

# CDRH THIRD PARTY REVIEW PROGRAM

*By Rosina Robinson*

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## What Is It?

Unlike the premarket authorisation process for new medical devices in the EU, where manufacturers/sponsors submit their technical files or design dossiers to Notified Bodies, the US Office of Device Evaluation of the Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH), has until recently been the sole reviewer of all premarket applications including applications for Investigational Device Exemption (IDE), premarket notifications (510(k)s), and premarket approval applications (PMAs). Eventually, the large number of applications processed annually resulted in progressively longer review times and application backlogs.

In 1996, CDRH initiated a pilot program that authorised non-FDA third party entities to conduct selected premarket reviews. A second third party review program was added later. Both programs are voluntary and the manufacturer/sponsor of the premarket application continues to have the option to submit the premarket notification directly to the FDA, even for those devices eligible for third party review.

The following discussion looks at the Third Party Review Program from the perspective of the medical device manufacturer/sponsor of the premarket notification, and does not address the requirements for and procedures followed for the accreditation of the third party or the requirements for maintaining third party status.

Many of the references mentioned in this article include descriptions of these requirements.

## Introduction

The Third Party Review Program is actually two separate programs. Both programs allow third parties authorised by the FDA to perform the preliminary review of selected premarket notifications. The first program is the Accredited Person (AP). The AP program is based on a 1996 pilot program that was later made into law by the *Food and Drug Administration Modernization Act of 1997* (FDAMA). The second program is the Conformity Assessment Body (CAB). The review of premarket notifications by CABs was developed as a single element of a comprehensive EU/US Mutual Recognition Agreement (MRA). Devices eligible for third party programs are published by CDRH on the Third Party review website<sup>1</sup>.

**Accredited Person and  
Conformity Assessment  
Body programs  
form Third Party  
Review Program**

## Accredited Person Program

### Overview

The 1996 pilot third party program was formalised by Section 523 of the *Federal Food, Drug and Cosmetic Act*, as amended by FDAMA<sup>2</sup>. It was part of a program referred to as 'reinventing government' that focused on more efficient use of FDA resources for higher risk Class III devices, while also serving the needs of the medical device industry by providing more rapid reviews of premarket notifications and, therefore, more rapid clearance decisions for low-to-moderate risk, non-exempt Class I and Class II devices. At the time of its inception, the 1996 pilot program was

very limited, with only 30 Class II product types eligible for review by APs.

**The main third party program in use is the AP program**

When the pilot program was made permanent by the *Medical Device User Fee Modernization Act*, many of the

informal restrictions for use of the program were also written into the law. The AP program is the primary third party program in current use.

#### *Who are the APs?*

APs are individuals trained and accredited by the FDA to review premarket notifications. CDRH

**APs are authorised to perform premarket notification reviews**

published the first list of APs on 23 September 1998. The updated list and their respective contact

information as well as a list of the devices that each AP is authorised to review is provided online at the FDA CDRH Third Party Review web page<sup>1</sup>. As of 5 October 2004 there were 13 APs:

- British Standards Institution;
- California Department of Health Services;
- Center for Measurement Standards;
- Cheiron BV;
- CITECH;
- ENTELA, Inc;
- Intertek Testing Services;
- KEMA Quality BV;
- NIOM – Scandinavian Institute of Dental Materials;
- Regulatory Technology Services, LLC;
- TÜV America, Inc;
- TÜV Rheinland of North America, Inc;
- Underwriters Laboratories, Inc.

#### *What are the eligible devices?*

While the number of device types has expanded greatly since the time of the pilot program, not all medical devices are eligible for review in the AP program

because of the restrictions that are part of the law.

#### *Classification/inherent risk*

Eligibility of a device type for review by an AP depends primarily on device classification. Class III devices are not eligible for participation in the AP program.

Eligibility also considers product risk. APs are only authorised to review low-to-moderate risk devices. Ineligible devices include the following:

- permanent implants;
- life-supporting or life sustaining devices;
- products that require clinical data to support the premarket notification.

#### *Non-CDRH review jurisdiction*

Devices outside CDRH review jurisdiction, such as devices reviewed by the Center for Biologics Evaluation and Research (CBER) or combination device/biologic or drug products for which CBER or the Center for Drug Evaluation and Research (CDER) is the lead Center are also ineligible for review by APs. For example, blood warmers were formally classified as medical devices (21 CFR §864.9205) and include three product types (product codes) within this classification. These devices are now reviewed by CBER and are, therefore, ineligible for the third party program.

