Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

INVESTIGATIONAL DEVICES: FOUR CASE STUDIES

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EXECUTIVE SUMMARY

PURPOSE

To assess in four case studies whether controls over clinical testing of investigational devices ensure patient safety and sound clinical research.

BACKGROUND

The Food and Drug Administration (FDA) oversees the development of new medical devices. For some medical devices, manufacturers must establish the safety and efficacy of the devices through clinical trials before FDA will clear the device for marketing. To further guard patient safety, Institutional Review Boards (IRBs) approve and monitor clinical research within local hospitals. The FDA requested that we assess various aspects of the testing process, particularly whether devices are being distributed outside approved clinical trials.

We used four case studies to develop a picture of clinical trials for investigational medical devices. We spoke with each device's manufacturer, and selected clinical investigators and IRB representatives. We reviewed FDA's files for the devices, obtained shipping records and other documents from the manufacturers, and inspected documents from the IRBs we visited.

FINDINGS

During our assessment of the testing process, we found problems in three major control areas: the accounting and tracking of investigational devices; and the local oversight by IRBs including the informed consent process. The exhibit below summarizes the kind of problems we found for each device.

Problems Found in Four Case Studies

	Device A	Device B	Device C	Device D
Device Tracking	✓	✓	✓	
IRB Oversight	✓	✓	✓	✓
Informed Consent		✓	✓	

We Uncovered Problems With The Distribution Or Accountability Of Three Investigational Devices.

Device A was distributed in excess of the approved protocol. This raised questions about whether patients were properly informed about the devices, and whether appropriate data was reported to FDA. Also, there was a lack of accountability for Devices B and C. Clinical investigators and hospitals are unclear regarding their responsibilities for tracking the use and disposal of investigational devices.

Our Case Studies Also Identified Potential Weaknesses In The Oversight Of Clinical Trials At Local Sites.

We found that IRBs are dependent on information provided by clinical investigators, have difficulty monitoring clinical trials, and have difficulty deciding whether a device study poses significant or non-significant risk. In addition, we found problems with the informed consent process including missing or incomplete informed consent documents, questions about how informed consent is obtained, and difficulty in reading informed consent documents.

CONCLUSION

We believe that in the current environment, investigational devices are often treated as if they were already approved as safe and effective. In particular, although the regulations clearly require the careful tracking and disposal of investigational devices, our case studies show that accounting mechanisms sometimes fail. In addition, some investigational devices are being used inappropriately outside of approved clinical trials.

Our case study method does not provide sufficient evidence to determine the precise extent of problems with the testing of medical devices. Nevertheless, it does raise serious concerns about systemic weaknesses and casts reasonable doubt on the efficacy and reliability of the current oversight process.

The FDA commented on the report (see Appendix D) and takes seriously our findings. The FDA intends to carefully review the regulations and policies regarding clinical investigations, and take whatever actions are warranted to ensure that clinical investigations of medical devices are conducted with high ethical standards and in accordance with all Federal rules pertaining to patient protection.

TABLE OF CONTENTS

INTRODUCTION

PURPOSE

To assess in four case studies whether controls over clinical testing of investigational devices ensure patient safety and sound clinical research.

BACKGROUND

Medical devices range from simple ear swabs and tongue depressors to highly complex diagnostic imaging equipment, surgical props and physical implants such as pacemakers. The Food and Drug Administration (FDA) oversees the development of new medical devices through the Center for Devices and Radiologic Health. The Center for Devices and Radiological Health requested that we conduct a study regarding the Investigational Device Exemption (IDE) process (see Appendix C.) The IDE regulation (21 CFR Part 812) sets forth the provisions for the conduct of clinical investigations of medical devices in the United States.

Medical Device Classifications

As established by the Medical Device Amendments of 1976, there are three classifications of medical devices. Class I devices consist of low-risk devices, such as bed pans and tongue depressors, and are subject to general controls that include premarket notification and prohibitions against misbranding. Class II devices, such as hearing aids and electrocardiogram machines, are subject to additional special controls that include performance standards and postmarket surveillance. Class III devices, such as pacemakers and catheters, generally sustain or support life, are implanted in the body, or pose a potential risk of illness or injury. Class III devices are subject to general controls, some special controls, as well as the more stringent Premarket Approval (PMA) process.

FDA Marketing Approval

Manufacturers gain marketing clearance for many Class I and Class II devices, and a limited number of Class III devices through the premarket notification process known as the 510(k) process. The 510(k) refers to that section of the Federal Food, Drug and Cosmetic Act (the Act) that allows a manufacturer to submit an application to FDA for a device that is substantially equivalent to a device previously approved for marketing by FDA. If FDA agrees that the devices are substantially equivalent, then the review time for the new device should be reduced. The FDA might require a manufacturer to conduct a clinical investigation of a device in support of their 510(k) application.

For devices that do not meet 510(k) specifications, a manufacturer applies for marketing clearance through the PMA process. Before submitting the PMA, the

manufacturer establishes the safety and efficacy of their device through clinical trials. The trial is conducted by a study sponsor, who may or may not be the manufacturer. (In this report, we use the term manufacturer to refer to manufacturers and study sponsors.) The data from these clinical trials are what FDA reviewers will analyze to determine that a device is safe and effective enough for commercial distribution.

