devices within that generic type, or, in the case of in vitro diagnostic devices, for which a misdiagnosis, as a result of using the device, would not be associated with high morbidity or mortality. Accordingly, a class II device listed in this document is not exempt if such device: (1) has an intended use that is different from the intended use of a legally marketed device in that generic type; e.g., the device is intended for a different medical purpose, or the device is intended for lay use instead of use by health care professionals; or (2) operates using a different fundamental scientific technology than that used by a legally marketed device in that generic type; e.g., a surgical instrument cuts tissue with a laser beam rather than with a sharpened metal blade, or an in vitro diagnostic device detects or identifies infectious agents by using a deoxyribonucleic acid (DNA) probe or nucleic acid hybridization or amplification technology rather than culture or immunoassay technology; or (3) is an in vitro device: that is intended for use in the diagnosis, monitoring or screening of neoplastic diseases with the exception of immunohistochemical devices; is intended for use in screening or diagnosis of familial and acquired genetic disorders, including inborn errors of metabolism; is intended for measuring an analyte which serves as a surrogate marker for screening, diagnosis, or monitoring life threatening diseases such as acquired immune deficiency syndrome(AIDS), chronic or active hepatitis, tuberculosis, or myocardial infarction, or to monitor therapy; is intended to assess the risk of cardiovascular diseases; is intended for use in diabetes management; is intended to identify or infer the identity of a microorganism directly from clinical material; is intended for detection of antibodies to microorganisms other than immunoglobulin G (IgG) and IgG assays when the results are not qualitative, or are used to determine immunity, or the assay is intended for use in matrices other than serum or plasma; uses noninvasive testing; is intended for near-patient testing (point of care).

Class II devices incorporating such changes or modifications are not exempt from premarket notification because FDA has determined that premarket notification is necessary to assure the safety and effectiveness of the device.

In addition to the general limitation on exemptions that applies to all class II devices that are described previously, FDA may limit the exemption from premarket notification requirements to certain devices within a generic

Attachment, page 2

class. For example, FDA is listing the exemption of the biofeedback device, but limits the exemption to prescription battery powered devices that are indicated for relaxation training and muscle reeducation. All other biofeedback devices are still subject to premarket notification requirements because FDA determined that premarket notification was necessary to provide a reasonable assurance of safety and effectiveness for these devices.

FDA advises, additionally, that an exemption from the requirement of premarket notification does not mean that the device is exempt from any other statutory or regulatory requirements, unless such exemption is explicitly provided by order or regulation. Indeed, FDA's determination that premarket notification was unnecessary to provide a reasonable assurance of safety and effectiveness for devices listed in this document is based, in part, on the assurance of safety and effectiveness that other regulatory controls, such as current good manufacturing practice requirements, provide.

To the Committee:

Several overview documents and, where available, additional reference materials on general controls, special controls, and premarket approval.

#### Overview Documents:

- FDA Classification of Medical Devices, 25 Mar 99
- Classify Your Medical Device, 28 May 99
- Device Classification Panels, 29 Jun 98

#### General Controls (Class I, II, III)

- Establishment Registration, 21 May 99
- Medical Device Listing, 21 May 99
- Instructions for the Completion of Medical Device Registration and Listing Forms FDA 2891, 2891a and 2892
- Good Manufacturing Practices (GMP)/Quality System (QS) Regulation, 17 Apr 98
- Labeling Requirements, 17 Apr 98
- Labeling Requirements, *In Vitro* Devices, 1 Jun 98
- Premarket Notification [510(k)], How to market a 510(k) Medical Device, 30 Jun 99

#### Special Controls (Class II)

- Draft Special Controls Matrix Table
- Postmarket Surveillance Studies

#### Premarket Approval (Class III)

- Information on Premarket Approval Applications
- Premarket Approval Manual (1st Chapter)

Center for Devices and Radiological Health

## FDA Classification of Medical Devices

*(This page last updated: March 25, 1999)*

<a href="#">CDRH Program Areas Page</a>	<a href="#">Device Advice</a>	<a href="#">DSMA Home</a>	<a href="#">CDRH Home</a>	<a href="#">FDA Home</a>	<a href="#">FDA Search</a>	<a href="#">CDRH Comments</a>
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This page describes the regulatory classes for all medical devices, which is the basis for determining the process for marketing a medical device in the United States.

- 
- [Class I - General Controls](#)
  - [Class II Special Controls](#)
  - [Class III - Premarket Approval/Product Development Protocol](#)
  - [Changes in Device Classification](#)

---

Medical devices vary widely in their complexity and their degree of risk or benefits. They do not all need the same degree of regulation. Thus, U.S. FDA places all medical devices into one of three regulatory classes based on the level of control necessary to assure safety and effectiveness of the device.

These classes are:

Class I	General Controls
Class II	General Controls and Special Controls
Class III	General Controls, Special Controls and Premarket Approval

The regulatory class of most devices, including a brief description of each device type, can be found in the classification regulations in Title 21 Code of Federal Regulations (CFR) Parts 862 through 892. This information is also available from the [Product Code Classification Database page](#). There are approximately 1,750 device classifications within 16 medical specialties. Of the 1,750 classified devices, 46% are Class I, 47% are Class II and 7% are Class III.

### Class I - General Controls

Class I devices are subject to the least regulatory control. They present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. Class I devices are subject to "General Controls" as are Class II and Class III devices.

General controls include:

1. Establishment registration (use Form FDA 2891) of companies which are required to register

under 21 CFR Part 807.20, such as manufacturers, distributors, repackagers and relabelers. Foreign establishments are not required, but are encouraged, to register their facilities with FDA.

2. Medical device listing (use Form FDA 2892) with FDA of devices to be marketed.
3. Manufacturing devices in accordance with the Good Manufacturing Practices (GMP) regulation in 21 CFR Part 820.
4. Labeling devices in accordance with labeling regulations in 21 CFR Part 801 or 809.
5. Submission of a Premarket Notification [510(k)] before marketing a device.

Approximately 729 or 93% of all Class I devices are exempt from the premarket notification process. The Medical Device Exemptions page, available in Device Advice, contains the current list of 510(k) exempt Class I and Class II products. It also indicates whether the devices are also exempt from the Good Manufacturing Practices (GMP or Quality Systems) regulations. Many Class I exempt devices are also exempt from most of the GMP requirements. Only 5 Class I devices are currently subject to the Design Control portion of the GMP requirements (see 21 CFR Part 820.30(a)(2)(ii)). All other Class I devices are exempt from Design Controls found in section 820.30.

### Class II Special Controls

Class II devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls. Special controls may include special labeling requirements, guidance documents, mandatory performance standards and postmarket surveillance.

FDAMA gave FDA regulatory authority to exempt Class II devices from the 510(k) requirement and provided a mechanism for interested persons to propose Class II devices for exemption to FDA. As of September of 1998, 62 Class II devices are now exempt from Premarket Notification, which leaves roughly 740 Class II's that are subject to 510(k). FDA is also considering further Class II exemptions in response to suggestions submitted to the Agency. Exempted Class II devices can be found under Device Advice at the Medical Device Exemptions page.

Guidelines on how to suggest additional Class II exemptions to FDA can be found on the CDRH web site under "FDA Modernization Act Information", "Guidance Pertaining to the FDA Modernization Act". The guidance document is: "Procedures for Class II Exemptions from Premarket Notification; Guidance for Industry and CDRH Staff". This document is available as a TEXT file and a PDF file.

### Class III - Premarket Approval

Class III is the most stringent regulatory category for devices. Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls. Devices classified into Class III are usually those which support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

At this time, only a small portion of the approximately 122 classified Class III preamendment devices are subject to the Premarket Approval (PMA) or, alternatively, the Product Development Protocol (PDP) process. Class III devices which require an approved PMA application or completed PDP to be marketed are those:

1. Class III preamendment devices which, by regulation in 21 CFR Parts 862-892, require a premarket approval application.
2. Devices found not substantially equivalent (NSE) following FDA review of a 510(k) application. A device found NSE is automatically classified into Class III.

The remaining Class III preamendment devices may be marketed through the premarket notification [510(k)] process until FDA publishes a 515(b) notice in the Federal Register for manufacturers of that device type to submit a PMA.

**Note:** CDRH is currently reviewing Class III preamendment devices which currently do not require a PMA/PDP. When this effort is completed, those devices retained in Class III will require a PMA/PDP to be marketed. The remaining devices will be reclassified into Class II or Class I.

Classified Class III devices are found in the classification regulations in 21 CFR Parts 862-892. The classification information for each one will indicate whether a PMA or PDP is required. The classification regulations are also in Device Advice at <http://www.fda.gov/cdrh/devadvice/313.html>, and can also be identified through the [Product Code Classification Database](#).

### Changes in Device Classification

The Act contains provisions for changing the classification of a device. Changes in classification are based on FDA's receipt of new information about a device. FDA may, on its own, or in response to an outside petition, change a device's classification by regulation.

A manufacturer who wishes to have a device reclassified to a lower class must convince FDA that the less stringent class requirements will be sufficient to provide reasonable assurance of safety and effectiveness.

For example, it is likely that number of Class III preamendment devices will be reclassified into Class II or Class I.

A device found not equivalent (NSE) following 510(k) review is automatically classified into Class III. An applicant who receives such an NSE decision may choose to use a new mechanism made possible through FDAMA and request that FDA reclassify the device. This petition must be received by FDA with 30 days of the NSE decision. The following guidance "[Evaluation of Automatic Class III Designation](#)" can be found under "Guidance Pertaining to the FDA Modernization Act" under FDAMA on the CDRH web site.

[Top of Classification of Medical Devices](#)

[Device Advice](#)

[Product Code Classification Database](#)

*If you have questions or comments concerning this page, please contact the Division of Small Manufacturers Assistance at [dsma@cdrh.fda.gov](mailto:dsma@cdrh.fda.gov).*

## Center for Devices and Radiological Health

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# Classify Your Medical Device

(This page last updated: May 28, 1999)

Page 3.1.3 will lead you through the process of determining the classification of a medical device.

[Top of page](#)

This page is currently being revised to include provisions of the FDA Modernization Act of 1997 (*the Modernization Act*) and resultant CDRH re-engineering efforts. In the interim, supplementary information and guidance on this topic area can be found in the "Overview of FDA Modernization Act of 1997, Medical Device Provisions."

- [Introduction](#)
- [How To Determine Classification](#)

**Do you know the meaning of the various device classes?**

YES	NO
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## Introduction

[Page Contents](#)

The Food and Drug Administration (FDA) has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

### Device Class and Regulatory Controls

1. Class I General Controls
  - o With Exemptions
  - o Without Exemptions
2. Class II General Controls and Special Controls
  - o With Exemptions
  - o Without Exemptions
3. Class III General Controls and Premarket Approval

The class to which your device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If your device is classified as Class I or

II, and if it is not exempt, a 510k will be required for marketing. All devices classified as exempt are suspect to the limitations on exemptions. For Class III devices, a premarket approval application (PMA) will be required unless your device is a preamendments device (on the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device) and PMA's have not been called for. In that case, a 510k will be the route to market.

Device classification depends on the *intended use* of the device and also upon *indications for use*. For example, a scalpel's intended use is to cut tissue. A subset of intended use arises when a more specialized indication is added in the device's labeling such as, "for making incisions in the cornea". Indications for use can be found in the device's labeling, but may also be conveyed orally during sale of the product. A discussion of the meaning of intended use is contained in Premarket Notification Review Program K86-3 which is Appendix C of the Premarket Notification [510(k)] Manual.

In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.

As indicated above all classes of devices as subject to General Controls. General Controls are the baseline requirements of the Food, Drug and Cosmetic (FD&C) Act that apply to all medical devices, Class I, II, and III.

**Do you know the classification of your device?**



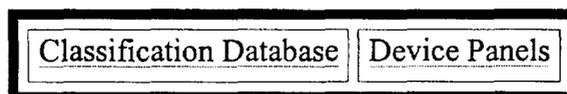
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**How to Determine Classification**

[Page Contents](#)

To find the classification of your device, as well as whether any exemptions may exist, you need to find the regulation number that is the classification regulation for your device. There are two methods for accomplishing this: go directly to the classification database and search for a part of the device name, or, if you know the device panel (medical specialty) to which your device belongs, go directly to the listing for that panel and identify your device and the corresponding regulation. You may make a choice now, or continue to read the background information below. If you continue to read, you will have another chance to go to these destinations.

**To Determine Classification of your device go to:**



If you already know the appropriate panel you can go directly to the CFR and find the classification for your device by reading through the list of classified devices, or if you're not sure, you can use the keyword directory in the PRODUCT CODE CLASSIFICATION DATABASE. In most cases this database will identify the classification regulation in the CFR. You can also check the classification regulations below and the Precedent Correspondence for information on various products and how they are regulated by CDRH.

Each classification panel in the CFR begins with a list of devices classified in that panel. Each classified device has a 7-digit number associated with it, e.g., 21 CFR 880.2920 - Clinical Mercury Thermometer. Once you find your device in the panel's beginning list, go to the section indicated: in this example, 21 CFR 880.2920 . It describes the device and says it is Class II. Similarly, in the Classification Database under "thermometer", you'll see several entries for various types of thermometers. The three letter product code, FLK in the database for Clinical Mercury Thermometer, is also the classification number which is used on the Medical Device Listing form, FDA-2892.

Once you have identified the correct classification regulation go to [What are the Classification Panels](#) below and click on the correct classification regulation or go to the [GPO CFR Search](#) page. Some Class I devices are exempt from the premarket notification and/or parts of the good manufacturing practices regulations. Approximately 572 or 74% of the Class I devices are exempt from the premarket notification process. These exemptions are listed in the classification regulations of 21 CFR and also has been collected together in the [Medical Device Exemptions](#) document.

**Do you want a description of each class of device?**

 YES NO Choose Another Topic Exit Device Advice

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**Center for Devices and Radiological Health**

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## Device Classification Panels

*(This page last updated: June 29, 1998)*

Page 3.1.3.1 describes the device classification panels and to locate classification regulations.

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This page is currently being revised to include provisions of the FDA Modernization Act of 1997 (*the Modernization Act*) and resultant CDRH re-engineering efforts. In the interim, supplementary information and guidance on this topic area can be found in the "Overview of FDA Modernization Act of 1997, Medical Device Provisions."

- [What are the Classification Panels](#)
- [How to Locate Classification Regulations](#)
- [Where to Proceed From Classification](#)

**Do you want to:**

[Read about the classification panels?](#)

[Locate classification regulations.](#)

### What are the Classification Panels

[Page Contents](#)

Most medical devices can be classified by finding the matching description of the device in Title 21 of the Code of Federal Regulations (CFR), Parts 862-892. FDA has classified and described over 1,700 distinct types of devices and organized them in the CFR into 16 medical specialty "panels" such as Cardiovascular devices or Ear, Nose, and Throat devices. These panels are found in Parts 862 through 892 in the CFR. For each of the devices classified by the FDA the CFR gives a general description including the intended use, the class to which the device belongs (i.e., Class I, II, or III), and information about marketing requirements. Your device should meet the definition in a classification regulation contained in 21 CFR 862-892.