#### *Availability of device-specific guidance/consensus standards*

In the early pilot program at the beginning of the AP program, only devices for which device-specific guidance documents were available and/or for which recognised consensus standards existed were eligible for the AP program. FDA subsequently expanded the program to include any devices not expressly prohibited by the law.

### *Unlisted Class I devices*

Unlisted Class I devices that are typically exempt from premarket notification may require premarket notification if they exceed their specified limitations on exemption. These Class I devices are eligible for third party review unless expressly prohibited by law.

## **Conformity Assessment Body Program**

### *Overview*

CABs were authorised by the MRA between the US and the EU that came into force on 7 December 1998<sup>3</sup>. The goals of the CABs are different from that of the AP program. The purpose of CABs is to facilitate trade between Europe and the US, while decreasing the manufacturer's cost of premarket compliance. Detailed information about the use of CABs and the MRA is available on the CDRH website<sup>4</sup>.

The Medical Device Annex to the MRA includes both the exchange of quality system information (all medical devices) and premarket evaluation for selected low-to-moderate risk devices. This article describes the premarket evaluations only. Under the MRA, a European CAB can perform premarket 510(k) evaluations for a European company to determine compliance with FDA requirements (and, therefore, substantial equivalence). The same would hold true for a US CAB that can perform the premarket evaluation for a US company for compliance with European requirements.

There are two significant differences between the AP and the CAB programs: (1) European CABs may only review premarket notifications that originate in Europe and US CABs may only review premarket evaluations that originate in the US and (2) the list of eligible devices for the CAB program was originally more limited than the AP program. The critical similarity between

the AP and the CAB programs is that both the APs and the European CABs perform the same type of 510(k) premarket notification review.

### *Who are the CABs?*

CABs are third parties that have demonstrated proficiency in conducting FDA type evaluations of premarket notifications (EU CABs) and EC-type evaluations (US CABs). According to Mr Eric Rechen<sup>5</sup>, Policy Analyst, Program Operations Staff, CDRH who is in charge of the third party programs, there are seven EU CABs:

- AMTAC;
- British Standards Institution;
- Danish Medical Devices Certification, DGM;
- G-MED;
- SGS United Kingdom;
- TÜV Product Service;
- Underwriters Laboratories International UK.

The list of US CABs has not yet been posted in Appendix 4 of the MRA. However, as of 13 February 2004, six US firms have been identified as moving forward to the confidence-building phase of the accreditation process:

- British Standards Institution;
- Intertek Services Corporation, Inc;
- KEMA Registered Quality, Inc;
- Orion Registrar, Inc;
- TÜV Rheinland of North America, Inc;
- Underwriters Laboratories, Inc.

While some organisations, such as the British Standards Institution and Underwriters Laboratories, Inc have both APs and CABs within them, not all locations of third parties are authorised to function in both the AP and CAB programs.

***CABs are accredited under the EC/US MRA***

***No US CABs have yet been authorised; seven EU CABs are authorised***

### *What are the eligible devices?*

According to Mr Rechen, the EU CABs are authorised to conduct reviews of 97 device categories. While the number of device types eligible for review by EU CABs was originally more limited, the US expanded the list to include the same devices eligible under the AP program, as applicable according to the

**A total of 97 device categories are currently eligible for CAB review**

European Medical Device Directive (Directive 93/42/EEC). As with the AP program, the individual CAB must

be authorised to conduct reviews for each specific device type.

### **Why Use the Third Party Program?**

#### *Review time*

The primary, if not the sole reason, for a manufacturer/sponsor to consider third party review of their premarket notification is to shorten the total review time. As will be shown below, total review time is usually shorter when a premarket notification is reviewed by third party than when it is submitted

**Program offers shorter overall review time**

directly to the FDA. In addition, there are cases when the review time is one of the

terms negotiated between the third party and the manufacturer/sponsor. Short third party review times may be subject to premium fees, however.

#### *Product familiarity*

Many of the third parties are also EU Notified Bodies that manufacturers/sponsors have already used for their CE marking process, making the third party very familiar with the device type or perhaps even the specific device. In addition, many have considerable experience with the utilisation of consensus standards to demonstrate conformity with safety and product performance requirements.