IDE Approval Process

To conduct a clinical investigation of a medical device, the manufacturer must first determine whether their study presents a significant risk or non-significant risk to the patients, known as study subjects. According to the FDA, a significant risk study poses potential harm to clinical trial subjects either from the device or other procedures in the study. For example studies using infusion pumps, pacemakers, and catheters are considered significant risk studies. If the study poses significant risk, the manufacturer submits an IDE application to FDA that details how the clinical trial will be conducted.

The IDE application includes (but is not limited to) a clinical trial protocol. The protocol should have well-defined trial end points (what constitutes success, failure, or complications with the device). The protocol also establishes the number of subjects that the device must be tested on to prove that the device will work safely and effectively in a larger population. The characterizations of the test subjects should also be defined; who in terms of age, medical condition and other factors will be allowed into the study. Well-defined historical controls or control groups to compare outcomes may also be necessary. The protocol will describe at how many sites, usually hospitals, the testing will be done, and how many subjects per site will be included in the trial. The protocol will also estimate how long it should take to conduct the trial. Clinical trials conducted at more than one site are called multi-site trials.

In addition to FDA, an Institutional Review Board (IRB) must approve the clinical trial protocol at the specific sites where the clinical trials take place. The IRBs are boards or committees within an institution which oversee the protection of human subjects involved in clinical trials. The IRBs review protocols and the informed consent forms given to the subjects of the clinical trials for both significant and non-significant risk studies. The IRBs must review all clinical trials occurring within their institutions on an on-going basis.

If a manufacturer determines that their study is non-significant risk, then only the IRBs at the sites where the manufacturer wants to conduct the trial will review the protocol. Examples of non-significant risk devices include daily wear contact lens, wound dressings and some magnetic resonance imaging devices. If the IRBs agree with the non-significant risk determination, they may grant what is known as an "abbreviated IDE" to the manufacturer and allow the manufacturer to begin the clinical trial at that institution. However, if any single IRB that reviews the protocol does not agree with the manufacturer that the study is non-significant risk, then the manufacturer must inform FDA of the IRB's decision. The FDA may agree with the

manufacturer that the study poses non-significant risk, and the manufacturer may conduct the study at any institution where the protocol is approved. However, if FDA determines the study is significant risk, then the manufacturer must submit a full IDE application to FDA.

IDE Clinical Investigators

Before or after a manufacturer obtains IDE approval, they may recruit the physicians, known as investigators, to conduct the clinical trial. These clinical investigators might be preeminent specialists in their field or major customers of the manufacturer. In some cases, the manufacturer recruits clinical investigators based on the referral of another investigator.

The clinical investigators are responsible for obtaining IRB approval for trial research conducted at their institutions. Once the clinical investigator secures IRB approval, they may begin recruiting subjects for the clinical trials. In most cases the subjects for device trials come from the clinical investigator's private practice. The clinical investigator is responsible for obtaining the subject's informed consent, recording study data and conducting subject follow-up.

Concerns about the IDE Process

There have been concerns about the IDE process and the quality of the clinical data obtained through this process. A recent report by FDA's Committee for Clinical Review found enough deficiencies in the design, conduct and analysis of clinical trials in enough medical device applications to suggest an industry-wide problem. In some cases, these deficiencies were determined serious enough to impede FDA's ability to judge the safety and efficacy of the device.

Adherence to Clinical Protocols

Some staff at the Center for Devices and Radiological Health have explained that one way clinical data is compromised is that clinical investigators and manufacturers do not adhere to the protocol subject limit and allow more subjects into the clinical trials than necessary. They may also admit subjects into the clinical trial that do not always meet the criteria for admission stated in the clinical protocol. If this happens, trial data could be compromised because investigators and/or manufacturers might only report the best outcomes of selected subjects.

There have been several documented cases where manufacturers have distributed investigational devices more widely than is stated in the clinical protocol. A report by the House Subcommittee on Oversight and Investigations cites a recent example of uncontrolled growth of a clinical trial involving a silicone angioplasty balloon used in controlling cranial bleeding. The company responded to the increased demand of

physicians by providing the device in uncontrolled numbers. According to FDA, the uncontrolled expansion of the trial compromised the validity of the clinical data.[1]

Cost Recovery Concerns

One possible reason why more subjects are admitted to clinical trials than necessary is that per the IDE regulations, manufacturers may recover the cost of developing and testing devices in the investigational stage. Drug manufacturers, on the other hand, are prohibited from recovering any costs until the drug has been approved, except in rare circumstances. The Congress allowed cost recovery of investigational medical devices to foster the development of new medical devices by small companies.

In addition to the manufacturer being permitted to recover costs, clinical investigators are allowed to charge the subjects not only for the device, but also for any procedures or services involving the device. This provision may lead some manufacturers and clinical investigators to include more subjects and to continue clinical trials beyond what is necessary to establish safety and efficacy.