### How to Locate Classification Regulations

[Page Contents](#)

Choose the appropriate classification panel below to obtain a listing of the associated classification regulations.

**The Device Classification Panels or Specialty Groups are:**

Anesthesiology	868	Hematology and Pathology	864
Cardiovascular	870	Immunology and Microbiology	866
Clinical Chemistry and Clinical Toxicology	862	Neurology	882
Dental	872	Obstetrical and Gynecological	884
Ear, Nose, and Throat	874	Ophthalmic	886
Gastroenterology and Urology	876	Orthopedic	888
General and Plastic Surgery	878	Physical Medicine	890
General Hospital and Personal Use	880	Radiology	892

Where to Proceed From Classification

[Page Contents](#)

If your device requires premarket notification [510(k)] proceed to the Premarket Notification [510(k)] page. For Class I devices exempt from [510(k)] the submission of a [510(k)] and marketing clearance from FDA is not required. If your Class I (or certain class II) device is exempt, subject to the limitations on exemptions, from the 510(k) process, this will be stated in the classification regulation. However, other General Controls such as registration, listing, labeling, and good manufacturing practices apply. If you have a Class III device requiring premarket approval (PMA) proceed to Premarket Approval (PMA) page.

You can also check the Precedent Correspondence for information on how various products are regulated by CDRH.

**Would you like to proceed to the appropriate market submission information?**

<a href="#">510(k)</a>	<a href="#">PMA</a>	<a href="#">Exempt</a>	<a href="#">Choose Another Topic</a>	<a href="#">Exit Device Advice</a>
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[Top of Device Classification Panels](#)

# General Controls

**Center for Devices and Radiological Health**

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## Establishment Registration

*(This page last updated: May 21, 1999)*

Page 3.4.1 details the FDA requirements for medical device establishment registration.

[Top of page](#)

This page is currently being revised to include provisions of the FDA Modernization Act of 1997 (*the Modernization Act*) and resultant CDRH re-engineering efforts. In the interim, supplementary information and guidance on this topic area can be found in the "Overview of FDA Modernization Act of 1997, Medical Device Provisions."

- [What is Establishment Registration](#)
- [Who Must Register](#)
- [How to Register](#)
- [When to Register](#)
- [Where to Send Registration Forms](#)
- [Updating Registration Data](#)
- [Obtaining Establishment Registration Data from CDRH](#)

### Do You Know What Device Registration Is?



### What is Establishment Registration

[Page Contents](#)

Establishments involved in the production and distribution of medical devices intended for marketing or leasing (commercial distribution) in the U.S. are required to register with the FDA. This process is known as initial registration. An establishment means any place of business under one management at one physical location at which a device is manufactured, assembled or otherwise processed for commercial distribution. The "owner/operator" of the establishment is responsible for registration. *Owner/operator* means the corporation, subsidiary, affiliated company, partnership, or proprietor directly responsible for the activities of the registering establishment.

Registration of an establishment is not an approval of the establishment or its devices by FDA, that is, it does not provide FDA clearance to market. Unless exempt, premarketing clearance is required before a device can be placed into commercial distribution in the U.S.

The regulation for registration can be found in Title 21 [Code of Federal Regulations, Part 807](#).

## Are You Certain that You Have to Register?



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### Who Must Register

- [Page Contents](#)

An owner/operator of an establishment not exempt under 21 CFR 807.65 who is engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of a medical device intended for commercial distribution (marketing) is required to register. That includes manufacturers, contract manufacturers, contract sterilizers, specification developers, repackagers or relabelers, manufacturers of components or accessories which are sold or leased directly to the end user, and/or distributors 21 CFR 807.20.

Wholesale distributors of devices, who do not manufacture, repackage, process, or relabel a device, are no longer required to register their establishment with the FDA. A "wholesale distributor" is defined as any person (other than the manufacturer or the initial importer) who distributes a device from the original place of manufacture to the person who makes the final delivery or sale of the device to the ultimate consumer or user.

Also, foreign establishments engaged in the manufacture, preparation, propagation, compounding, or processing of a device that is imported, or offered for import, into the U.S. must register their establishments and provide the FDA with the name of the U.S. agent representing their establishment. Foreign establishments must also continue to provide FDA with a list of the devices that they are exporting to the U.S. FDA is also authorized to enter into cooperative agreements with foreign countries to ensure that non-compliant products are refused entry into the U.S. The requirement for registration of foreign manufacturers will not take effect until the final regulation has been published. The target date for that regulation is January 31, 2000.

## Are You Required to Register?



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### How to Register

[Page Contents](#)

To register an establishment, form FDA 2891, "Initial Registration of Medical Device Establishment" must be completed by the owner/operator and submitted to FDA. Essential to completing the FDA 2891 is the Instructions for Completion of Medical Device Registration and Listing Forms FDA 2891, 2891a and 2892. It contains information on the registration process, and specific instructions for completion of FDA 2891 as well as a sample form.

When registering, owner/operators should bear these points in mind.

- Do not use post office (P.O.) box numbers as addresses on the FDA 2891. FDA will not accept P.O. box numbers. The actual street address must be used.
- In the case of small businesses, the name of the owner/operator usually is the same as the name

of the registering establishment.

- The official correspondent is an important person for purposes of registration and listing. This is the person designated by the owner/operator to be responsible for:
  - the annual registration of the establishment;
  - contact with FDA for medical device listing;
  - maintenance and submission of a current list of officers and directors to FDA upon request;
  - the receipt of pertinent correspondence from FDA directed to and involving the owner/operator and/or any of the firms establishments.

Availability of forms are addressed in Appendix 2 of the Instructions for Completion of Medical Device Registration and Listing Forms.

**Instructions for Registration & Listing**

**Obtaining Forms**

### When to Register

Page Contents

An owner/operator of an establishment must register within 30 days after entering into any activity requiring registration, including processing devices for exportation. Establishments also required to list their devices must do so at the same time they register.

### **Do You Know Where to Send the Registration Forms?**

**YES**

**NO**

### Where to Send Registration Forms

Page Contents

All copies of the completed FDA 2891 (you should make a photocopy for your own records) and any correspondence regarding registration should be mailed to:

Food and Drug Administration  
Center for Devices and Radiological Health  
Office Automation and Information Processing Branch (HFZ-308)  
2098 Gaither Road  
Rockville, MD 20850

FDA will return to the registered establishment a validated copy of the FDA 2891. This will include the establishment registration number and owner/operator ID number.

### **Do You Know When to Update Registration Information?**



---

## Updating Registration Data

[Page Contents](#)

An owner/operator of an establishment must update registration information annually after receiving annual registration form FDA-2891a. FDA will mail the FDA-2891a to the owner/operator of registered establishments automatically each year on an alphabetical schedule (21 CFR 807.21).

**However, when changes occur in ownership, establishment name, official corespondent, or addresses, FDA must be notified in writing at the address above within 30 days of such changes. This notification should be a letter that identifies the registered establishment's registration and owner/operator ID numbers and updates to the aforementioned information.**

---

## Obtaining Establishment Registration Data from CDRH

[Page Contents](#)

CDRH Freedom of Information (FOI) releasable establishment registration information is now available directly from this web site without having to submit a FOI request.

<a href="#">Releasable Establishment Registration Information</a>
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<a href="#">Medical Device Listing</a>
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<a href="#">Choose Another Topic</a>
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**Center for Devices and Radiological Health**

<a href="#">Parent Page</a>	<a href="#">Device Advice Home</a>	<a href="#">Device Advice Assistance &amp; Help</a>	<a href="#">DSMA Home</a>	<a href="#">CDRH Home</a>	<a href="#">FDA Home</a>	<a href="#">FDA Search</a>	<a href="#">CDRH Comments</a>
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# Medical Device Listing

*(This page last updated: May 21, 1999)*

Page 3.4.2 provides the FDA requirements for medical device listing (FDA Form 2892).

[Top of page](#)

- [What Is Medical Device Listing](#)
- [Who Must List](#)
- [How To List](#)
- [When To List](#)
- [Where To Send Listing Forms](#)
- [Updating Listing Data](#)
- [Obtaining Medical Device Listing Data from CDRH](#)

**Note:** Unless you are familiar with [Establishment Registration](#) it is essential to review that requirement before proceeding with Medical Device Listing.

Do You Know What Device Listing Is?

YES	NO
-----	----

## What Is Medical Device Listing

[Page Contents](#)

Most medical device establishments required to register with FDA must list the devices they have in commercial distribution including devices produced exclusively for export. This process is known as medical device listing and is a means of keeping FDA advised of the generic category(s) of devices an establishment is marketing. Medical device listing is to be done by generic category, that is, by the classification name that FDA has assigned to the device. FDA has established approximately 1700 generic categories or classification names for which most medical devices will fall. Each generic category is represented by a separate classification regulation found in Title 21 Code of Federal Regulations Parts 862-892. Furthermore, more than one type of medical device (each device having its own unique product code) may fall within one classification name. For example, there are numerous types of devices that fall into the classification name, "Manual Surgical Instruments for General Use", 21 CFR 878.4800. Devices including suturing needles, scalpels, forceps and hemostats all fall within this classification regulation.

**Listing of a medical device is not approval of the establishment or a device by FDA.**  
 Unless exempt, premarketing clearance is required before a device can be marketed, that is placed into commercial distribution in the U.S.

Are You Certain that You Have to List?

YES	NO
-----	----

---

Who Must List

[Page Contents](#)

An owner/operator of an establishment not exempt under 21 CFR 807.65 who is engaged in the manufacture, preparation, propagation, compounding, assembly or processing of a medical device intended for commercial distribution (marketing) is required to list.

This includes manufacturers, repackagers and relabelers, specification developers, and manufacturers (both U.S. and foreign) of accessories and components sold directly to the end user (21 CFR 807.20). Contract manufacturers, contract sterilizers and distributors required to register are not required to list.

Do You Know How to Device List?

YES	NO
-----	----

---

How To List

[Page Contents](#)

Necessary Tools for Listing

<a href="#">Instructions</a>	<a href="#">Obtaining Forms</a>	<a href="#">Classification Database</a>
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Listing of a medical device is done by completing form FDA 2892, "Medical Device Listing". Essential in completing FDA 2892 is Instructions for Completion of Medical Device Registration and Listing Forms FDA 2891, 2891a and 2892. It contains information on the listing process, and specific instructions as well as a sample form. In addition FDA has developed a PRODUCT CODE CLASSIFICATION DATABASE necessary for identifying the correct generic category, that is, classification name, which is a key element of the FDA 2892. When listing, owner/operators should bear in mind:

- The Classification Database contains classification names and codes to be placed in blocks 8 and 9, of FDA 2892. The classification name and code identify the generic category of device

for FDA. Final classification regulations are also in the 21 CFR 862-892 (external). However, the docket numbers or regulation numbers in the actual regulation are not put in blocks 8 and 9. Pay particular attention to the instructions for blocks 8 and 9, classification name and code, and to "multiple classification names" and "related items" that may exist.

- Only one FDA 2892 is required for each generic category (classification name) of device. Therefore, for various sizes of syringes that fall within the same generic category or classification name, an owner/operator fills out only one FDA 2892.
- The owner/operator should keep the bottom copy of the FDA 2892 because, unlike registration, no validated copy of the form FDA 2892 is returned by FDA. The bottom copy of the FDA 2892 retained by the owner/operator is proof of listing.

Assistance in determining the correct product code may be obtained by sending an inquiry to [dsma@cdrh.fda.gov](mailto:dsma@cdrh.fda.gov), or via facsimile to DSMA at 301-443-8818.

### Do You Know When to Submit Your Listing Form?

YES	NO
-----	----

### When To List

[Page Contents](#)

An owner/operator of an establishment required to list should do so within 30 days of any activity requiring listing. Usually, owner/operators list within 30 days of entering a device into commercial distribution in the U.S. An important note is that for establishments required to submit initial registration and listing they must do so at the same time, that is both the Establishment Registration Form (2891) and FDA 2892 must be submitted together.

### Do You Know Where to Submit Listing Information?

YES	NO
-----	----

### Where To Send Listing Forms

[Page Contents](#)

The completed listing forms should be mailed to:

Food and Drug Administration Center for Devices and Radiological Health Office Automation and Information Processing Branch (HFZ-308) 2098 Gaither Road Rockville, MD 20850
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### Do You Know When to Update Listing Information?

YES	NO
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---

Updating Listing Data

[Page Contents](#)

Unlike registration, listing is not updated yearly. Owner/operators are responsible for keeping data on their listing forms current. Updating is accomplished through the submission of another FDA 2892 at the time the change occurs, or each June and December. Updating is required when one of the following occurs:

- A "new" device is marketed with a classification name that is not currently listed;
- The intended use of a listed device changes in such a way that would result in its being more appropriately classified under a different generic category (classification name);
- The marketing of all models or variations of the listed device is discontinued;
- A discontinued device (not listed) is re-marketed; or
- Any of the information changes that must be supplied on the FDA 2892, other than changes in proprietary and common or usual name (blocks 9 and 10).

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Obtaining Medical Device Listing Data from CDRH

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CDRH Freedom of Information (FOI) releasable medical device listing information is now available directly from this web site without having to submit a FOI request.

<a href="#">Releasable Medical Device Listing Information</a>	<a href="#">Establishment Registration</a>	<a href="#">Choose Another Topic</a>	<a href="#">Exit Device Advice</a>
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[Top of Medical Device Listing](#)

Center for Devices and Radiological Health

## Guidance For Industry

# INSTRUCTIONS FOR COMPLETION OF MEDICAL DEVICE REGISTRATION AND LISTING FORMS FDA 2891, 2891a AND 2892

Prepared by  
Division of Small Manufacturers Assistance  
Office of Health and Industry Programs

Project Officer  
Bryan H. Benesch

July 1997

Comments on these instructions should be submitted for agency consideration by writing to Bryan H. Benesch, CDRH, 1350 Piccard Drive, HFZ-220, Rockville, MD 20850 or by E-mail to [bhb@cdrh.fda.gov](mailto:bhb@cdrh.fda.gov). For questions regarding the use of this guidance, also contact the Division of Small Manufacturers Assistance at (301) 443-6597 or (800) 638-2041; or the Information Processing and Office Automation Branch, Office of Compliance at (301) 827-4555 (press 6, then press 2 for registration and listing)

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Devices and Radiological Health  
Rockville, Maryland 20850

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INSTRUCTIONS FOR COMPLETION OF "ANNUAL REGISTRATION OF DEVICE ESTABLISHMENT,"  
FORM FDA 2891a

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**Although this guidance does not create or confer any rights, for or on any person, and does not operate to bind FDA or the public, it does represent the agency's current thinking on the Registration and Listing regulations.**

**Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.**

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## ESTABLISHMENT REGISTRATION AND MEDICAL DEVICE LISTING

### INTRODUCTION

Section 510 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that domestic establishments engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of medical devices intended for human use and commercial distribution register their establishments with the Food and Drug Administration (FDA). This is accomplished by completing FDA Form 2891, "Initial Registration of Device Establishment." The term "device" is defined in section 201(h) of the FD&C Act and includes all in vitro diagnostic products and in vitro diagnostic biological products not subject to licensing under section 351 of the Public Health Service Act (42 U.S.C. 262). Foreign manufacturers commercially distributing devices in the United States (U.S.) are not required to register; however, they are encouraged to do so. Refurbishers/reconditioners are not required to register or list, however, FDA will accept voluntary registration and listings from firms that wish to be registered with FDA.