### *Reviewer accessibility*

When FDA initiated the pilot AP program, many manufacturers/sponsors were having difficulties communicating with their FDA reviewers. Some manufacturers/sponsors believed that because the workload of the AP was not as great as that of the FDA reviewer and because the manufacturer/sponsor was paying the AP for the review, it would be easier to reach their individual reviewer.

### *Exemption from the FDA medical device user fee*

Now that the FDA is levying a user fee for review of the premarket notification, the cost of third party review, which exempts the manufacturer/sponsor from the FDA fee, is perceived as being less burdensome. It will be interesting to see if the utilisation of third parties has increased with the advent of the medical device user fee. However, review fees levied by third parties are typically higher than the medical device user fees that are paid to the FDA.

### **How Do I Use the Third Party Review Program?**

The use of the third party program is only slightly more complex than submission of the premarket notification directly to the FDA. Four basic steps are described below. This overview assumes that your product is both a medical device and is subject to the requirements for 510(k) premarket notification.

#### *Step 1. Determine if your device is eligible for third party review*

Identify your device on the list of eligible devices on the CDRH website<sup>6</sup>. This information is arranged as follows:

- the classification regulation for the device as found in the Title 21 of the US Code of Federal Regulations (by medical specialty);

- the regulation name that identifies the device and one or more product codes (three letter code) and device name;
  - the regulatory class of the device (Class I or II);
  - status of the device as part of an expansion pilot program (no device-specific guidance or consensus standards);
  - links to relevant guidance documents and standards that apply to the particular device.
- Center for Measurements Standards;
  - CITECH;
  - ENTELA, Inc;
  - KEMA Quality BV;
  - Regulatory Technology Services, LLC;
  - TÜV America, Inc;
  - TÜV Rheinland of North America, Inc;
  - Underwriters Laboratories, Inc.

**Ten of the 13 APs listed are able to review 510(k)s for nebulisers**

*Step 3. Select the third party for review of your premarket notification*

Because third parties are not all the same, talk to several about their experience with the specific product type, if there will be a delay in starting the review once the premarket notification is provided, average and range of review times, and review fees. This may be one of the considerations for selection of your third party since the FDA has not placed any limitations upon these fees.

**Points to consider when choosing a third party...**

Obtain formal quotes and talk to companies who have used their services in the past. Select the third party that meets your specific needs in accordance with your company's purchasing controls. Finally, sign the contract and prepare the premarket notification.

*Step 4. Prepare and submit the premarket notification*

The premarket notification submitted to a third party must include the same information submitted to the FDA and specified in the regulations and applicable FDA guidance documents. Make it a high quality submission that is easy for the third party and FDA to review. One additional element for a premarket notification reviewed by a third party is a letter from the manufacturer/sponsor that authorises the third party to submit the

**510(k)s submitted by third parties should contain additional items**

To use this list easily, you should know either the classification regulation of your device or at least the medical specialty in which it is classified. For example, if your device is a nebuliser, it is listed in the Anaesthesiology Devices section with a classification number of 868.5630. It is not designated as 'Pilot' and is, therefore, eligible for review in the third party program. Links to relevant device-specific guidance documents are provided in the last column of the table. When in doubt about the eligibility of the device for third party review, it is prudent to contact the FDA staff to verify eligibility.

*Step 2. Identify third parties authorised to review premarket notifications for your device type*

After you know that your device is eligible for review by an AP or CAB, it is time to select the AP or CAB to conduct the review of your premarket notification. APs are also listed on the CDRH website<sup>7</sup>. This page provides the contact information for each of the APs and lists the devices they are authorised to review. Using the same example of a nebuliser, we find that out of the 13 APs, 10 are authorised to review premarket notifications for nebulisers as follows:

- British Standards Institution;
- California Department of Health Services;

510(k) to the FDA and to discuss the 510(k) with the FDA. The third party will add several other items to the submission package when they submit it to the FDA.