Promotion Concerns

Additional concerns exist that some manufacturers are promoting devices as safe and effective while still in the investigational stage. Although manufacturers can recover the actual cost of development, under FDA regulations, manufacturers may not describe an investigational device as safe or effective, commercially distribute the device beyond the scope of the clinical trial, or recover costs beyond what is reasonable for device development before FDA approves the device.

One example of how a manufacturer used their IDE to commercially promote a device was described in an Office of Inspector General report dated February 1991. In this case, the manufacturer developed a device which had a 510(k) approval for one use and an IDE for another use. However, the manufacturer, through training seminars, catalogs, videotapes and technical manuals, commercially promoted the experimental use of the device.[2]

Health Care Industry Environment

The general environment of the health care industry may promote the distribution and use of unapproved medical devices beyond clinical protocol design. Hospitals

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[1]Less Than the Sum of Its Parts, Subcommittee on Oversight and Investigations, May 1993, page 12.

[2]FDA Medical Device Regulation From Premarket Review to Recall, Office of Inspector General, February 1991, page 8.

experience pressure to acquire the latest in equipment to compete with other hospitals, and physicians also want to stay competitive as well as provide their subjects with potentially more effective treatments.

Informed Consent Process

Questions have also been raised regarding the informed consent process both in investigational device studies and other studies. The Congress held hearings in 1994 regarding informed consent and some of the potential problems with subjects not giving informed consent. The hearing also discussed the appropriateness of using investigational devices without a subject's informed consent.

FDA Efforts

The FDA is attempting to improve the quality of clinical data it receives by more outreach and education of the medical device industry about clinical protocol design and conduct. The FDA also attempts to ensure the integrity of the clinical trial data through its Bioresearch Monitoring program. Through this program, FDA audits manufacturers, IRBs and clinical investigators.

METHODOLOGY

We were asked by the Center for Devices and Radiological Health to examine the IDE process, particularly whether manufacturers were using the IDE process to commercialize investigational medical devices. To understand how and why medical devices might be commercialized, we believed that we needed to fully assess the environment in which medical devices are tested. To accomplish these tasks, we choose a case study methodology.

Using a case study approach presents both limitations and advantages. Devices chosen for the case study and any problems found may not be representative of all investigational medical devices. However, the case study approach provides a comprehensive picture of how investigational medical devices are developed. A shallower, though broader based review would not provide this understanding.

Selection of Devices

To select the investigational medical devices for inclusion in our case study, we examined FDA's entire IDE database which is used for tracking the status of an IDE application. There were 1,509 IDE applications in the database. Over one-third of the IDE applications were denied by FDA. We automatically dropped these applications for our case study review.

We did not consider IDE applications dated before January 1986. We dropped from consideration IDE applications for intraocular lens since these applications are

regulated by a different set of regulations than IDE applications for investigational medical devices.

We eventually narrowed the number of IDE applications for review to 30 files. Included in these files were several devices and device types suggested by FDA. After a comprehensive review of these 30 files, we eliminated seven IDE applications for devices with previous 510(k) or PMA approval. We eliminated these applications because of the difficulty in distinguishing those devices shipped for use in clinical trials and those devices shipped for commercial distribution. We also eliminated seven IDE applications that were single-sites because we thought that commercialization would be more prevalent in multi-site trials.

We chose devices that were used in different regions of the body. This allowed us to speak with clinical investigators in different medical specialties. Once we selected an IDE application, we eliminated any similar devices.

Ultimately, we selected four devices for our review. One of these devices was suggested by FDA because of their suspicions about commercialization of the device. A description of the devices are located in Appendix A. The names of the devices are protected from disclosure under the Freedom of Information Act because of the proprietary nature of the information.

Information Gathered

For each device selected, we spoke with the device's sponsor or manufacturer.[3] We asked general questions about the current IDE process. We also asked specific questions about the device selected for the case study. One manufacturer, on advice of attorney, would not discuss the specifics of the clinical trials for the device selected.

We spoke with selected clinical investigators and institutional review board chairpersons or their designates for each of the devices. We did not interview every clinical investigator or IRB representative involved in the clinical trials. We selected the clinical investigators and IRBs based on their geographic location. In our interviews with IRB representatives, we asked about their experiences not only with the case study device, but also with investigational devices in general.

In addition, for Devices A and B, we obtained information from FDA audits of clinical investigators or IRBs. For one of the devices, we spoke with the FDA reviewers. Exhibit 1 summarizes the total number of the devices' investigative sites and out of that number, how many clinical investigators and IRB representatives we interviewed and/or reviewed files for the study.

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[3]For one device, the manufacturer sold the technology. In this case, we spoke with both the original manufacturer and the current manufacturer.

Exhibit 1

DEVICE	Total # of Investigative Sites in the Clinical Trial	# of Investigators We Reviewed	# of IRBs We Reviewed
A	9	4	4
B	13	5	5
C	47	10	8
D	11	2	3

We reviewed the IDE files for each device. We reviewed in depth the original application, and any amendments or supplements to the application. When applicable, we also reviewed the PMA for the device.