Section 510 of the Federal Food, Drug, and Cosmetic Act requires both domestic and foreign manufacturers to list their devices with FDA if the devices are in commercial distribution. Devices are listed by their classification name on form FDA 2892. A classification name is a generic category the device being listed would be placed in.

Neither registration nor listing constitutes FDA clearance or approval for marketing or commercial distribution in the U.S. Unless the device is exempt from the clearance or approval

process, a premarket notification submission [510(k)] or a premarket approval application (PMA) is required before commercial distribution commences.

Registration of a device establishment or submission of device listing does not in any way denote approval of the establishment or its products by FDA. A firm may not advertise or distribute promotional material with any statement relating to its registration with FDA. Any labeling or other representation that creates an impression of official FDA approval is misleading and constitutes misbranding as referenced in section 301 of the FD&C Act and 21 CFR 807.39.

The regulations for registration and listing are in 21 CFR Part 807.

## 1. ESTABLISHMENT REGISTRATION

### How To Register

To register an establishment, form FDA 2891, "Initial Registration of Device Establishment," must be completed. To order copies of the form see [Appendix 2](#).

When registering, consider the following points:

- Submit all four (4) copies of the original registration form to the Center for Devices and Radiological Health (CDRH) to the address printed on the form.
- Do not use post office (P.O.) box numbers as addresses in Sections "A or B" of form FDA 2891. FDA will not accept P.O. box numbers. The actual street address must be used unless the only street address is a rural route box number or a highway mile number.

### Where To Submit

All copies of form FDA 2891 are to be submitted to the following address:

Food and Drug Administration  
Center for Devices and Radiological Health (HFZ-308)  
2098 Gaither Road  
Rockville, Maryland 20850  
Telephone No. 301-827-4555 (Press 6, then press 2 for registration and listing)

Keep a photocopy of the registration form for your records.

### INSTRUCTIONS FOR COMPLETION OF "INITIAL REGISTRATION OF DEVICE ESTABLISHMENT," FORM FDA 2891

All of the information provided on form FDA 2891 must be in English. When necessary, supplemental sheets can be used to complete or clarify your submission. Supplemental sheets must be letter size (8 ½ x 11 inches or A4) and have typed or printed in the upper right hand corner, the establishment business name from Block 2.

The numbers below refer to the item numbers on form [FDA 2891](#).

1. Registration No. Leave this space blank. The Food and Drug Administration (FDA) will assign a unique registration number to each establishment.

**SECTION A. The purpose of this section is to obtain specific information about the registering establishment.**

2. **Establishment Business Name.** Enter the legal name of the establishment involved in registration activity and limit the entry to 50 characters (abbreviate only if necessary).
3. **Record Date.** Enter the month, day, and year the form is completed using a MM/DD/YYYY date format. All entries must be numeric and two/four digits each as shown below for July 4, 1997:

Mo Day Year  
07 04 1997

4. **Number and Street.** Enter the number and street at which the registering establishment is located. Do not use Postal Box or Rural Route numbers. Limit entry to 60 characters for the street address

**Domestic Establishments:**

5. **City and Foreign State.** Enter the city name in which the establishment is located. Limit entry to 30 characters.
6. **State.** Enter the two-character State code of the U.S. Postal Service for the State, territory, or possession.
7. **ZIP Code +4.** Enter the U.S. Postal ZIP Code +4.
8. **Foreign Country.** Leave blank.

**Foreign Establishments:**

5. **City and Foreign State.** Enter the city and foreign state (i.e., province, prefecture, region, territory) names in which the establishment is located. Limit entry to 30 characters, abbreviate if necessary (e.g., Vancouver, B.C.)
6. **State.** Leave blank.
7. **Zip Code/Postal Code.** Enter the foreign country Postal Code/Zip Code. Limit entry to 10 characters.
8. **Foreign Country.** Enter the foreign country name.

**Both Domestic and Foreign Establishments:**

9. **Establishment Type.** Space is provided for each designated code for establishment type. Select from the following list of establishment types the appropriate codes that reflect the device activities of the establishment. Definitions for each establishment type appear in Appendix 3. Circle all of the letter designation(s) that apply to the establishment (e.g., M and C, or S and ID, etc.)

C	CERTIFYING SITE/MDR REPORTING SITE.
DD**	DOMESTIC DISTRIBUTOR.
E*	CONTRACT MANUFACTURER.
M	MANUFACTURER.
R	REPACKAGER AND/OR RELABELER.
S	SPECIFICATION DEVELOPER.
T*	CONTRACT STERILIZER.
UU.S.	DESIGNATED AGENT.
X	REMANUFACTURER.
ID	INITIAL DISTRIBUTOR.
K***	REFURBISHER/RECONDITIONER.

**\* NOTE: A September 1, 1993 Federal Register notice erroneously exempted contract manufacturers and contract sterilizers from registration. That exemption will be revoked.**

**\*\*NOTE: Since 1995, FDA has exercised its enforcement discretion and is not currently requiring or accepting registration or listing forms from domestic distributors.**

**\*\*\*NOTE: Refurbishers/reconditioners are not required to register and list, however, CDRH will accept voluntary registrations and listings. To do so, print or type the letter "K" in one of the empty boxes in Block number 9.**

- 10. Pre-production Registration. To be used only when registering prior to commencing actual production, otherwise check NO. A pre-production registration will be held by CDRH for only one (1) year. After one year CDRH automatically notifies the firm that it must register as an active firm. If the establishment does not notify CDRH that it has begun an activity that requires registration, the pre-production registration form will then be archived without further processing. The establishment must notify CDRH by letter when their status has changed to "in production or active" and submit a Device Listing form, FDA 2892, if one is required. At that time the initial registration form will be further processed and a registration number issued.**

**SECTION B. The purpose of this section is to obtain information about the owner or operator of the registering establishment.**

#### **Both Domestic and Foreign Establishments**

- 11. Owner/Operator Business Name. Enter the business trading name of the corporation, subsidiary, affiliated company, or partnership that is the owner or operator of the registering establishment. Only enter the proprietor's name if no other business trading name exists. Limit entry to 50 characters (abbreviate only if necessary).**
- 12. Owner/Operator I.D. Fill in if an Owner or Operator I.D. number has been previously issued by CDRH. Leave this space blank if no identification number has been issued by CDRH. CDRH will assign an identification number and provide this to the registrant.**
- 13. Number and Street. Enter the number and street at which the owner or operator is located. Limit entry to 60 characters for the street address.**

#### **Domestic Establishments**

- 14. City and Foreign State. Enter the city in which the owner or operator is located. Limit entry to 30 characters.**

15. **State.** Enter the two-character State code of the U.S. Postal Service for the State, territory, or possession.
16. **ZIP Code +4.** Enter the U.S. Postal ZIP Code +4.
17. **Foreign Country.** Leave blank.
18. **Telephone Number.** Enter the area code and/or country plus city codes and telephone number, including extension, only if the number is different from that of the official correspondent. If there is a toll free (800 or 888) number, CDRH requests it be given.

#### **Foreign Establishments**

14. **City and Foreign State.** Enter the city and foreign state names (i.e., province, prefecture, region, territory) in which the owner or operator is located. Limit entry to 30 characters.
15. **State.** Leave blank.
16. **Zip Code/Postal Code.** Enter the foreign country Postal Code. Limit entry to 10 characters.
17. **Foreign Country.** Enter the foreign country name.
18. **Telephone Number.** Enter the country code, city code and telephone number, including extension, only if the number is different from that of the official correspondent.

**SECTION C.** The purpose of this section is to identify the individual designated as official correspondent. FDA will direct important correspondence to the individual identified in this section.

19. **Official Correspondent/U.S. Designated Agent.** Enter the name of the individual designated as the official correspondent for registration and listing purposes. The name must be neatly printed or typed.

The requirement in 21 CFR 807.40 to have a U.S. Designated Agent has been placed in abeyance, as of July 23, 1996, so do not provide this information. There is no existing requirement to employ a U.S. Designated Agent, so foreign establishments do not need to hire one. The Official Correspondent requirement is not in abeyance and must be completed.

20. **Registration Number.** Leave blank since this was intended for the registration number of the U.S. Designated Agent.
21. **Business Name.** Enter the name of the establishment, owner or operator, or other place of business, as applicable, with which the official correspondent is associated. This may be the same name as, or different from, Block 2 or Block 11. Limit entry to 50 characters.
22. **Number and Street.** Enter the number and street or post office box of the official correspondent's place of business. A Post Office box number is acceptable in Section C, since this address will be used for FDA mailings. Limit entry to 60 characters for the street address.

#### **Domestic Establishments:**

23. **City.** Enter the city name in which the official correspondent's place of business is

located. Limit entry to 30 characters.

- 24. **State.** Enter the two-character State code of the U.S. Postal Service for the State, territory, or possession.
- 25. **ZIP Code +4.** Enter the U.S. Postal ZIP Code +4.

**Foreign Establishments:**

- 23. **City, Foreign State and Country.** Enter the city, state and country name in which the official correspondent's place of business is located. Limit entry to 30 characters. The form does not have a separate item for State and Country because the U.S. Designated Agent provision required all official correspondent's to be located in the United States. While this provision is in abeyance, please provide the Foreign State and Country information in this block or on a supplemental page.
- 24. **State.** Leave blank.
- 25. **Postal Code/ZIP Code.** Enter the foreign country Postal Code. Limit entry to 10 characters.

**Both Domestic and Foreign Establishments:**

- 26. **Telephone Number.** Enter the area code and/or country plus city codes and telephone number, including extension, of the official correspondent, as it would be dialed from the U.S. If there is a toll free (800 or 888) number, CDRH requests it be given.
- 27. **FAX Number.** Enter the area code and/or country plus city codes and the FAX machine number of the official correspondent, as it would be dialed from the U.S.

**SECTION D.** The purpose of this section is to record other names for the registering establishment that relate to device activities and that are different from the name entered in Section A.

- 28. **Other Business Trading Name.** Enter any other establishment names used, using one of the six blocks for each name. This can include "d.b.a." (doing business as) names. Limit entry in each block to 50 characters. Use an attached sheet if the number of names exceeds six. Do not include the names of distributors for whom this establishment makes devices. Do not list registered trademarks in use by the firm.

**SECTION E.** The signature (29) and title (30) of the designated official correspondent must appear in this section.

Exhibit 1: FDA form 2891

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION <b>INITIAL REGISTRATION OF DEVICE ESTABLISHMENT</b> <i>(Shaded Areas are for FDA Use Only)</i>	Form Approved: OMB No. 0910-0059. Expiration Date: February 28, 1999  <b>VALIDATION</b>
<b>RETURN THIS FORM TO:</b> Food and Drug Administration, Center for Devices and Radiological Health, (HFZ-308), 2098 Gaither Road, Rockville, MD 20850	<b>1. REGISTRATION NO.</b>
Public reporting burden for this collection of information is estimated to average .25 hour 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 (0910-0316)  
 Hubert H. Humphrey Building, Room 531-H  
 200 Independence Avenue, S.W.  
 Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address,

NOTE: This form is authorized by Section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360). Failure to report this information is a violation of Section 301(p) of the Act(21 U.S.C. 331(p)). Persons who violate this provision may, if convicted, be subject to a fine or imprisonment or both. The submission of any report that is false or misleading in any material respect is a violation of Section 301(q)(2), (21 U.S.C. 331(q)(2) and may be a violation of 18 U.S.C. 1001.

**SECTION A**

<b>2. ESTABLISHMENT BUSINESS NAME</b>		<b>3. RECORD DATE</b> (Mo.)                      (Day)                      (Yr.)	
<b>4. NUMBER AND STREET</b>	<b>5. CITY AND FOREIGN STATE</b>	<b>6. STATE</b>	<b>7. ZIP CODE</b>
<b>8. FOREIGN COUNTRY</b>	<b>9. ESTABLISHMENT TYPE (See Instructions Booklet)</b>  C   DD   E   M   R   S   T   U   X   ID 	<b>10. PREPRODUCTION REGISTRATION</b> __ YES __ NO	

**SECTION B**

<b>11. OWNER/OPERATOR BUSINESS NAME</b>		<b>12. OWNER/OPERATOR I.D.</b>	
<b>13. NUMBER AND STREET</b>	<b>14. CITY AND FOREIGN STATE</b>	<b>15. STATE</b>	<b>16. ZIP CODE</b>
<b>17. FOREIGN COUNTRY</b>	<b>18. TELEPHONE NUMBER- IF DIFFERENT FROM THAT OF OFFICIAL CORRESPONDENT (Area Code) (Number &amp; Extension)</b>		

**SECTION C**

<b>19. OFFICIAL CORRESPONDENT/U.S. DESIGNATED AGENT</b>		<b>20. REGISTRATION NUMBER</b>	
<b>21. BUSINESS NAME</b>			
<b>22. NUMBER AND STREET</b>	<b>23. CITY</b>	<b>24. STATE</b>	<b>25. ZIP CODE</b>
<b>26. TELEPHONE NUMBER (Area Code) (Number and Extension)</b>		<b>27. FAX NUMBER (Area Code) (Number)</b>	

**SECTION D**

**28. OTHER BUSINESS TRADING NAMES**  
 (Enter any other name which the establishment in field #2 uses. Do not list Registered trademarks or names of private label distributors. This is usually any name such as a brand name which is not the firm name).

SEQ	BUSINESS NAME	SEQ	BUSINESS NAME
SO1		SO4	
SO2		SO5	
SO3		SO6	

**SECTION E**

<b>29. SIGNATURE OF OFFICIAL CORRESPONDENT</b>	<b>30. TITLE</b>
--	------------------

FORM FDA 2891 (5/96)

PREVIOUS EDITIONS ARE OBSOLETE.