### Third Party Review Performance Data<sup>8</sup>

#### Utilisation of third party review

According to Mr Rechen, there are currently a total of 670 types (product codes) of non-exempt Class I and II devices that are eligible for third party review and these device types account for more than 65% of all device submissions. There

**Take-up on third party reviews is very low**

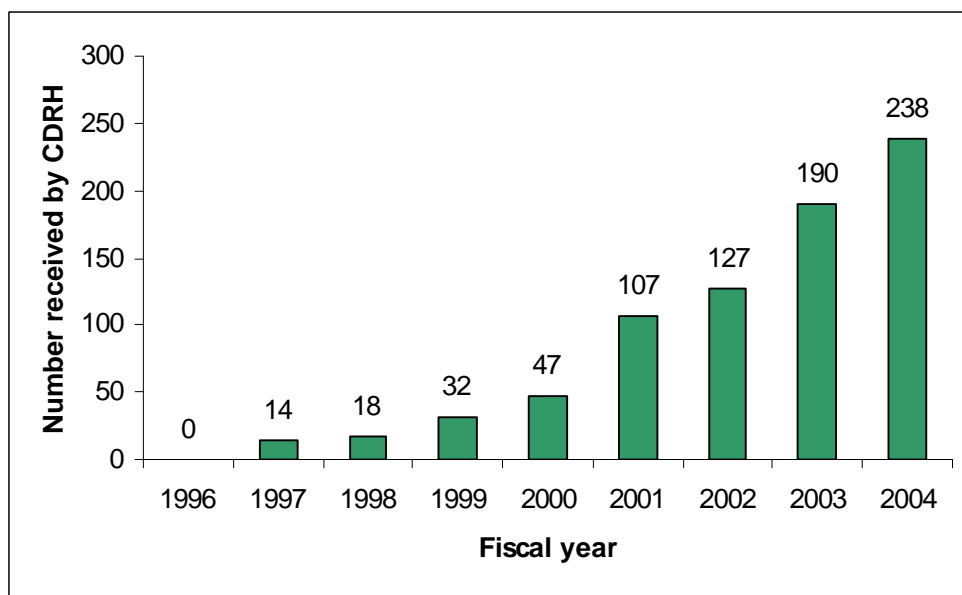
seems, however, to be considerable under-utilisation of third parties since third party reviews represent only 10% of the eligible 510(k)s. There also seems to be considerable disparity in the utilisation of third parties across product types. For example, third party reviews account for 29% of eligible premarket notifications submitted for radiological devices but none of the eligible orthopaedic devices.

Figure 1 below shows the number of premarket notifications reviewed by third parties that were received by CDRH since the inception of the Third Party Review Program in 1996. As shown in Figure 1, the activity has steadily increased. The values given for fiscal year 2004 are estimates based CDRH historical data.

#### Review times

For fiscal year 2003, the average elapsed review time for third party reviews was 74 days (date of receipt by the third party to date of FDA final decision) while the average elapsed review time for devices reviewed by the FDA within the same product codes averaged 112 days. Excluding Special 510(k)s, for which the statutory review time is limited to 30 days, the average review time for premarket notifications for which the FDA has issued device-specific guidance documents was 72 days for third parties and 105 days for CDRH. For devices without guidance documents, third party review times averaged 83 days, while CDRH time averaged 156 days.

**Figure 1. Third party reviews received by CDRH**



## Is Third Party Review The Right Choice?

Clearly only the manufacturer/sponsor can decide if the third party program is the right choice for the circumstances at hand. However, the third party review program may not be the best choice in the following situations:

### *Special 510(k)s*

Special 510(k)s for device modifications have a statutory review clock of not more than 30 days. Using a third party for the review of a Special 510(k) would increase the review time because the third party would review the Special 510(k) and then send it to the FDA with their recommendations. The FDA then has 30 days to make a final determination.

### *Devices for which the third party has limited experience*

Review times typically decrease as the third party becomes more familiar with a specific product type and the device-specific issues. It may be unwise to be one of the first of a kind that a third party has reviewed after being authorized by the FDA.

### *Devices whose eligibility is uncertain*

Devices that are not explicitly approved for third party review or whose premarket notification may need supporting clinical data are best submitted directly to the FDA.

### *Manufacturers/sponsors whose devices are not ready to market*

Manufacturers/sponsors whose devices are not ready to market may save money (third party review fees versus medical device user fees) by submitting their premarket notifications to the FDA during their scale up to full production.