We obtained the shipping records for each of the devices. For the device that was sold, the current manufacturer could not find the original shipping invoices, but was able to provide us with a spreadsheet detailing how many were shipped, how many were returned and how many were used. The manufacturers also provided us with copies of investigator agreements, informed consent documents, clinical protocols, and other information relevant to the devices.

We obtained pertinent documents from the IRBs we visited. These documents included any material submitted to the IRB by the clinical investigator, correspondence between the IRB and the clinical investigator, or the IRB and the manufacturer, progress reports, and copies of the minutes of the IRB meetings where the device was discussed. From one hospital, we obtained hospital purchase orders for the investigational device.

We supplemented our interviews and data gathered through a review of FDA audit reports for the devices selected. We also accompanied FDA inspectors during their audits of two separate clinical investigators for one of the devices. During these audits, we completed a file review of subjects involved in the clinical study.

Data Analysis

We entered all the shipping records received into a database. We analyzed this database and related records to determine whether investigational devices had been shipped in excess of protocol limits. We reviewed all other submitted and gathered documents.

We also subjected informed consent documents to the computer based application Grammatik IV, which analyzes overall readability of documents, and calculates an index of reading difficulty for written material.

We conducted this inspection in accordance with the Quality Standards for Inspections as developed by the President's Council on Integrity and Efficiency.

FINDINGS

During our assessment of the IDE process in four case studies, we found problems in three major control areas: the accounting and tracking of investigational devices; and the local oversight by IRBs including the informed consent process. Exhibit 2 summarizes what kind of problems we found for each device.

Exhibit 2

	Device A	Device B	Device C	Device D
Device Tracking	✓	✓	✓	
IRB Oversight	✓	✓	✓	✓
Informed Consent		✓	✓	

The first finding below discusses in detail the accounting and tracking issues that FDA asked us to look at. The second finding describes problems we discovered regarding IRB oversight and informed consent as we looked at the broader IDE environment.

WE UNCOVERED PROBLEMS WITH THE DISTRIBUTION OR ACCOUNTABILITY OF THREE INVESTIGATIONAL DEVICES.

One of the most important elements of clinical trial design is total number of subjects the device will be tested on, and the defined characteristics of those subjects, including age and medical conditions. The FDA reviewers must be sure that the data from the studies they analyze accurately reflects the outcomes and effects from the use of the device. Limiting the numbers of subjects in a clinical trial protects the overall population until determinations of safety and efficacy can be made. The distribution and use of investigational devices beyond the protocol limit potentially compromises the data; investigators or manufacturers might only report on the best outcomes, or not report poor outcomes, or certain side effects. To ensure that subject limits are being complied with, accurate distribution, use, and disposal records must be kept. While not generalizable to all clinical investigations of devices, these problems portray how unchecked distribution can happen, and why it is difficult to monitor.

Device A Was Distributed In Excess of the Approved Protocol

The approved clinical trial for Device A consists of nine separate sites. Each site may test no more than 75 devices. We analyzed the shipping records for Device A.

Device A consists of three separate components. Each component is available in different sizes. We limited the analysis to one of the three types of components used in the device. No more than two of these components can be used in a surgery, with a majority of surgeries only utilizing one component.

Our initial analysis of the shipping records for all nine clinical investigators for Device A showed significantly more of these components shipped than reported to FDA as implanted. The manufacturer's 1994 annual progress report to FDA says a total of 284 components were implanted nationwide; however, the shipping records show that 1,319 components were shipped. The manufacturer explained that the large number of devices shipped were warranted because of the need to have a number of different sizes in stock and available at the time of surgery.

To check the manufacturer's assertion, we reviewed documents for two different clinical investigators for Device A.

For one of the clinical investigators, we obtained hospital purchase orders for Device A. According to the hospital representative, in addition to their use for accounting purposes, the purchase orders are also used to track subjects who received the device. The purchase order date for the device is usually the day of surgery or within 1 to 2 days following the surgery.

Analysis of the shipping records for this clinical investigator show that the manufacturer shipped a total of 327 components to the regional distributor who supplies the clinical investigator with the investigational device. The hospital purchase orders show that a total of 264 components were implanted in 258 subjects by either the clinical investigator or the co-investigators. However, the 1994 annual progress report submitted by the manufacturer to FDA and by the clinical investigator to the IRB says that a total of only 37 components were used by this clinical investigator. Clearly the clinical investigator has exceeded the 75 case limit of the approved protocol at the local sites.

It is unknown whether this clinical investigator or the manufacturer only reported data on the first 37 subjects who entered the study, if the clinical investigator or manufacturer selected certain subjects to report on, or if these 37 cases were the only subjects who met the subject selection criteria. In any case, it raises questions on the quality of information being reported to FDA.

We also reviewed an FDA audit report for a Device A clinical investigator who died in December 1992. According to the FDA audit report, the clinical investigator reported completing a total of 19 device implants during the entire trial period. Our analysis of the manufacturer's shipping records show that a total of 77 components were shipped to the distributor for the clinical investigator. After the death of the clinical investigator, the distributor returned only 15 components, leaving 43 components unaccounted for. We are unsure of the status of these 43 components

since the components should have been returned to the manufacturer when the clinical protocol was terminated.