\*U.S. GPO:1996-404-897/41025

**INSTRUCTIONS FOR COMPLETION OF "ANNUAL REGISTRATION OF DEVICE ESTABLISHMENT," FORM FDA 2891a**

**Introduction**

Each year active, registered establishments will receive a pre-printed annual registration form FDA 2891a from CDRH. This form is to be used to notify FDA of changes to the current registration information for the establishment. Only those items needing changes or corrections need be completed. This form must be returned to CDRH even if no changes have occurred. The form comes with three parts and is pre-addressed for return to CDRH. After detaching Parts 1 and 3 and retaining for your company files, fold Part 2 in half and it becomes a mailer requiring only the addition of first class or air mail postage.

All of the information provided on form FDA 2891a must be in English. When necessary, supplemental sheets can be used to complete or clarify your submission. Supplemental sheets must be letter size (8 ½ x 11 inches or A4) and have typed or printed in the upper right hand corner, the registration number of the firm.

iii The letters below refer to the block letters on form FDA 2891a.

A. Type of Submission. Complete block A by checking one box according to the following instructions:

*No Change.* Check this box if all of the information printed to the left of Blocks B, C, D, E, or F is correct and complete. Check the "NO CHANGE" box on the outside of the mailer.

*Correction.* Check this box if any information printed to the left of Blocks B, C, D, E, or F is incorrect or incomplete. Make corrections, additions, or deletions in the corresponding blocks. Check the "CHANGE" box on the outside of the mailer.

*No Longer Device Establishment.* Check this box if the establishment is no longer engaged in activities (see establishment types in Appendix 3) which require it to be registered as a medical device establishment, but the establishment is still in existence for other activities or purposes. If any of the information printed to the left of Blocks B, D, or F is incorrect, this information should be corrected. Check the "CHANGE" box on the outside of the mailer.

*Out of Business.* Check this box if the establishment has ceased to exist as an identifiable organization. Make changes to information printed to the left of Blocks B, C, D, E, or F so that the information reflects the current information at the time the establishment went out of business. Check the "CHANGE" box on the outside of the mailer.

- B. Registered Establishment Information. Indicate any changes or corrections to the information in block B. If the establishment type has changed to M, R or S, then a new or initial Device Listing form FDA 2892 must be submitted for all the medical devices marketed by the firm that are affected by this change. Previously listed devices may also need to have updated forms FDA 2892 submitted.
- C. Establishment Type. Indicate any changes or corrections to the information in block C. (See Establishment Types in Appendix 3).
- D. Owner/Operator Information. Indicate any changes or corrections to the information in block D.

**E. Other Business Trading Names.** Indicate any changes or corrections to the information in block E.

**F. Official Correspondent/U.S. Designated Agent Information.** Indicate any changes or corrections to the information in block F. The U.S. Designated Agent provision is in abeyance, as of July 23, 1996, so do not provide this information.

**G. Official Correspondent Signature and Title Line.** The official correspondent must sign, date, and print or type title.

**Mailing Instructions**

After Part 2 of the form is completed, it should be folded in half with the CDRH address on the outside. Tape (DO NOT STAPLE) where indicated. Check the "CHANGE" or "NO CHANGE" box as appropriate on front of the mailer. Affix first-class or air mail postage and mail. Retain Part 1 for your records, do not return Part 1 to CDRH.

Exhibit 2: FDA Form 2891a - Front Page

REGISTRATION NO.: FOR:	DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	NOTE: This form is authorized by Section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360). Failure to report this information is a violation of Section 301(p) of the Act (21 U.S.C. 331(p)). Persons who violate this provision may, if convicted be subject to a fine or imprisonment or both. The submission of any report that is false or misleading in any material respect is a violation of Section 301(q)(2), (21 U.S.C. 331(q)(2)) and may be a violation of 18 U.S.C. 1001.
OWNER/OPERATOR NO.:	ANNUAL REGISTRATION OF DEVICE ESTABLISHMENT	
REGISTERED ESTABLISHMENT	OWNER/OPERATOR	
OFFICIAL CORRESPONDENT	ESTABLISHMENT TYPE	
Detach Part 1 and Keep as Proof of Registration. Complete and Return Part 2. Detach and Refer to Part 3 for Specific Instructions.		
Form FDA 2891(a) (5/96)	Part 1 - Keep for Your Records	Form Approved: OMB No. 0910-0059 Expiration Date: February 28, 1999
(BAR CODE)	DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION ANNUAL REGISTRATION OF DEVICE ESTABLISHMENT	
A) TYPE OF SUBMISSION <input type="checkbox"/> No Change <input type="checkbox"/> No Longer Device Establishment (Mark one [X] only) <input type="checkbox"/> Correction <input type="checkbox"/> Out of Business		
REGISTERED ESTABLISHMENT INFORMATION	B) CORRECTIONS TO REGISTERED ESTABLISHMENT INFORMATION	
	Establishment Name	
	Number and Street	
	City	State
	Zip	Country
ESTABLISHMENT TYPES (If information below is inaccurate, correct in column to right)	C) CORRECTIONS TO ESTABLISHMENT TYPE (To correct, mark all which correctly apply)	
<input type="checkbox"/> C Certifying Site/MDR Rptng. Site <input type="checkbox"/> R Repackager and/or Relabeler	<input checked="" type="checkbox"/> X Remanufacture <input type="checkbox"/> E Contract Manufacturer	<input type="checkbox"/> C Certifying Site/MDR Rptng. Site <input type="checkbox"/> R Repackager and/or Relabeler
		<input checked="" type="checkbox"/> X Remanufacture <input type="checkbox"/> E Contract Manufacturer

<input type="checkbox"/> ID Initial Distributor <input type="checkbox"/> DD Distributor <input type="checkbox"/> S Specification Dev.	<input type="checkbox"/> T Contract Sterilizer <input type="checkbox"/> M Manufacturer <input type="checkbox"/> U U.S. Designated Agent	<input type="checkbox"/> ID Initial Distributor <input type="checkbox"/> DD Distributor <input type="checkbox"/> S Specification Dev.	<input type="checkbox"/> T Contract Sterilizer <input type="checkbox"/> M Manufacturer <input type="checkbox"/> U U.S. Designated Agent
<b>OWNER/OPERATOR INFORMATION</b>		<b>D  CORRECTIONS TO OWNER/OPERATOR INFORMATION</b>	
		Business Name	
		Number and Street	
		Number and Street	
		City	State
		Zip	Country
		Phone No. ( )	Ext.
		Owner/Operator Number	
<b>OTHER BUSINESS TRADING NAMES</b>		<b>E  CORRECTIONS TO TRADING NAMES (If name on left has errors, write corrected name on line to its right. If no longer used, write "DELETE". Write new names last, preceded by and asterisk.</b>	
<b>OFFICIAL CORRESPONDENT INFORMATION</b>		<b>F  CORRECTIONS TO RESPONDENT / U.S. DESIGNATED AGENT</b>	
		Name of Individuals	
		Business Name	
		Number and Street	
		Number and Street	
		City	State Zip
		Registration Number	
		Phone No. ( )	Ext. FAX No.( )
<b>G  SIGNATURE OF OFFICIAL CORRESPONDENT / U.S. DESIGNATED AGENT</b>		<b>TITLE OF OFFICIAL CORRESPONDENT / U.S. DESIGNATED AGENT</b>	<b>DATE SIGNED</b>

Form FDA 2891 Part 2 - Complete and Return Form Approved: OMB No. 0910-0059 Expiration Date: February 28, 1999 (BAR CODE)

**INSTRUCTIONS FOR COMPLETING FORM FDA 2891a  
ANNUAL REGISTRATION OF DEVICE ESTABLISHMENT**

1. DETACH PART 1. *KEEP THIS PART FOR YOUR RECORDS AS PROOF OF REGISTRATION*
2. Review Part 2 for changes and corrections. Complete Block A by checking one box according to the instructions below. Make corrections in Blocks B, C, D, E, and F as indicated. See reverse side of Part 3 for definitions.
  - No Change** - Check this box if all of the information printed to the left of Blocks B, C, D, E, and F is correct and complete. Check the "NO CHANGE" box on the outside of the mailer.
  - Correction** - Check this box if any information printed to the left of Blocks B, C, D, E, or F is incorrect or incomplete. Make corrections, additions, or deletions in the corresponding blocks. Check the "CHANGE" box on the outside of the mailer.
  - No Longer Device Establishment** - Check this box if the establishment is no longer engaged in activities (see establishment types) which require it to be registered as a medical device establishment, but the establishment is still in existence for other activities or purposes. If any of the information printed to the left of Blocks B, D, or F is incorrect, this information should be corrected. Check the "CHANGE" box on the outside of the mailer.
  - Out of Business** - Check this box if the establishment has ceased to exist as an identifiable organization. Make changes to information printed to the left of Blocks B, C, D, E, or F so that the information reflects the current information at the time the establishment went out of business. Check the "CHANGE" box on the outside of the mailer.
3. Sign and Mail Part 2.
  - Sign** - Official Correspondent must sign, date, and provide title in Block G. Photocopy Part 2 for your records, if desired.
  - Mail** - Fold form in half with FDA address to outside. Tape (do NOT staple) where indicated. Check "CHANGE" or "NO CHANGE" box as appropriate on front of mailer. Affix first class postage and mail.

## Part 3 - Instructions

## Exhibit 2: FDA Form 2891a - Back Page

Food and Drug Administration  
 Center for Devices and Radiological Health  
 Information Processing and  
 Office Automation Branch (HFZ-308)  
 2098 Galther Road  
 Rockville, MD 20850-4015

     CHANGE  
     NO CHANGE

## ESTABLISHMENT TYPE DEFINITIONS

**ESTABLISHMENT TYPE** - Space is provided for each designated code for establishment type. Select from the following descriptions the appropriate code or codes that reflect the device activity of the of the establishment. Enter the letter designation(s) in the space provided.

**C CERTIFYING SITE/MDR REPORTING SITE**-Registered site responsible for submission of the annual certification of the number of MDR reports submitted.

**DD DISTRIBUTOR** - Is any person who furthers the marketing of a device from the original place of manufacture, to the person who makes final delivery or sale to the ultimate consumer or user, but does not repackage, or otherwise change the container, wrapper, or labeling of the device or device package. This also includes, but is not limited to, direct sale, mailorder, leasing, distributing promotional samples, distributing demonstration units, and drop shipping. Distributor does not include brokers or other persons who do not own the device, but merely perform a service for the person (other than the ultimate consumer) who does own the device. *NOTE: The requirement for registration of a domestic distributor is currently not being enforced pending revocation of this requirement.*

**E \*CONTRACT MANUFACTURER**- Manufactures a finished device to another establishment's specifications. The manufacturing establishment does not commercially distribute the device under its own name.

**M MANUFACTURER**-Makes by chemical, physical, biological, or other procedures, any article that meets the definition of device of "device" in section 201(h) of the Federal Food, Drug, and Cosmetic (FD&C) Act.

**R REPACKAGER AND/OR RELABELER**- *Repackager:* Packages finished devices from bulk or repackages devices made for the establishment by a manufacturer into different containers (excluding shipping containers). *Relabeler:* Changes the content of the labeling from that supplied from the original manufacturer for distribution under the establishment's own name. (This does not include establishments that do not change the original labeling but merely add their own name.)

**S SPECIFICATION DEVELOPER**-Develops specifications for a device that is distributed under the establishment's own name but performs no manufacturing.

**T CONTRACT STERILIZER**-Provides a sterilization service for another establishment's devices.

**U U.S. DESIGNATED AGENT**-Person designated by owner or operator of a foreign establishment responsible for the annual certification of the number of MDR reports.

**ID INITIAL DISTRIBUTOR**-Takes first title to imported devices.

**X REMANUFACTURE**-Persons who rebuild used device to new operating specifications for the purpose of redistribution.

*\*NOTE: A September 1, 1993 Federal Register notice erroneously exempted contract manufacturers and contract sterilizers from registration. That exemption will be revoked.*

FORM FDA 2891a (5/96)

Before sealing, did you remember to

1. Check a box in Block A?
2. Sign and Date Block G?
3. Check "Change" or "No Change" on the front mailer?
4. Affix first class postage?

Public reporting burden for this collection of information is estimated to average .25 hour 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 (0910-0059)  
 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.

RETAIN FOR YOUR RECORD

FORM FDA 2891a (5/96)

## 2. MEDICAL DEVICE LISTING

### How To List

**Listing a device is done by completing form FDA 2892, Device Listing. To aid in completing this form, CDRH provides an on-line, searchable product classification database on its World Wide Web Home Page, <http://www.fda.gov/cdrh/prodcode.html>. See Appendix 4 for instructions on how to use the database for obtaining the proper classification name(s) and number(s) to complete Blocks 7 and 8 of Form FDA 2892. This information can also be found in the CDRH publication titled, "Classification Names for Medical Devices and In Vitro Diagnostic Products." Copies can be obtained from the Division of Small Manufacturers Assistance (DSMA) or the Information Processing and Office Automation Branch (IPOAB) (See Appendix 2 for ordering information).**

**When listing, remember these points:**

- **Submit only original listing forms. Form FDA 2892 must not be reproduced because of the preprinted document number. The preprinted document number in Block 1 represents the company and the product listed on the form. CDRH will not accept photocopies of form FDA 2892. CDRH will now accept computer-generated facsimiles of the form FDA 2892 which use the document number from a preprinted form. The blank preprinted form must then be attached to the computer-generated facsimile so that its unique number is not used again. The original copy of the computer-generated form must be submitted. To receive approval to use computer-generated facsimiles of the FDA 2892, submit a copy of the proposed facsimile to the IPOAB (see Appendix 2 for address).**
- **When completing Blocks 7 and 8 of the device listing form, pay particular attention to the classification name and number as they represent the generic category of devices an establishment intends to market. The classification number is also referred to as the FDA product code or FDA code. You will find both product codes and classification names in the on-line database mentioned above, or FDA publication titled, "Classification Names for Medical Devices and In Vitro Diagnostic Products." If you cannot find a classification name or number, then contact DSMA or IPOAB. Additional classification names and numbers are periodically added or updated by CDRH and may not be in the publication**

but will be in the on-line database. In addition, the classification number can be found in your marketing clearance letter for 510(k) and PMA applications cleared starting in 1994. You may also attach a description of the device to the FDA 2892 and request assistance in determining the classification name and/or number. To assist CDRH, this description should include a copy of the device labeling, possible classification names or numbers, and 510(k) or PMA numbers.

### **Listing For Foreign Establishments**

Foreign establishments that export medical devices to the United States are required to list the devices with FDA on form FDA 2892, "Device Listing."

Things to remember are that:

- Foreign establishments may list their products directly with FDA by completing and submitting the device listing form FDA 2892.
- Foreign establishments for which there exists joint ownership and control with a domestic U.S. establishment may have the domestic establishment submit the device listing form FDA 2892. A letter explaining this relationship must be submitted to FDA by the foreign establishment with the appropriate forms, FDA 2891 (Initial Registration form) or FDA 2892.
- Foreign establishments for which there is no joint ownership and control with a domestic U.S. establishment may comply with the listing requirement by authorizing a sole initial U.S. distributor to complete the listing form FDA 2892 on their behalf. A sole initial distributor is an "exclusive distributor of a specific device imported from a foreign manufacturer," that is, they are the only distributor in the U.S. importing specific devices from a specific manufacturer.