## Summary and Conclusions

The FDA Third Party Review Program (AP and CAB) offers manufacturers/sponsors a voluntary alternative to submission of selected premarket notifications directly to the FDA. Third party review can decrease total review time. Depending on the third party, the experience of the third party with the specific device type/manufacturer may provide some measure of increased assurance of review by knowledgeable reviewers. Just as with any service, however, the manufacturer/sponsor must evaluate the device to be reviewed and the qualifications of the service provider to be sure that it is the most appropriate strategy.

***In certain cases, third party review may not be the best option***

## References

1. [www.fda.gov/cdrh/thirdparty](http://www.fda.gov/cdrh/thirdparty).
2. *Implementation of Third Party Programs Under the FDA Modernization Act of 1997: Final Guidance for Staff, Industry, and Third Parties*, 2 February 2001 ([www.fda.gov/cdrh/thirdparty/apguide13.pdf](http://www.fda.gov/cdrh/thirdparty/apguide13.pdf)).
3. *Guidance for Staff, Industry, and Third Parties – Third Party Programs under the Sectoral Annex on Medical Devices to the Agreement on Mutual Recognition Between the United States of America and the European Community*, 1 June 1999 ([www.fda.gov/cdrh/modact/eumra.pdf](http://www.fda.gov/cdrh/modact/eumra.pdf)).
4. [www.fda.gov/cdrh/mra/](http://www.fda.gov/cdrh/mra/).
5. Presentation by Mr Eric Rechen, Policy Analyst, Program Operations Staff, CDRH at Regulatory Affairs Professionals Society, Washington, DC, 12 October 2004.
6. *List of Devices for Third Party Review under the FDA Modernization Act of 1997*, 7 February 2002 ([www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/current.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/current.cfm)).
7. *Current List of Accredited Persons*, 5 November 2004 ([www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/accredit.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/accredit.cfm)).
8. Data and figures reprinted with permission of Mr Eric Rechen, Policy Analyst, Program Operations Staff, CDRH, as presented at the Regulatory Affairs Professionals Society in Washington, DC, 12 October 2004.

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# CLINICAL DATA IN THE EU

By Haroon Atchia

The regulations for placement of medical devices on the market in the EU are prescribed in the various European Directives but are not well defined. Concentrating on Council Directive 93/42/EEC (commonly known as the Medical Device Directive, MDD), this discussion explains the requirements, distinguishes the various options available for demonstrating clinical utility of a given medical device, and explores the role of the Competent Authority (CA) in dealing with applications for commencement of a clinical investigation for the purposes of CE marking.

## Distinction Between Investigation and Data

Clinical data are always required in order to place a medical device on the market with the CE marking, irrespective of the EC product class of the device, when

**Meaning of clinical 'data' differs from our day-to-day understanding**

conformity with one or more Essential Requirements (ERs) or performances specified by the manufacturer cannot otherwise be demonstrated. Confusingly, however, the meaning of 'data' is specific and different from our day-to-day understanding.

## Clinical evaluation

The obligations for evaluating the clinical suitability of medical devices to be placed on the market with the CE mark are outlined in Article 15 of the MDD. Annex X provides further requirements on how clinical data should be obtained. Within the meaning of the MDD, clinical data constitutes either of the following:

- formal, systematic clinical investigation according to a defined protocol for establishing evidence to confirm conformity with one or more ER(s);
- critical appraisal of relevant scientific and clinical literature for establishing evidence to confirm conformity with one or more ER(s).

Any other form of clinical evaluation is not specifically prescribed but one method is now customary: comparative evaluation of the test product against a CE-marked reference product legitimately on the market.

Determination of whether clinical evaluation is necessary resides with the manufacturer (except in France). It is therefore possible that a product may undergo conformity assessment with insufficient or inadequate clinical

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## Further Reading

- I. *Premarket Notification 510(k) Regulatory Requirements for Medical Devices*, August 1995.
- II. *In Vitro Diagnostic Products: Guidance for the Preparation of 510(k) Submissions*, January 1997.
- III. *Guidance for Third Parties and FDA Staff; Third Party Review of Premarket Notifications*,

28 September 2004.

- IV. *Determination of Intended Use for 510(k) Devices - Guidance for Industry and CDRH Staff*, January 1998.
- V. *Guidance on the Recognition and Use of Consensus Standards*, February 1998.
- VI. *Guidance on the Use of Standards in Substantial Equivalence Determinations*, March 2000.

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