A recent FDA audit of the manufacturer found that the manufacturer could not account for up to 25 percent of all the components shipped.

There Was A Lack of Accountability for Devices C and B

Under the IDE regulations, clinical investigators are responsible for documenting the receipt and distribution of investigational medical devices: the type and quantity, the names of all persons who received the device, and why and how many were returned, repaired or otherwise disposed of. However, according to 12 of 20 of the clinical investigators we spoke with, the responsibility for maintaining the inventory of investigational medical devices lies with the hospital, and not the investigator. The hospital may or may not choose to track these devices.

Our analysis of the shipping records for Device C indicate that the number of devices shipped to various clinical investigators exceed the number of cases reported to FDA. These numbers range from one or two extra devices per investigator, up to 100 extra devices. According to one investigator we spoke with, in some circumstances, a device may be opened in surgery (thereby destroying its viability for future use), but not used on a subject. However, we were unable to determine whether some devices were actually used in unreported subjects or whether the devices were disposed of by the clinical investigator. There was no accountability or tracking for these extra devices by the clinical investigators we reviewed.

The use of an investigational device is supposed to be limited to subjects enrolled in clinical trials or in rare emergency use with the IRB and FDA approval after obtaining the subject's informed consent. Our inability to account for the devices raises questions regarding whether the devices were used, whether subjects were informed, and whether data was collected and submitted on the subjects.

During an FDA audit, one of the clinical investigators for Device B claimed that all tracking records for the device were kept by the hospital. However, the hospital could not produce any records because they did not keep them. The FDA auditor had to rely solely on records provided by the manufacturer.

OUR CASE STUDIES ALSO IDENTIFIED POTENTIAL WEAKNESSES IN THE OVERSIGHT OF CLINICAL TRIALS AT LOCAL SITES.

During the course of our study, we attempted to understand how clinical trials are conducted. We were struck by how the current system of clinical trials for medical devices merges scientific research with patient care. Physicians practicing in their normal environment are asked to conduct scientific research on patients.

We realize that physicians are concerned about obtaining potentially more effective treatments for their patients. While becoming a clinical investigator may ensure the supply of these potentially more effective treatments, it also adds to the physician's responsibilities. For many physicians, clinical research is an area where they have little training or experience.

We found that FDA, manufacturers, IRBs and clinical investigators are all responsible for ensuring that clinical trials are properly conducted. If clinical trials are not conducted properly at all levels then the study results may be invalid. We focused our review on the local levels of oversight and controls in the IDE process.

Two major controls in the IDE process are local oversight of clinical investigators by institutional review boards and the informed consent process for human subjects. These controls not only ensure proper clinical trials, but also ensure subject safety and the collection of reliable data from clinical trials.

We found that IRBs are dependent on information provided by clinical investigators, have difficulty monitoring clinical trials, and have difficulty deciding whether a device is a significant risk versus non-significant risk device. In addition, we found problems with the informed consent process including missing or incomplete informed consent documents, questions about the informed consent process, and reading level difficulty of informed consent documents. While these problems may not be representative of all clinical trials being conducted in the United States, we found one or more problems in 11 of 20 sites we examined.

Local Oversight of Clinical Investigators by Institutional Review Boards

Institutional Review Boards monitor human subject research occurring within their hospital or institution. Members of an IRB generally include physicians - usually of different specialties - nurses, pharmacists, hospital administrators, a lay member of the community, and often a member of the clergy or a medical ethicist. The IRBs in our case studies ranged from large university based teaching hospitals with 26 members overseeing 2,600 ongoing studies to small community hospitals with 8 members and 55 ongoing studies.

To conduct its oversight of all protocols, including devices, an IRB will first review a clinical protocol submitted by a potential investigator, primarily to determine the risk versus benefit to the subject in the clinical trial. An IRB can require that changes be made to a protocol. The IRBs also focus attention on the informed consent document, and may require content or wording changes. In addition, IRBs have the authority to suspend or terminate studies within their institutions.

Reliance on information provided by clinical investigators

The IRBs generally rely exclusively on information provided to them by the investigator, and sometimes a manufacturer. As noted earlier, in one of our case

studies the investigator reported in an annual report that 37 cases had been completed using Device A. Our review of that hospital's invoice records showed that 264 investigational devices had been implanted by the date of the annual review. Relying on the information provided by the investigator, the IRB continued to approve the study which had an institutional limit of 50 to 75 implants, even though the hospital records indicate that the clinical investigator had far exceeded that limit.

For Device D, the clinical investigator reported to the IRB that zero devices were implanted during the course of the study. Reports from the manufacturer showed that three devices had been implanted at that institution, including one device that was implanted after the investigator informed the IRB that the study was closed.