To authorize a sole initial distributor to list on behalf of a foreign manufacturer and maintain a historical listing file, the foreign manufacturer must provide the distributor with a "letter of authorization." This letter should state that: "[named distributor] is the sole initial domestic U.S. distributor of a [specific device] and they are authorized to list on behalf of [the manufacturer] and maintain their historical listing file." The "letter of authorization" must accompany the Device Listing form FDA 2892, be on the foreign establishment's letterhead and be in English, for the device listings to be valid. In addition, the "letter of authorization" should only pertain to the specific device for which the importer will be the sole source.

## **INSTRUCTIONS FOR COMPLETION OF MEDICAL DEVICE LISTING FORM FDA 2892**

### **Introduction**

All of the information provided on form FDA 2892 must be in English. When necessary, supplemental sheets can be used to complete or clarify your submission. Supplemental sheets must be letter size (8 ½ x 11 inches or A4) and have typed or printed in the upper right hand corner, the preprinted document number from Block 1 for that submission.

Any item(s) submitted for listing purposes (i.e., letter of authorization, labeling may be needed to determine classification name and number, catalog pages, etc.) must have the document number from Block 1 of Form 2892 for that submission entered on each separate item. This material is only necessary if a firm cannot determine the appropriate classification name or

number to use.

### Completion Of Form FDA 2892

The FDA controls all listing submissions based upon the preprinted document number in Block 1 of form FDA 2892. Form FDA 2892 is a three-part form. The yellow copy is a file copy for the owner or operator and must be detached before sending the two white copies to CDRH.

- The two white copies of the form FDA 2892 are to be submitted to the following address:

**Food and Drug Administration  
Center for Devices and Radiological Health  
Information Processing and Office Automation Branch (HFZ-308)  
2098 Gaither Road  
Rockville, Maryland 20850 USA**

Any correspondence with CDRH relating to a specific listing must reference its document number from Block 1. The document number is not to be interpreted as a license or approval number and it shall not be used on your device labeling.

The numbers below correspond to block numbers on form FDA 2892:

1. **Document Number.** Preprinted number which is to be referenced in any correspondence with FDA regarding a specific device.
2. **Reason for Submission.** Check the appropriate reason.
3. **Report Date.** Enter the actual date that the form FDA 2892 was completed by you. The date format is 07/04/1997 or MM/DD/YYYY.
4. **Owner/Operator ID Number.** Enter in Block 4 the seven-digit number assigned to the owner or operator when the establishment registered with FDA. The owner or operator ID is located in Block 12 of form FDA 2891, and is also on form FDA 2891a. If the firm has not previously registered or listed, and therefore no owner or operator number has been received at the time of making an initial listing, then leave this block blank. The owner/operator ID number will be entered by CDRH when assigned.

Foreign establishments that are not registered will leave Block 4 blank. CDRH will assign an owner or operator ID number and send the firm a letter specifying what the number is. After CDRH has assigned this number, it should be used on all FDA 2892 forms subsequently submitted.

5. **Owner/Operator Name.**

**Domestic:** Enter in Block 5 the business trading name of the corporation, subsidiary, affiliated company, or partnership that is responsible for completing and submitting the device listing information.

**Foreign:** Enter in Block 5 the foreign owner or operator's business trading name of the corporation, subsidiary, affiliated company, or partnership that is responsible for completing and submitting the device listing information.

**Domestic or Foreign:** Only enter the proprietor's name if no other business trading name exists. When applicable, this name should be the same name as was entered in Block 11

on form FDA 2891, "Initial Registration of Device Establishment" or in Section D of form FDA 2891a, "Annual Registration of Medical Device Establishment."

6. **Address.** Enter the full street, city, state/foreign state, zip code +4 or postal code and foreign country. If this address is the same as submitted on form FDA 2891, please check the box provided, but still complete this block in its entirety.
7. **Classification Name.** Enter the classification name for the generic category of the device. The classification name can be found in the on-line product classification database (see Appendix 4), or in the CDRH publication entitled "Classification Names for Medical Devices and In Vitro Diagnostic Products." **DO NOT ENTER "NONE" OR "MULTIPLE" IN THIS BLOCK.** If you cannot determine the classification name, consult your marketing clearance letter, or provide the 510(k) number or PMA number or regulation number of the product. Otherwise contact DSMA for assistance.
8. **Classification Number (FDA Code or FDA Product Code).** Enter the three letter alpha character code (ignore the two numbers) from the classification list that corresponds to the classification name you have selected, or enter the code that appears on the marketing clearance letter. Again, the classification list appears in the on-line database, or in the CDRH publication entitled "Classification Names for Medical Devices and In Vitro Diagnostic Products." If you can not determine the classification number provide the 510(k), PMA or regulation number of the device. Otherwise, contact DSMA for assistance. Do not confuse this number with the seven digit regulation number assigned to each type of device classified in the Code of Federal Regulations, Parts 862-892.
9. **Proprietary Name (Brand Name).** Enter the proprietary name, such as the trade, brand or catalog name of the device. Use only those abbreviations in the proprietary name that appear on the label or labeling. Exclude as part of the device proprietary name any reference to physical characteristics such as size, package shape, or color. If more than one proprietary name is used for the device or devices being listed, enter "Multiple" in Block 9. Limit entry to 80 characters.
10. **Common or Usual Name.** FDA recognizes that no "established names" for devices have been designated pursuant to section 508 of the Act and that few "official titles" for devices are recognized in an official compendium. Consequently, the common or usual name must be provided in order to satisfy the listing requirement. The common or usual name can be any descriptive phrase and does not have to have industry-wide or user acceptance. Limit entry to 80 characters.

If the common or usual name is the same as that entered for the proprietary name, enter "SAME" in Block 10.

If more than one device is being listed under one classification name, enter a descriptive phrase which represents the group of devices, i.e., "Various Types of Rongeurs," or "Various Models of X-Ray Systems."

If one or more devices represented by a classification name is labeled and marketed as "sterile," include the word sterile as part of the common or usual name, i.e., "Various Types of Sterile and Non-sterile Syringes."

If the device is an "accessory" or a "kit," then include these words as part of the common or usual name, i.e., "Accessory to an Endoscope," "Wound Dressing Kit," "First Aid Kit."

11. **U.S. Designated Agent.** This requirement is not in effect so leave it blank. The requirement in 21 CFR 807.40 to have a U.S. Designated Agent has been placed in abeyance, as of July 23, 1996, so do not provide this information. There is no existing

requirement to employ a U.S. Designated Agent, so foreign establishments do not need to hire one.

**12. Establishment Name and Address.**

Provide registration number, name and address, and establishment type information as follows:

**Registration No.:** If you have already registered, enter in Block 12, line A the registration number of the manufacturing site from your copy of form FDA 2891 or FDA 2891a. If the establishment is not registered, then leave blank. The only firms to be listed in Block 12 are those registered by the owner or operator listed in Block 5 or foreign establishments that elect not to register.

Foreign owner or operators that do not have a registration number should enter "NONE" under registration number in Block 12. Foreign owner or operators should not identify their sole initial distributors unless the distributors are owned by the foreign firm and they are required to be listed.

**Name and Address.** Enter in Block 12 the name of the establishment where the listed device is produced. "Establishments" include those performing specifications development and repackaging or relabeling activities. For registered establishments the name should be identical to the name on your copy of form FDA 2891 or FDA 2891a. The only names to be entered in block 12 are those associated with, owned or substantially controlled by, the owner or operator listed in Block 5 and are the actual locations or where listed devices are manufactured. No contract manufacturer names should be listed unless owned or substantially controlled by owner or operator listed in Block 5.

**Establishment Type.**

**Foreign Establishments:** If your company is a manufacturer then place a mark (X) below "M" on Line A.

**Domestic Establishments:** Place a mark (X) in Block 12 under the appropriate letter code or codes from the list of establishment types that appear in Appendix 3 that describe the activities that occur at the establishment. You may check as many codes as apply.

**Examples:**

- a. If an establishment site is involved only in the development of specifications, enter a mark (X) in the "S" column for that establishment.
- b. If an establishment site manufactures and labels a device with its company name(s) only, enter a mark (X) in the "M" column for that establishment.

**13. Signature.** The Official Correspondent, or sole initial distributor completing form FDA 2892 must sign in the space provided.

**14. Name.** Type or print neatly the name of the individual who signed Block 13.

Exhibit 3: FDA Form 2892

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION <b>DEVICE LISTING</b>		Form Approved: OMB No. 0910-0059. Expiration Date: February 28, 1999							
<b>Complete and Return to:</b>		Food and Drug Administration Center for Devices and Radiological Health Information Processing and Office Automation Branch (HFZ-308) 2098 Gaither Road Rockville, MD 20850							
<b>NOTE:</b> This form is authorized by Section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360). Failure to report this information is a violation of Section 301(p) of the Act (21 U.S.C. 331(p)). Persons who violate this provision may, if convicted be subject to a fine or imprisonment or both. The submission of any report that is false or misleading in any material respect is a violation of Section 301(q)(2),(21 U.S.C. 331(g)(2) and may be a violation of 18 U.S.C. 1001.									
1. DOCUMENT NUMBER	2.	<b>REASON FOR SUBMISSION</b> <input type="checkbox"/> New Listing <input type="checkbox"/> Update to Device <input type="checkbox"/> Already Listed <input type="checkbox"/> Delete Listing	<b>3. REPORT DATE</b> MO.   DAY   YR.     						
		4. OWNER/OPERATOR ID NUMBER							
5. OWNER/OPERATOR NAME									
6. ADDRESS (Check if same as submitted on FDA Form 2891)									
a. NUMBER and STREET									
b. CITY, STATE, ZIP CODE			c. FOREIGN COUNTRY						
7. CLASSIFICATION NAME			8. CLASSIFICATION NUMBER						
9. PROPRIETARY NAME (Brand Name)									
10. COMMON OR USUAL NAME									
11. FOR U.S. DESIGNATED AGENTS OF FOREIGN ESTABLISHMENTS									
a. NAME		B. REGISTRATION NUMBER							
12.									
<b>ESTABLISHMENT NAME AND ADDRESS</b> (Identification of Sites Where Listed Device is Produced) Registration No.(Name, Street Number, City, State or County, ZIP or Postal Code)ESTABLISHMENT TYPE									
A	M	R	S	T	X				
B									
C									
D									
Public reporting burden for this collection of information is estimated to average 30 minutes 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 (0910-0059)person is An agency may not conduct or sponsor, and a									

Paperwork Reduction Project (0910-0059) person is not Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. OMB Washington, DC 20201

required to respond to a collection of information unless it displays a currently valid control number.

Please **DO NOT RETURN** this form to this address,

13. SIGNATURE

14. TYPED OR PRINTED NAME

FORM FDA 2892 (5/96) PREVIOUS EDITIONS ARE OBSOLETE. \* U.S. GPO: 1996-416-979/40511

## APPENDIX 1

### ERRATA INFORMATION REGARDING 21 CFR 807

**Due to changes in the location of the Center for Devices and Radiological Health and new registration and listing forms, certain information in the 1996 edition of the Title 21 Code of Federal Regulations is incorrect. The following is a partial list of corrected information by section number.**

**§807.25(f)(2), (f)(3), (f)(5), (f)(6)(i), (f)(6)(iii) are not currently being asked for on the Form FDA 2892.**

**§807.30 The Block numbers cited in this section are all incorrect. Here are the correct citations:**

**§807.30(a): Block 2 is no longer used to indicate the preprinted original document number of the 2892 used to initially list the device. This information now appears in Block 1.**

**§807.30(b)(5)(i): The owner or operator name is now Block 5. The owner or operator number is now Block 4.**

**§807.30(b)(5)(ii): The information previously in Blocks 12, 12a, 13, 13a and 14 is no longer requested. The information previously in Blocks 15, 16 and 17 is now in Block 12.**

**§807.30(b)(6): The information previously in Blocks 10 and 11 is in Blocks 9 and 10.**

## APPENDIX 2

### HOW TO ORDER REGISTRATION AND DEVICE LISTING FORMS AND CLASSIFICATION NAMES BOOK

**Forms FDA 2891 and 2892 may be ordered in quantity (>100 copies) from:**

**Consolidated Forms and Publication Center  
Washington Commerce Center  
3222 Hubbard Road  
Landover, MD 20785 USA**

**Forms FDA 2891 and 2892 and their instructions may be ordered in any quantity from:**

1. **Publications, HFZ-220**  
**Division of Small Manufacturers Assistance**  
**Office of Health and Industry Programs**  
**Center for Devices and Radiological Health**  
**1350 Piccard Drive**  
**Rockville, MD 20850 USA**  
**Phone No. 800-638-2041 x 102, 301-443-6597 x102, or Fax No. 301-443-8818**

and

2. **Information Processing and Office Automation Branch, HFZ-307**  
**Office of Compliance**  
**Center for Devices and Radiological Health**  
**2098 Gaither Road**  
**Rockville, MD 20850 USA**  
**Phone No. 301-827-4555 (Press 6, then press 2 for registration and listing)**

HFZ-308 is used just for identifying mail containing registration and listing forms and updates.

#### **CLASSIFICATION NAMES for MEDICAL DEVICES and IN-VITRO DIAGNOSTICS PRODUCTS**

This publication can also be ordered from the Division of Small Manufacturers Assistance at the address listed above item 1.

### **APPENDIX 3**

#### **ESTABLISHMENT TYPE DEFINITIONS**

- C** CERTIFYING SITE/MDR REPORTING SITE. Registered site responsible for submission of the annual certification of the number of MDR reports submitted.
- DD** DOMESTIC DISTRIBUTOR. Any person who furthers the marketing of a device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user, but does not repackage, or otherwise change the container, wrapper, or labeling of the device or device package. This category also includes, but is not limited to, direct sale, mail order, leasing, distributing promotional samples, distributing demonstration units, and drop shipping. Distributor does not include brokers or other persons who do not own the device, but merely perform a service for the person (other than the ultimate consumer) who does own the device. *NOTE: Since 1995, the requirement for registration of a domestic distributor has not been enforced pending revocation of this requirement.*
- \*E** CONTRACT MANUFACTURER. Manufactures a finished device to

another establishment's specifications. The manufacturing establishment does not commercially distribute the device under its own name.

M MANUFACTURER. Makes by chemical, physical, biological, or other procedures, any article that meets the definition of "device" in section 201 (h) of the Federal Food, Drug, and Cosmetic (FD&C) Act.

R REPACKAGER AND/OR RELABELER

Repackager: Packages finished devices from bulk or repackages devices made for the establishment by a manufacturer into different containers (excluding shipping containers).

Relabeler: Changes the content of the labeling from that supplied from the original manufacturer for distribution under the establishment's own name. A relabeler does not include establishments that do not change the original labeling but merely add their own name.

S SPECIFICATION DEVELOPER. Develops specifications for a device that is distributed under the establishment's own name but performs no manufacturing.

\*T CONTRACT STERILIZER. Provides a sterilization service for another establishment's devices.

U U.S. DESIGNATED AGENT. Person designated by the owner or operator of a foreign establishment responsible for the annual certification of the number of MDR reports. [This requirement has been in abeyance since July 23, 1996.]

X REMANUFACTURER. Any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that significantly changes the finished device's performance or safety specifications, or intended use.

ID INITIAL DISTRIBUTOR. Takes first title to devices imported into the United States.

K\*\*\* REFURBISHERS: persons who, for the purpose of resale or redistribution, visually inspect, functionally test and service devices, as may be required, to demonstrate that the device is in good repair and performing all the functions for which it is designed. The device may or may not be cosmetically enhanced. Preventive maintenance procedures are performed. Refurbishers do not significantly change a finished device's performance or safety specifications, or intended use.

RECONDITIONERS: persons who, for the purpose of resale or redistribution, visually inspect, functionally test and service devices, as may be required, to demonstrate that the device is in good repair and performing all the functions for which it is designed. The device may or may not be cosmetically enhanced. Preventive maintenance is not performed. Reconditioners do not significantly change a finished device's performance or safety specifications, or intended use.

*\* NOTE: A September 1, 1993 Federal Register notice erroneously exempted contract manufacturers and contract sterilizers from registration. That exemption will be revoked.*

**\*\*\*NOTE:** Refurbishers/reconditioners are not required to register or list, however, FDA will accept voluntary registration and listings from firms that which to be registered with FDA.

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#### APPENDIX 4

### HOW TO OBTAIN CLASSIFICATION NAME, CLASSIFICATION NUMBER OR PRODUCT CODE (PROCEDURE) INFORMATION FROM THE CDRH HOME PAGE

The Center for Devices and Radiological Health (CDRH) maintains a home page on the World Wide Web. This page contains a wealth of information about medical devices. To assist establishments with the device listing and premarket notification processes, CDRH is providing an on-line searchable database of product classification names and numbers, device classification information and their 510(k) exemption status.

The database can be accessed by going to the CDRH Home Page (<http://www.fda.gov/cdrh>) using any Internet browser software. The database is located at:

<http://www.fda.gov/cdrh/prodcode.html>

This takes you to an introduction page entitled Product Code Classification Database. At the bottom of the page, click on "Go directly to the Product Code Database search." This takes you to the "Search" page. You can either enter and search on the name of the device, or go to the medical specialty or panel that you think the product is in. The medical specialty option will find all the classification names for that panel of products.

Once you find the classification name and product code, enter this information in Blocks 7 and 8, respectively, on form FDA 2892.



*(Updated September 3, 1997)*

## Center for Devices and Radiological Health

<a href="#">Parent Page</a>	<a href="#">Device Advice Home</a>	<a href="#">Device Advice Assistance &amp; Help</a>	<a href="#">DSMA Home</a>	<a href="#">CDRH Home</a>	<a href="#">FDA Home</a>	<a href="#">FDA Search</a>	<a href="#">CDRH Comments</a>
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# Good Manufacturing Practices (GMP) / Quality System (QS) Regulation

(This page last updated: April 17, 1998)

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Page 3.2 provides information on the good manufacturing practice (GMP) requirements of the quality system (QS) regulation.

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- [Introduction](#)
- [Flexibility of the GMP](#)
- [Applicability of the GMP](#)
- [GMP Exemptions](#)
- [Types of Establishments Subject to the GMP](#)
- [GMP Guidance Documents - Good Manufacturing Practice \(GMP\) Quality System Regulation Information page](#)

**Do you have a general understanding of the QS Regulation and GMP Requirements?**

<input type="checkbox"/> YES	<input type="checkbox"/> NO
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## Introduction

[Page Contents](#)

The current Good Manufacturing Practice (GMP) requirements set forth in the Quality System (QS) regulation are promulgated under section 520 of the Food, Drug and Cosmetic (FD&C) Act. They require that domestic or foreign manufacturers have a quality system for the design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices intended for commercial distribution in the United States. The regulation requires that various specifications and controls be established for devices; that devices be designed under a quality system to meet these specifications; that devices be manufactured under a quality system; that finished devices meet these specifications; that devices be correctly installed, checked and serviced; that quality data be analyzed to identify and correct quality problems; and that complaints be processed. Thus, the QS regulation helps assure that medical devices are safe and effective for their intended use. The Food and Drug Administration (FDA) monitors device problem data and inspects the operations and records of device developers and manufacturers to determine compliance with the GMP requirements in the QS regulation.

The *QS Regulation* is contained in Title 21 Part 820 of the Code of Federal Regulations. This

regulation covers quality management and organization, device design, buildings, equipment, purchase and handling of components, production and process controls, packaging and labeling control, device evaluation, distribution, installation, complaint handling, servicing, and records. The preamble describes the public comments received during the development of the QS regulation and describes the FDA Commissioner's resolution of the comments. Thus, the preamble contains valuable insight into the meaning and intent of the QS regulation.

The Good Manufacturing Practice (GMP) / Quality System Regulation page has a link to the Medical Device Quality Systems Manual: A Small Entity Compliance Guide, First Edition which details the requirements of the new QS regulation and provides detailed guidance in the following areas:

1. obtaining information on GMP requirements;
2. determining the appropriate quality system needed to control the design, production and distribution of the proposed device;
3. designing products and processes;
4. training employees;
5. acquiring adequate facilities;
6. purchasing and installing processing equipment;
7. drafting the device master record;
8. noting how to change the device master records;
9. procuring components and materials;
10. producing devices;
11. labeling devices;
12. evaluating finished devices;
13. packaging devices;
14. distributing devices;
15. processing complaints and analyzing service and repair data;
16. servicing devices;
17. auditing and correcting deficiencies in the quality system; and
18. preparing for an FDA inspection.

**Are you aware of the Flexibility of the QS regulation?**

YES	NO
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## Flexibility of the GMP

[Page Contents](#)

Manufacturers should use good judgment when developing their quality system and apply those sections of the QS regulation that are applicable to their specific products and operations, 21 CFR 820.5 of the QS regulation. Operating within this flexibility, it is the responsibility of each manufacturer to establish requirements for each type or family of devices that will result in devices that are safe and effective, and to establish methods and procedures to design, produce, and distribute devices that meet the quality system requirements. FDA has identified in the QS regulation the essential elements that a quality system shall embody for design, production and distribution, without prescribing specific ways to establish these elements. Because the QS regulation covers a broad spectrum of devices and production processes, it allows some leeway in the details of quality system elements. It is left to manufacturers to determine the necessity for, or extent of, some quality elements and to develop and implement specific procedures tailored to their particular processes and devices. For example, if it is impossible to mix up labels at a manufacturer because there is only one label or one product, then there is no necessity for the manufacturer to comply with all of the GMP requirements under device labeling.

The medical device QS regulation requires an "umbrella" quality system intended to cover the design, production, and distribution of all medical devices from simple surgical hand tools to very complex computerized axial tomography (CAT) scanners. It is not practical for a regulation to specify details of quality system elements for such a wide range of products. Rather, the QS regulation specifies general objectives such as use of trained employees, design reviews, design validation, calibrated equipment, process controls, etc., rather than methods, because a specific method would not be appropriate to all operations.

In most cases, it is left to the manufacturer to determine the best methods to attain quality objectives. In some cases, however, the QS regulation does specify the particular type of method to be used, such as written procedures or written instructions. This does not mean, however, that manufacturers cannot vary from the method specified if the intent of the GMP requirement can be met by another method such as using an engineering drawing plus a model device as manufacturing instructions. Written procedures are not restricted to paper copies. Written procedures may be filed and distributed by automated data processing equipment. This flexibility is allowed by section 21 CFR 820.180.

Typically, large manufacturers will have a quality system that exceeds the medical device QS regulation. Small manufacturers will typically have a proportionally simpler system. FDA recognizes that a small manufacturer may not need the same amount of documentation that a large manufacturer does in order to achieve a state-of-control; and, that some of the records maintained to fulfill the GMP requirements for written procedures may not be as long and complex for a small manufacturer.

After a manufacturer establishes a quality system, it should be maintained. Each manufacturer should assure that with growth and process or product changes their quality system is still adequate. This assurance is obtained through change control, day-to-day observance of operations, and by periodic audits of the quality system. The auditor should first identify the elements of the company's quality system. Next the audit should determine how well each element is functioning, and then determine its adequacy with respect to the intent of the device GMP requirements and meeting the company's quality claims.

### Do you know the extent of GMP applicability?

YES	NO
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## Applicability of the GMP

[Page Contents](#)

The QS regulation applies to finished devices intended to be commercially distributed for human use unless there is an approved exemption in effect. GMP exemptions are codified in the Classification Regulations 21 CFR 862 to 892. The exemption of most Class I devices from design controls is in section 21 CFR 820.30 (a).

Certain components such as blood tubing and major diagnostic x-ray components are considered by FDA to be finished devices because they are accessories to finished devices. The manufacturer of such accessories is subject to the QS regulation when the accessory device is labeled and sold separately from the primary device for a health-related purpose to a hospital, physician, or other user.

The designation of a device as a "custom" or "customized" device does not confer a GMP exemption.

Contract manufacturers and specification developers shall comply with the sections of the QS regulation that apply to the functions they perform.

Contract test laboratories are considered an extension of a manufacturer's quality system and presently are not routinely scheduled for GMP inspections. The finished device manufacturer shall meet the requirement of the QS regulation, particularly 21 CFR 820.50, Purchasing, when they obtain products or services. Internal test laboratories, however, that are part of a corporate manufacturer that provides services to individual corporation factories should meet GMP requirements. Internal laboratories are inspected as part of the FDA GMP inspection of the member factories.

Situations are discussed in the remainder of this chapter where various manufacturers are exempt from the QS regulation or are not routinely inspected. However, these manufacturers are still subject to the FD&C Act. If these manufacturers or any manufacturer render devices unsafe or ineffective, the devices are adulterated and/or misbranded and the manufacturers are subject to the penalties of the FD&C Act.

## Do You Know What Type of Establishments are Exempt from GMPs?




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### GMP Exemptions

Page Contents

FDA has determined that certain types of establishments are exempt from GMP requirements; and FDA has defined GMP responsibilities for others. Exemption from the GMP requirements does not exempt manufacturers of finished devices from keeping complaint files ( 21 CFR 820.198) or from general requirements concerning records 21 CFR 820.180. Sterile devices are never exempted from GMP requirements. Medical devices manufactured under an investigational device exemption (IDE) are not exempt from design control requirements under 21 CFR 820.30. A device that normally would be subject to GMP requirements may be exempt under the following conditions:

When FDA has issued an exemption order in response to a citizen's petition for exemption;

When FDA, in the absence of a petition, has exempted the device and published the exemption in the Federal Register;

When the device is exempted by FDA classification regulations published in the Federal Register and codified in 21 CFR 862 to 892;

When the device is an intraocular lens (IOL) under an IDE and meets the requirements of the IDE regulation for IOL's (except for design controls 21 CFR 820.30); and

Through a policy statement, FDA may decide not to apply GMP requirements to some types of devices and processes although the devices may not have been exempted from GMP requirements.

Manufacturers should be aware of the GMP exemption status of their devices. In addition, manufacturers should keep on file records of any specific GMP exemption granted to them by FDA. Upon request during a factory visit, the exemption records need to be shown during normal business

hours to the FDA investigator in order to verify that an exemption has been granted.

## Types of Establishments Exempt from GMP

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### Component Manufacturers

[Chapter Contents](#)

A "component" is defined by 21 CFR 820.3 (c) as "any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device." Component manufacturers are excluded from the QS regulation by 21 CFR 820.1 (a)(1). Current FDA policy is to rely upon the finished device manufacturer to assure that components are acceptable for use. Component manufacturers are not routinely scheduled for GMP inspections; however, FDA encourages them to use the QS regulation as guidance for their quality system.

When finished device manufacturers produce components specifically for use in medical devices they produce, whether in the same building or another location, such production of components is considered part of the device manufacturing operations, and the production should comply with the QS regulation as detailed under Manufacturers of Accessories.

## Types of Establishments Subject to the GMP

[Page Contents](#)

- o [Remanufacturers](#)
- o [Custom Device Manufacturers](#)
- o [Contract Manufacturers](#)
- o [Contract Testing Labs](#)
- o [Repackagers, Relabelers, and Specification Developers](#)
- o [Manufacturers of Accessories](#)
- o [Initial Distributors](#)

---

### Remanufacturers

[Chapter Contents](#)

A remanufacturer as defined in 21 CFR 820.3 (w) is any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that changes the finished device's performance or safety specifications or intended use. Remanufacturers are considered manufacturers. As such, these manufacturers are subject to inspection by FDA and shall meet the applicable requirements of the medical device QS regulation. These manufacturers shall establish and implement quality systems to assure the safety and effectiveness of the devices that are distributed. Such activities include drafting of device master records, rebuilding per the device master records, inspection and testing, calibration of measurement equipment, control of components, updating of labeling, processing of complaints, and any other GMP requirement applicable to the activities being performed.

Remanufacturers are also required to comply with the labeling requirements of 21 CFR 801.1 (c). This labeling regulation requires that where the person or manufacturer named on the label of the device is not the original manufacturer, the name shall be qualified by an appropriate phrase which reveals the connection that person has with the device, e.g., remanufactured by XYZ Company.

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### Custom Device Manufacturers

[Chapter Contents](#)

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Section 520(b) of the FD&C Act and the IDE regulation (21 CFR 812.3 (b)) defines a custom device. Custom devices are exempt from certain statutory requirements. For example, manufacturers of custom devices are not required to comply with premarket approval requirements (Section 515) and are exempt from premarket notification requirements [Section 510(k)]. Custom devices are NOT exempt from the GMP requirements. Manufacturers of custom devices should comply with the GMP requirements while considering the flexibility allowed.

---

### Contract Manufacturers

[Chapter Contents](#)

A person(s) that manufactures a finished device under the terms of a contract with another manufacturer is a contract manufacturer. The agreement between the manufacturers should be documented in a written contract. Contract manufacturers of finished devices shall comply with applicable requirements of the quality system and shall register their establishment with FDA. Depending on the circumstances, both the contractor and manufacturer may be held jointly responsible by FDA for the activities performed.