Monitoring a clinical trial

Although IRBs have authority to suspend or terminate studies, they do not always follow up or verify that their orders have been carried out. A clinical investigator for Device A was told to suspend the investigation, pending submission of an annual report. This investigator implanted 15 investigational devices during the six week period of the suspension. It also appears that the same investigator implanted two devices prior to FDA or IRB approval for the device.

In an example from Device B, the IRB approved the protocol pending changes to the informed consent document. The investigator responded that the changes would be made, yet we found they were not. The IRB had not followed up to see if the changes had been made.

Two IRBs for Device A were not aware of a change made by the manufacturer to the protocol during the course of the study. This change involved the addition of a different sized device to the study. The IRBs should have been made aware of and approved this change as it affects the rights, safety, and welfare of the trial subjects. However, the IRB must rely on investigators and manufacturers to submit this information.

In another example, an investigator for Device B did not inform the IRB that he had moved to another city, and was no longer practicing at that institution. The IRB only became aware that the investigator had moved when a human subject from the trial went to a hospital clinic complaining of pain in the investigational device implant area. The investigator had referred the trial subjects to this clinic, without ever officially transferring the study and the participating subjects to a new investigator. The IRB then assigned a new investigator to the study. In further communication with the IRB, the former investigator did not understand why such a transfer needed to occur, as he intended to conduct follow-up during periodic visits to the city. The IRB informed the investigator that the subjects were human subjects in a trial at an institution, not private patients. This example raises some questions regarding the respective responsibilities of IRBs and manufacturers. Who should educate the clinical

investigator regarding reporting and subject care responsibilities in a clinical trial, as these differ from private practice?

Deciding Whether a Clinical Trial poses Significant or Non-significant Risk

One of the duties that FDA has delegated to IRBs is the determination of significant versus non-significant risk device studies. This in an important determination, because all significant risk studies must receive an IDE from FDA before beginning a clinical trial. If a manufacturer determines that its study poses non-significant risk, and if the IRBs also determine the study is non-significant risk, the manufacturer can begin a clinical trial on the device without knowledge or approval from FDA.

Our interviews with IRB representatives revealed that many IRBs are confused or unclear about what constitutes significant risk studies. In some cases, an IRB bases its determination by comparing the risk of the device or procedure to other approved devices. Thus, an IRB might consider the implantation of a pacemaker to be non-significant risk, because the risk is compared to the risk of implanting an approved pacemaker. Our review of IRB records revealed that 3 out of 10 IRBs for Device B determined the study as non-significant risk. The FDA through its own study of this issue found that nearly one-quarter of the non-significant risk devices approved should have been significant risk decisions. Although FDA is available to answer IRB questions about this and other matters, an IRB will not call if they believe they have made a correct determination.

Informed Consent for Human Subjects

Most medical ethicists view informed consent as a **process** in which the investigator thoroughly communicates to the subject the significance of their participation in a clinical trial. Informed consent means that subjects clearly understand that they are participating in research for devices that have not yet been proven safe or effective. Although informed consent ideally involves both verbal and written communication, most government officials, manufacturers, IRBs, and clinical investigators deem that informed consent has been given when a subject signs the informed consent document. However, as Exhibit 3 illustrates, the extensive and sometimes complicated information that must be

Exhibit 3

Informed Consent Should:

- Explain that the device has not been approved as safe and effective by FDA.
- Describe any potential risks and benefits expected from participating in the clinical trial.
- Describe the length, nature and number of subjects in the clinical trial.
- Explain the patient's rights including that their participation is voluntary and they can withdraw at any time.
- Explain who they should contact if they have any questions about the research or their rights as research subjects.
- Explain the patient's responsibilities as a research subject including their responsibilities for follow-up visits for data collection.

relayed through an informed consent document makes the verbal process of informed consent that much more important.

Missing or incomplete documents

We found no informed consent documents in the individual case files of one investigator for Device C. There were surgical release forms, but no informed consent documents. The surgical consent forms did not explain that the device was investigational and the risks associated with the device. Although the investigator claimed that all research subjects received informed consent, an interview with the investigator's assistant revealed that while the subjects for another study for a similar device received informed consent, the subjects for the Device C study did not.

A review of a clinical investigator's files for Device B revealed that the informed consent document was missing information about who (other than the investigator) the subject should contact with questions or complaints about the study. This was the case, even though the IRB requested that the informed consent document be amended to show who to contact regarding questions about the study.

Questions about the process

Two clinical investigators for Device C sometimes waited to obtain subjects' informed consent until after the surgery was performed. The physician would decide during the surgery whether the subject should receive the investigational device or some other device. Both physicians claimed that the investigational nature of the device was discussed with the subject prior to surgery. Because of this practice, one of these clinical investigators never obtained informed consent from some of the subjects.

For Device B, FDA received complaints from a physician (not an investigator for the device) alleging that a subject was not aware that the implanted device was investigational. To date FDA has not completed an audit of the clinical investigator and we are unsure if the subject signed the informed consent document. Nevertheless, even if the subject had signed an informed consent document, this allegation indicates that some subjects might not know what they are signing.