---

### Contract Testing Laboratories

[Chapter Contents](#)

Contract laboratories that designs or test components or finished devices for a manufacturer according to the manufacturer's specifications are considered an extension of the manufacturer's quality system. These laboratories may provide services to a number of customers, many of which are not medical device manufacturers. These contract laboratories are not subject to routine GMP inspections. Through the conduct of purchasing assessment, the finished device manufacturer is responsible for assuring that equipment and procedures used by a lab are adequate and appropriate (21 CFR 820.50). However, an internal test laboratory, if part of a manufacturer that does testing for various facilities within the corporation, is subject to inspection when FDA GMP inspections are conducted at the individual manufacturing facilities. That is, the test laboratory is simply a part of a medical device manufacturer of which all device-related divisions shall comply with the QS regulation.

---

### Repackagers, Relabelers, and Specification Developers

[Chapter Contents](#)

Repackaging and relabeling of a device and specification development are defined as manufacturing in 21 CFR 820.3(o) and 21 CFR Part 807, Establishment Registration and Device Listing for Manufacturers of Devices. Some definitions from 21 CFR 807.3 (d) are reprinted below because they affect the applications of the QS regulation.

(d) "Manufacture, preparation, propagating, compounding, assembly, or processing" of a device means the making by chemical, physical, biological, or other procedures of any article that meets the definition of a device in section 201(h) of the Act. These terms include the following activities:

1. Repackaging or otherwise changing the container, wrapper, or labeling of any device package in furtherance of the distribution of the device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer;
2. Distribution of domestic or imported devices; or
3. Initiation of specifications for devices that are manufactured by a second party for subsequent

commercial distribution by the person initiating specifications".

As defined above, repackaging and relabeling are manufacturing operations. Further, a repacker, repackager or relabeler is a manufacturer per 21 CFR 820.3 (o) and subject to the applicable requirements of the QS regulation. Individuals are repackers or relabelers if they:

- package and/or label previously manufactured finished devices or accessories;
- receive finished devices in bulk (e.g., surgical tubing, syringes, media, etc.,) and repacks them into individual packages and label them;
- receive previously manufactured devices that have been packaged and labeled by another manufacturer, and combine them into a kit with other unpackaged devices which are received in bulk.

Individuals are not considered repackers or relabelers or a manufacturer for purposes of applying the QS regulation if they pack only previously packaged and labeled individual devices into packages for the convenience of the user. (Note that this activity is essentially the same as a drug store employee placing packaged items into a bag labeled with the name of the drug store.)

A distributor who only adds a label bearing their name and address is exempt from the GMP requirements. A manufacturer simply affixing a sticker label bearing the distributor's name and address would not require record keeping demonstrating compliance with labeling controls requirements.

Specification developers provide specifications to contract manufacturers, who produce devices to meet the specifications. The contract manufacturer may package and label the device, or the finished device may be shipped to the specification developer for packaging and labeling.

Specification developers are manufacturers and are subject to the GMP requirements that apply to the activities they conduct, such as various design controls including correct transfer of the design information to a contract manufacturer [21 CFR 820.30 (h)]. This activity, in turn, requires an adequate device master record (21 CFR 820.181) and adequate document change control [21 CFR 820.40 (b)]. Further, if the product carries the specification developer's label, the developer is responsible for maintaining a complaint file and processing complaints, plus maintaining the device specifications and other appropriate documents in the device master record.

## Manufacturers of Accessories

Chapter Contents

When finished device manufacturers produce components specifically for use in medical devices they produce, whether in the same building or another location, such production of components is considered part of the device manufacturing operations, and the production should comply with the QS regulation.

Accessory devices are discussed in 21 CFR Part 807, Establishment Registration and Device Listing for Manufacturers of Devices [21 CFR 807.20 (a)(5)]. These devices, such as hemodialysis tubing or major diagnostic x-ray components, that are packaged, labeled, and distributed separately to a hospital, physician, etc., for health-related purposes are sometimes inappropriately referred to as components. However, FDA considers them finished devices because they are suitable for use or capable of functioning and are distributed for health-related purposes; and the QS regulation applies to their manufacture. Similarly, a device or component including software that is sold as an addition to a finished medical device to augment or supplement its performance is also termed an accessory. An accessory to a medical device is considered a finished device and, therefore, is subject to the QS regulation.

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Initial Distributors of Imported Devices[Chapter Contents](#)

The initial distributor is the foreign manufacturer's official correspondent with the FDA. With regards to the GMP, this initial distributor is responsible for maintaining complaint files and general record keeping requirements. A procedure shall be established and maintained for receiving, reviewing, and evaluating complaints. All complaints, including oral complaints, are to be processed in a uniform and timely manner. These complaints shall be evaluated to determine whether or not they require reporting to FDA under Medical Device Reporting, 21 CFR Part 804 or 803. The initial distributor is also required to evaluate all complaints to determine whether an investigation is necessary, as well as complying with all other requirements in 21 CFR 820.198, Complaint Files.

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# Labeling Requirements

*(This page last updated: April 17, 1998)*

Page 3.3 provides information on labeling requirements for medical devices, in vitro diagnostic devices, and radiation emitting products. [Top of page](#)

This page is currently being revised to include provisions of the FDA Modernization Act of 1997 (*the Modernization Act*) and resultant CDRH re-engineering efforts. In the interim, supplementary information and guidance on this topic area can be found in the "Overview of FDA Modernization Act of 1997, Medical Device Provisions."

- [Introduction to Medical Device Labeling](#)
- [General Device Labeling Requirements - Page 3.3.1](#)
  - [Labeling Requirements for OTC Devices - Page 3.3.1.1](#)
  - [Exemptions from Adequate Directions for use - Page 3.3.1.2](#)
  - [Other Exemptions - Page 3.3.1.3](#)
  - [Labeling for Specific Devices - Page 3.3.1.4](#)
  - [Misbranding - Page 3.3.1.5](#)
- [In Vitro Diagnostic Device Labeling Requirements - Page 3.3.2](#)
- [Investigational Device Labeling Requirements - Page 3.1.7](#)
- [Quality System Regulation Labeling Requirements - Page 3.3.4](#)
- [Radiation Emitting Device and Product Requirements - Page 3.3.5](#)

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Do you want information on the new draft labeling guidance?

<a href="#">YES</a>	<a href="#">NO</a>
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Do you understand the distinction between the label and labeling?

<a href="#">YES</a>	<a href="#">NO</a>
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## INTRODUCTION TO MEDICAL DEVICE LABELING

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The U.S. Food and Drug Administration (FDA) develops and administers regulations under authority granted by laws passed by Congress that apply to food, drugs, cosmetics, biologics, radiation-emitting electronic products, and medical devices. Labeling regulations pertaining to medical devices are found in the following Parts of Title 21 of the Code of Federal Regulations (CFR).

General Device Labeling	- 21 CFR Part 801
In Vitro Diagnostic Products	- 21 CFR Part 809
Investigational Device Exemptions	- 21 CFR Part 812
Good Manufacturing Practices	- 21 CFR Part 820
General Electronic Products	- 21 CFR Part 1010

The Federal Food, Drug and Cosmetic Act (FFDCA) is the law under which the FDA takes action against regulated products. Specifically:

Section 201(k) defines "label" as a:

- "display of written, printed, or graphic matter upon the immediate container of any article..."

The term "immediate container" does not include package liners. Any word, statement, or other information appearing on the immediate container must also appear "on the outside container or wrapper, if any there be, of the retain package of such article, or is easily legible through the outside container of wrapper."

Section 201(m) defines "labeling" as:

- "all labels and other written, printed, or graphic matter
  - (1) upon any article or any of its containers or wrappers, or
  - (2) accompanying such article" at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce.

The term "accompanying" is interpreted liberally to mean more than physical association with the product. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc. "Accompanying" also includes labeling that is brought together with the device after shipment or delivery for shipment in interstate commerce.

### Advertising

According to an appellate court decision: "Most, if not all advertising, is labeling. The term 'labeling' is defined in the FFDCA as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising."

Do you know the general labeling requirements for medical devices?

<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> Choose Another Topic	<input type="checkbox"/> Exit Device Advice
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# Labeling Requirements

## In Vitro Diagnostic Devices

*(This page last updated: June 1, 1998)*

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Page 3.3.2: In Vitro Diagnostic Device Labeling Requirements

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- [Label Requirements for the Immediate Container](#)
- [Labeling Requirements for Inserts and Outer packaging](#)
- [Exemptions from Labeling Requirements](#)
- [Labeling for General Purpose Reagents and Equipment](#)

**Is your product an in vitro diagnostic product?**

<input type="checkbox"/> YES	<input type="checkbox"/> NO	<input type="checkbox"/> Unsure
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### Introduction

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In vitro diagnostic products (IVD's) are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. In vitro diagnostic (IVD) labeling requirements are located in 21 CFR Part 809. Numbers appearing in parentheses next to subject headings are the corresponding sections of 21 CFR. This section contains the basis requirements for label and labeling (package insert) as specified in the labeling regulations for in vitro diagnostic products.

---

### Label Requirements for the Immediate Container [21 CFR 809.10(a)]

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The label for IVD's must state the following information, except in cases where it is not applicable. In addition, all information must appear on the outside container or wrapper, or be easily legible through the outside container or wrapper.

If the presence of any label information will interfere with the test, the information may appear on the outside wrapper or container instead of the label.

If the immediate containers are too small, or otherwise unable to bear labels with sufficient space, then the required labeling as listed below annotated with an asterisk (\*) may appear on the outer container **labeling** only.

Label requirements are as follows:

- The established and proprietary names of the product, e.g., cholesterol meters;
- \* The intended use or uses, e.g., pregnancy detection, diabetes screening, etc.; -
- A statement of warnings or precautions for users listed in 16 CFR part 1500 (hazardous substances) and any other warnings appropriate to user hazards, and a statement "For In Vitro Diagnostic Use;"
- Name and place of business of the manufacturer, packer, or distributor;
- Lot or control number traceable to the production history
  - - Multiple unit products must have traceability of the individual units;
  - - Instrument lot numbers must allow for traceability of subassemblies; and
  - - A multiple unit product that requires use of its components as a system should have the same lot number, or other suitable uniform identification, on all units.
- \* For Reagents:
  - - Established (common or usual) name;
  - - Quantity, proportion, or concentration of all active ingredients; e.g., mg., weight per unit volume, mg./dl etc., and for reagents derived from biological materials the source and measure of its activity, e.g., bovine, I.U., etc.;
  - - Storage instructions adequate to protect the stability of the product, i.e., temperature, humidity, etc.;
  - - Instructions for manipulation of products requiring mixing or reconstitution, along with instructions for storage of products that have been reconstituted or mixed;
  - - Means to assure that the product meets appropriate standards of purity, quality, etc., at the time of use, including one or more of the following:
    - i. expiration date (date beyond which the product is not to be used);
    - \* ii. statement of any visual indication of alteration;
    - \* iii. Instructions for a simple check to assure product usefulness;
  - \* - The net quantity of contents.

**Do you want information for inserts and outer packaging?**

YES	NO
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Labeling Requirements for Inserts and Outer Packaging 21 CFR 809.10  
(b)

[Page Contents](#)

Labeling must contain in one place the following information in the FORMAT and ORDER listed below, except where information is not applicable, or as specified in a standard for a particular product class.

If the device is a reagent intended as a replacement in a diagnostic system, labeling may be limited to that information necessary to adequately identify the reagent and to describe its use in the system.

If the device is a multiple purpose instrument used for diagnostic purposes, and not committed to specific diagnostic procedures or systems, labeling can be restricted to those points annotated by an

asterisk (\*).

- \* The proprietary and established product name;
- \* The intended use of the product and whether it is a qualitative or quantitative type of procedure, e.g., screening, physician's office, home use, etc.;
- Summary and explanation of the test, including a short history containing methodology and the special merits and limitations of the test;
- The chemical, physical, physiological, or biological principles of the procedure.
- For Reagents:
  - - The common name, if any, and quantity, proportion, or concentration of each reactive ingredient; and for biological material, the source and measure of its activity;
  - - Appropriate cautions or warnings listed in 16 CFR Part 1500; the statement: "For In Vitro Diagnostic Use;" and any other limiting statements appropriate to the intended use of the product;
  - - Adequate directions for reconstitution, mixing, dilution, etc.;
  - - Appropriate storage instructions;
  - - A statement of purification or treatment required for use; and
  - - Physical, biological, or chemical indications of instability or deterioration.
- \* For Instruments:
  - - Use or function;
  - - Installation procedures and requirements;
  - - Principles of operation;
  - - Performance characteristics and specifications;
  - - Operating instructions;
  - - Calibration procedures, including equipment and/or materials;
  - - Operational precautions and limitations;
  - - Hazards; and
  - - Service and maintenance information
- Specimen collection and preparation for analysis, describing;
  - - Special precautions/preparations;
  - - Additives necessary to maintain specimen integrity;
  - - Known interfering substances; and
  - - Recommended specimen storage, handling, and shipping instructions.
- A step by step outline of recommended procedures from the reception of the specimen to the obtaining of results. In addition to the following, this should include a list of any points that might improve precision or accuracy:
  - - A list of materials provided and instruction for use, e.g., reagents, equipment, etc.;
  - - A list of necessary materials that are not provided (include details such as sizes, numbers, types, and quality);
  - - A description of the amounts of reagents necessary, and parameters such as time, temperature etc.;
  - - A statement related to final reaction stability and any time restrictions on accurate measurements;
  - - Details of calibration, identifying and listing and necessary preparation of the reference materials, samples, and blanks. Describe the calibration range including the highest and lowest values measured; and
  - - Details of necessary quality control procedures and materials, e.g., positive and negative controls, acceptable performance limits.
- Explanation of the procedure for calculating the unknown, including the definition of each component of the formula, a sample calculation, and the number of significant figures appropriate for the answer;
- Limitations of the procedure, e.g., identify situations which will have an adverse impact on test results. If further testing either more specific or more sensitive, is indicated in all cases where certain results are obtained, the need for the additional test shall be stated;
- Expected values including how the range(s) was established and identify the populations on which it was established;

- Specific performance characteristics as appropriate including accuracy, specificity, precision, and sensitivity;
- \* Bibliography;
- \* Name and place of business of the manufacturer, packer, or distributor; and
- \* Date of issuance of the last labeling revision by the firm.

**Do you want information on exemptions?**

YES	NO
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## Exemptions from Labeling Requirements

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Shipments or other deliveries of IVD devices are exempt from label and labeling requirements in the above headings and from standards listed under Part 861 provided the following conditions are met:

- A shipment or delivery for an investigation subject to Part 812, Investigational Device Exemption (IDE), if the device is in compliance with the subject IDE; or
- A shipment or delivery for an investigation that is not in compliance with Part 812 (most IVD's are exempt from the IDE because of the following labeling) if the following conditions are met
  - - A product in the laboratory research phase, not represented as an IVD, that is prominently labeled: "For Research Use Only. Not for use in diagnostic procedures;" and
  - - A product that is being shipped or delivered for product testing prior to full commercial marketing that is prominently labeled: "For Investigational Use Only. The performance characteristics of this product have not been established."

**Do you want information on general purpose reagents and equipment?**

YES	NO
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## Labeling of General Purpose Reagents and Equipment

[Page Contents](#)

General purpose items include routine laboratory reagents such as hydrochloric acid and equipment such as glassware whose uses are generally known by persons trained in their use. They do not need to bear the directions for use listed under Label Requirements for the Immediate Container and Labeling Requirements for Inserts and Outer Packaging, if their labeling meets the requirements listed below. If the product packaging is too small to accommodate a label with sufficient space for the labeling, and if the product is packaged in an outer container which has all of following on its labeling, then only those portions annotated with an asterisk (\*) must be on the product label.

- Reagents:
  - \* - A declaration of the established name, if any, and quantity, proportion, or concentration of the reagent ingredient stated in a system generally recognized by the

- user;
  - - A statement of the purity and quality including a qualitative statement of any impurities. This can be satisfied by using a statement of conformity with a generally recognized and available standard;
  - - A statement of warnings or precautions for users as contained in the regulations in 16 CFR Part 1500 and any other appropriate warnings, and the statement: "For Laboratory Use;"
  - - Net quantity of contents in terms of weight or volume, or numerical count, or any combination thereof;
  - - Appropriate storage instructions;
  - \* - Name and place of business of the manufacturer, packer, or distributor;
  - \* - A lot or control number traceable to the manufacturing history of the product; and.
  - - A statement indicating the presence of and characterizing any catalytic or nonreactive ingredients e.g., buffers, preservatives, stabilizers.
- 
- Equipment
    - - Product labeling need include only a statement adequately describing the product, its composition, and physical characteristics if necessary for its proper use.

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<a href="#">Information on other labeling Issues</a>	<a href="#">Choose Another Topic</a>	<a href="#">Exit Device Advice</a>
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**Center for Devices and Radiological Health**

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## Premarket Notification [510(k)]

### How to market a 510(k) Medical Device

*(This page last updated: June 30, 1998)*

Page 3.1.4 provides an overview of FDA requirements for premarket notification [510(k)].

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This page was revised to include provisions of the FDA Modernization Act of 1997 (*the Modernization Act*) and resultant CDRH re-engineering efforts. Supplementary information and guidance on this topic area can be found in the "Overview of FDA Modernization Act of 1997, Medical Device Provisions."

- [What is Premarket Notification \[510\(k\)\]](#)
- [What is Substantial Equivalence](#)
- [Who is Required to Submit a 510\(k\)](#)
- [When is a 510\(k\) Required](#)
- [When is a 510\(k\) Not Required](#)
- [The Modernization Act and the 510\(k\) Submission Process - Different Types of Submissions for Differing Situations](#)
- [How to Prepare a 510\(k\) Submission](#)
- [Third Party Pilot Review Program - Page 3.1.4.3](#)

Are you required to submit a 510(k)?

YES	NO	UNSURE
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[What is Premarket Notification \[510\(k\)\]](#)

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Each person who wants to market Class I, II and some III devices intended for human use in the U.S. must submit a 510(k) to FDA at least 90 days before marketing unless the device is exempt from 510(k) requirements. There is no 510(k) form but instead a format for the submission described in [21 CFR 807](#) and in the pages that follow.

A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is

as safe and effective, that is, substantially equivalent (SE), to a legally marketed device that is not subject to premarket approval(PMA). Applicants must compare their 510(k) device to one or more similar devices currently on the U.S. market and make and support their substantial equivalency claims. A legally marketed device is a device that was legally marketed prior to May 28, 1976 (preamendments device), or a device which has been reclassified from Class III to Class II or I, a device which has been found to be substantially equivalent to such a device through the 510(k) process, or one established through Evaluation of Automatic Class III Definition. The legally marketed device(s) to which equivalence is drawn is known as the "predicate" device(s).

Applicants must submit descriptive data and, when necessary, performance data to establish that their device is SE to a predicate device. Again, the data in a 510(k) is to show comparability, that is, substantial equivalency (SE) of a new device to a predicate device.

Do you understand substantial equivalence?

YES	NO
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What is Substantial Equivalence

Page Contents

Unlike PMA, which requires demonstration of reasonable safety and effectiveness, 510(k) requires demonstration of substantial equivalence. SE means that the new device is as safe and effective as the predicate device(s).

A device is SE if, in comparison to a predicate device it:

- has the same intended use as the predicate device; **and**
- has the same technological characteristics as the predicate device; **or**
- has different technological characteristics, that do not raise new questions of safety and effectiveness, and the sponsor demonstrates that the device is as safe and effective as the legally marketed device.

A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, performance, safety, effectiveness, labeling, biocompatibility, standards, and other applicable characteristics. Detailed information on how FDA determines substantial equivalence can be found in the Premarket Notification Review Program 6/30/86 (K86-3) blue book memorandum.

Until the applicant receives an order declaring a device SE, they may not proceed to market the device. Once the device is determined to be SE, it can then be marketed in the U.S. If FDA determines that a device is **not** SE, the applicant may resubmit another 510(k) with new data, file a reclassification petition, or submit a premarket approval application (PMA). The SE determination is usually made within 90 days and is made based on the information submitted by the applicant.

Are you certain you must submit?

YES	NO
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Who is Required to Submit a 510(k)

Page Contents

The Food, Drug and Cosmetic (FD&C) Act and 510(k) regulations in 21 CFR 807 do not specify who must apply for a 510(k) - anyone may do so. Instead, they specify which actions, such as introducing a device to the U.S. market, require a 510(k) submission.

Based on the specified actions, the following four categories of parties must submit a 510(k) to the FDA:

1. Domestic manufacturers introducing a device to the U.S. market;

Finished device manufacturers have to submit a 510(k) if they assemble a device according to their own specifications and market it in the U.S. However, manufacturers of device components are not required to submit a 510(k) unless such components are promoted for sale to an end user as replacement parts. Also, contract manufacturers, those firms assembling devices on contract according to someone else's specifications, are not required to submit a 510(k).

2. Specification developers introducing a device to the U.S. market;

FDA views specification developers almost the same as manufacturers. These are persons who develop specifications for a finished device, but have it manufactured under contract by another firm or entity. The specification developer submits the 510(k), not the contract manufacturer.

3. Repackers or relabelers who make labeling changes, or whose operations significantly affect the device.

Repackagers or relabelers may be required to submit a premarket notification if they significantly change the labeling or otherwise affect any condition of the device. Here you must ascertain if you are significantly changing labeling, by modifying manuals, deleting or adding warnings, contraindications, etc., and if your packaging operation could alter the condition of the device. However, most repackagers or relabelers are not required to submit a 510(k).

4. Foreign manufacturers/exporters or U.S. representatives of foreign manufacturers/exporters introducing a device to the U.S. market.

Are you certain you must submit?

YES	NO
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When is a 510(k) Required

Page Contents

A 510(k) is required when:

1. Introducing a device into commercial distribution (marketing) for the first time. After May 28, 1976 (effective date of the Medical Device Amendments to the FD&C Act), anyone who wants

to sell a device in the U.S. has been required to make a 510(k) submission at least 90 days prior to offering the device for sale, even though it may have been under development or clinical investigation before that date. If your device was not marketed by your firm before May 28, 1976 a 510(k) is required. Refer to the guidance entitled Deciding When to Submit a 510(k) for a Change to an Existing Device

2. You propose a different intended use for a device which you already have in commercial distribution. The 510(k) regulation (21 CFR 807) specifically requires a premarket notification submission for **major** changes in intended use. Intended use is indicated by claims made for a device in labeling or advertising. However, most, if not all changes in intended use will require a 510(k).
3. There is a change or modification of a device you already market, if that change could significantly affect its safety or effectiveness.

The burden is on you to decide whether or not a modification could significantly affect safety or effectiveness. Whatever your conclusion, make a record which should be reflected in your device master record and change control records, required under the medical device good manufacturing practices. Then, if you're challenged, you will be able to document that in good faith you evaluated the change.

Device or labeling modification	How to submit a 510(k)	When is a 510(k) Not Required
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When is a 510(k) Not Required

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The following are 7 examples of when a 510(k) is not required.

1. If you sell unfinished devices to another firm for further processing, including components to be used in the assembling of devices by other firms. However, if your components are to be sold directly to end users as replacement parts, a 510(k) is required
2. If your device is not being marketed or commercially distributed. You do not need a 510(k) to develop, evaluate, or test a device. This includes clinical evaluation. It is important to mention that if you do perform clinical trials with your device, you may be subject to the Investigational Device Exemption (IDE) Regulation.
3. If you distribute other firm's domestically manufactured devices you need not submit a 510(k). You may place a label on the device "Distributed by ABC Firm", and sell it to end users without submission of a 510(k).
4. In most cases if you are a repackager or a relabeler you are not required to submit a 510(k) if the existing labeling or condition of the device is not significantly changed.
5. If your device was legally in commercial distribution before May 28, 1976, you do not have to submit a 510(k) unless it has been modified or there has been a change in its intended use. These devices are "grandfathered".
6. If you are an importer of a foreign made medical device a 510(k) is not required if one has been submitted by the foreign manufacturer or another importer. If one importer submits a 510(k) for a device manufactured by the same foreign manufacturer, all other importers of that device received from the same manufacturer are not required to submit a 510(k) for that device.
7. If your device is exempted from this requirement by final classification regulation subject to the limitations on exemptions. That means certain Class I or II devices can be marketed for the first time without having to submit a 510(k). A compilation of the Class I and II exempted devices can be found in the MEDICAL DEVICE EXEMPTIONS page.

For more information go [Deciding When to Submit a 510\(k\) for a Change to an Existing Device](#) page especially for numbers 3 and 4.

Are you aware of the Modernization Act changes to the 510(k) process?

YES	NO
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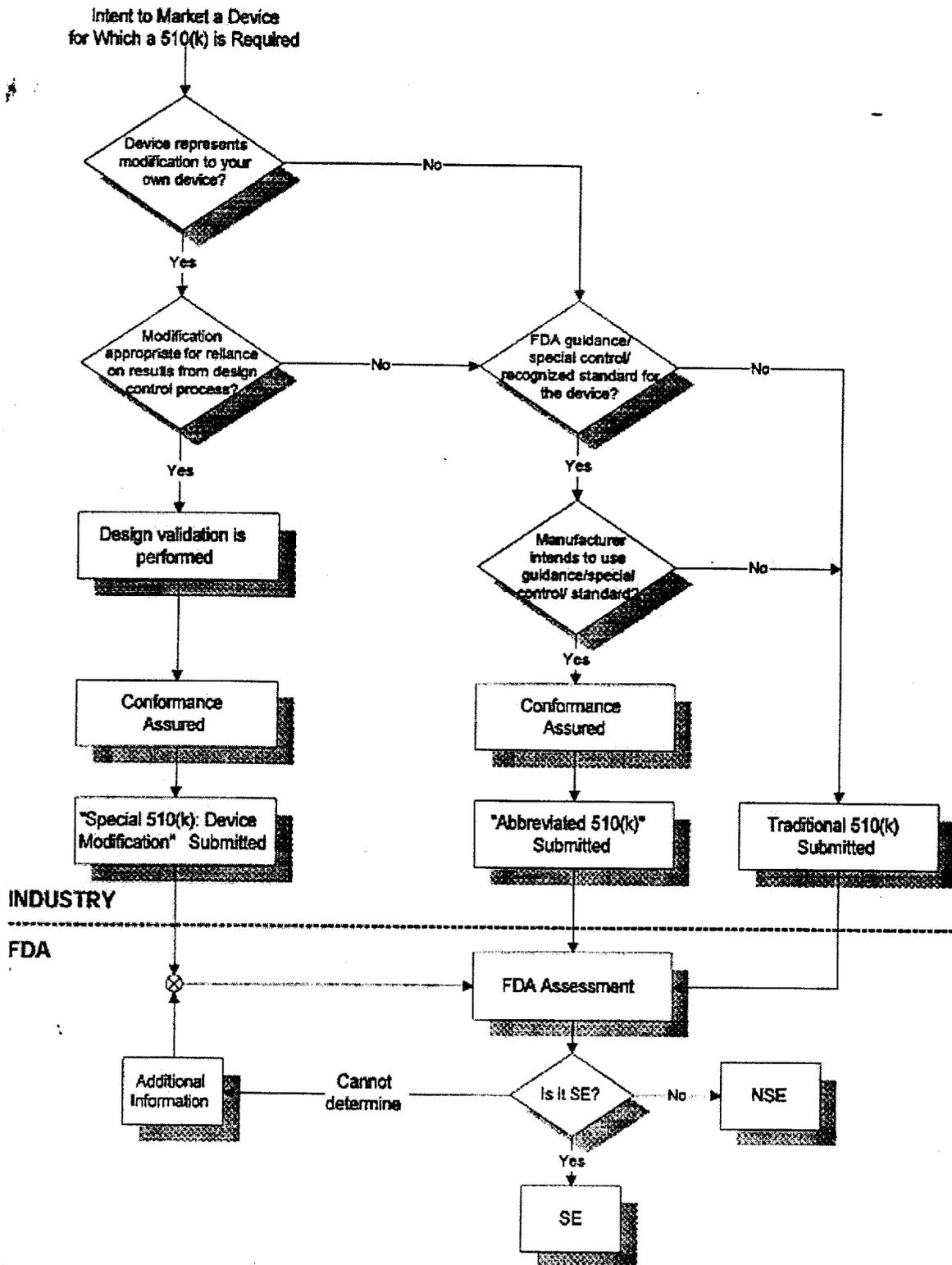
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[The Modernization Act and the 510\(k\) Submission Process - Different Types of Submissions for Differing Situations](#)

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To streamline the evaluation of premarket notifications for the reserved Class I devices, Class II devices subject to premarket notification, and preamendments Class III devices for which FDA has not yet called for PMAs, the Agency has developed [The New 510\(k\) Paradigm](#) which in certain instances presents device manufacturers with two new optional approaches for obtaining marketing clearance for devices subject to 510(k) requirements. The document contains the following reference chart for use in determining which type of 510(k) is suitable for a given set of circumstances.

# The New 510(k) Paradigm



This flowchart should only be considered in conjunction with the accompanying proposed text.

While the New Paradigm maintains the Traditional 510(k) method of demonstrating substantial equivalence under section 510(k) of the Act, it also presents the Special 510(k):Device Modification option, which utilizes certain aspects of the Quality System Regulation, and the Abbreviated 510(k) option, which relies on the use of guidance documents, special controls, and recognized standards to facilitate 510(k) review. Use of either alternative, however, does not affect FDA's ability to obtain any information authorized by the statute or regulations.

Are you aware of the additional requirements for marketing a medical device?

YES	NO
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How to Prepare a 510(k) Submission

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<a href="#">How to prepare a traditional 510(k)</a>	<a href="#">How to prepare a special 510(k)</a>	<a href="#">How to prepare a abbreviated 510(k)</a>	<a href="#">Choose Another Topic</a>	<a href="#">Exit Device Advice</a>
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