In several cases, investigators we interviewed acknowledged that they have little to do with actually informing the subject about the study or device. This communication is usually left up to an assistant or nurse. While this may not lead to subjects not being informed, it does add to the "business as usual" atmosphere in doctor's offices where medical device research is conducted. The investigator behaves more as a treating physician than as a clinical investigator.

Evidence obtained during a FDA audit of an investigator for Device B, showed that most subjects signed the informed consent documents the day before surgery. This, we were informed, is the norm for many clinical investigations. Furthermore, the regulations do not indicate when, prior to a procedure or surgery, informed consent

must be given. Technically, there is nothing wrong with this practice. However, the process of informed consent means that subjects understand and volunteer for participation in a study before agreeing to surgeries with investigational devices. Considering that most physicians schedule non-emergency surgeries in advance, this raises questions as to why the informed consent documents are not signed before scheduling surgery. There is no evidence that a subject has been verbally informed of the investigational nature of the device. An informed consent document signed 1 day before surgery could easily be lost among the other hospital forms, including surgical release forms, that must be signed before surgeries.

Difficulty reading informed consent documents

We gathered samples of informed consent documents from each of the investigators we interviewed. Because of IRB requirements, and limited manufacturer guidelines, documents may vary from site to site. Overall we found informed consent documents range from providing direct, numbered, and simple statements, to convoluted and long paragraphs. In any case, due to the extent of the information that must be provided, these documents usually run four pages or more.

A reading difficulty and fog index analysis of four of the informed consent documents (one for each device in our case studies) revealed reading grade levels of college level to graduate level ability, and reading difficulty from fairly difficult to difficult. Some of the verbage involved, such as technical device names and other medical terminology, contribute to such high levels. Yet the question remains, do patients understand what they are signing, and if not, is it adequately explained?

CONCLUSION

We believe that in the current environment, investigational devices are often treated as if they were already approved as safe and effective. In particular, although the regulations clearly require the careful tracking and disposal of investigational devices, our case studies show that accounting mechanisms sometimes fail. In addition, some investigational devices are being used inappropriately outside of approved clinical trials.

Our case study method does not provide sufficient evidence to determine the precise extent of problems with the testing of medical devices. Nevertheless, it does raise serious concerns about systemic weaknesses and casts reasonable doubt on the efficacy and reliability of the current oversight process.

The FDA commented on the report (see Appendix D) and takes seriously our findings. The FDA intends to carefully review the regulations and policies regarding clinical investigations, and take whatever actions are warranted to ensure that clinical investigations of medical devices are conducted with high ethical standards and in accordance with all Federal rules pertaining to patient protection.

APPENDIX A

Device Descriptions

Device A

This is a prosthetic device with a chemical coating to promote bone growth. The FDA has approved versions of the device without the coating for marketing.

The manufacturer submitted an application for an IDE in September 1988. The FDA initially denied the application citing concerns with the material used in the device and questions regarding the clinical protocol. The manufacturer amended their original application. The FDA approved the IDE in February 1989.

In July 1989, the manufacturer submitted a supplement to their IDE requesting FDA approval to manufacture and test two modifications of the device. The FDA approved the modifications in November 1989 and set a limit for the clinical study of 600 implants at 15 institutions.

The manufacturer originally recruited a total of 11 clinical investigators to conduct clinical trials at their respective institutions. However, two clinical investigators dropped out before the study began. A total of nine clinical investigators participated in the study.

The clinical trials are currently active and ongoing.

Device B

This is an orthopedic device which promotes the growth of bone mass between two bones. The device comes both coated with a chemical substance to promote bone growth and uncoated.

The manufacturer submitted an original IDE application in January 1991. The FDA had concerns with the application. The manufacturer submitted a number of amendments addressing FDA's concerns. The FDA approved the IDE in September 1991.

The FDA limited the number of subjects in the study to 240 at 15 centers. A total of number of 13 clinical investigators participated at 10 institutions.

The clinical trials are currently nearing completion with a planned PMA submission.

Device C

This opthalmic device is used in eye surgeries. Originally, nine individual sponsor-investigators received IDE approval from FDA for use of the device. In 1988, FDA requested that one sponsor apply for an IDE under which a number of clinical investigators would be covered.

The sponsor submitted a PMA which initially was not accepted by FDA. The original sponsor transferred the IDE to another sponsor. This sponsor submitted a PMA which was accepted by FDA in March 1992. A number of individual clinical investigators applied for their IDE to receive the investigational device. The FDA granted most of the IDE applications submitted. In total 47 clinical investigators conducted clinical trials on the device. The total number of subjects that were allowed to participate is difficult to distinguish because of the number of independent IDEs.

The FDA has approved the device for marketing.

Device D

The device treats urinary obstructions. The manufacturer submitted their original IDE application in April 1991. The FDA initially disapproved the application citing concerns about the performance of the device and the clinical protocol. The manufacturer submitted an amendment to their original IDE addressing FDA's concerns. The FDA approved the IDE in July 1991.

The FDA approved a limit of 150 subjects at 10 investigational sites for the clinical study. However, during the course of the study the number of sites increased to 11.

The clinical trials are closed with no further subject enrollment.

APPENDIX B

Glossary

Terms are described in terms of medical device development and research.

Center for Devices and Radiological Health (CDRH) - the Center within the Food and Drug Administration which regulates the development and marketing of medical devices in the United States.

Clinical Investigator or Investigator - the person, usually a physician, who tests an investigational device on a human subject.

Clinical Trial - a study involving humans in which a medical device, is tested to establish safety, efficacy, or new indications.

Federal Food, Drug, and Cosmetic Act (the Act) - the legislation that established FDA's oversight of, among other things, medical devices.

Food and Drug Administration (FDA) - the Agency within the Public Health Service of the United States Department of Health and Human Services which protects the public health by, among other duties, regulating medical devices.

510(k) - the section of the Federal Food, Drug, and Cosmetic Act which allows a manufacturer of a medical device to bring a new device to the United States market because it is substantially equivalent to a device that is already on the market.

Human Subject or Subject - a person who undergoes the testing of a medical device.

Informed Consent - the cognizant approval of a human being to participate as a test subject in medical research.

Informed Consent Document - the form which explains the purpose and description of a clinical trial, as well as the rights of participating human subjects. A human subject is deemed to have given their informed consent to participate in the described research when they sign the informed consent document.

Institutional Review Board (IRB) - the committee or board that reviews and approves research involving human subjects at a local institution.

Investigational Device Exemption (IDE) - the regulation (21 CFR Part 812) that sets forth the provisions for the conduct of clinical trials for medical devices in the United States.

Manufacturer - the company that makes the medical device.

Medical Device - any equipment that is used in the diagnosis and/or treatment of a medical condition. Medical devices range from band-aids to pacemakers.

Premarket Approval (PMA) - the process and application to FDA by which a manufacturer of a new medical device brings their new device to the United States market.

Protocol - the design of a clinical trial, simply put, what will be tested, how it will be tested, on whom will it be tested, how many will be tested, how long it will be tested, and what will be established through the testing.

Significant and Non-Significant Risk Studies - before conducting a clinical trial for medical devices, a sponsor must determine if their study poses significant risk for harm to the human subjects participating in the study. The determination of significant risk for a study requires that a study sponsor or manufacturer apply for an IDE from FDA in order to conduct the study in the United States.

Study Sponsor or Sponsor - the person or persons who organize and run the clinical trial. This may be the manufacturer, or someone the manufacturer has contracted with to perform the duties.

Sponsor/Investigator - a clinical investigator who is both the sponsor and the investigator in a clinical trial. Usually a sponsor/investigator has a single-site trial.

APPENDIX C

FDA Study Request

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date MAR 2 1994

From Director, Center for Devices and Radiological Health (HFZ-1)

Subject Request for OIG Study

To Mr. George Grob
Deputy Inspector General for Evaluations and Inspections

CDRH is currently considering possible revisions of the Investigational Device Exemption (IDE) regulation, 21 C.F.R. § 812 *et seq.* The IDE regulation encourages the development of useful new medical devices, while protecting the safety and rights of study participants, by establishing procedures for the conduct of clinical studies of devices. During the course of a study under the IDE regulation, the investigational device is exempt from many FDA requirements that would otherwise apply, such as performance standards and premarket approval requirements.

Among the revisions we are considering are changes affecting FDA's controls over commercialization of investigational devices. To help determine the extent the regulation needs to be revised, it would be helpful to have objective data on the degree to which inappropriate commercialization is occurring and on the economic and public health significance of such commercialization. It would be useful to have data for three types of investigations:

- Studies of significant-risk devices. An IDE application and FDA approval are required for a study of an investigational device that presents significant risks.
- Studies of non-significant-risk devices. No IDE application is required to study a device that does not present significant risks, but an institutional review board (IRB) must approve and monitor the study.
- Studies of diagnostic devices. Diagnostic devices, such as *in vitro* diagnostics, that are non-invasive and are not used as a diagnostic procedure without confirmation through another, medically-established, diagnostic product or procedure are currently exempt from the IDE regulation.

CDRH would need reliable data within six months to be of use in revising the IDE regulation. If OIG is willing to undertake this effort, I would ask that you work with Robert Eccleston of my office to define measurable objectives for the study and to develop an appropriate study plan. Mr. Eccleston can be reached on (301) 443-4690.

D Bruce Burlington

D. Bruce Burlington, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Date April 14, 1995

From

Commissioner of Food and Drugs

Subject FDA Response to the Office of Inspector General Evaluation of Investigational Device Practices

To

Inspector General
Department of Health and Human Services

I am appreciative of the recently completed evaluation by the OIG Office of Evaluations and Inspections of the Food and Drug Administration's regulatory controls over clinical studies involving investigational medical devices and the cooperative spirit with which it was conducted.

Notwithstanding the limited scope of the evaluation, FDA takes seriously the findings presented in the report. Following a careful review of them, we will take whatever actions are warranted to further assure that investigational device studies are conducted in accordance with the highest ethical standards and all applicable Federal rules designed to protect patients. This could include actions against individual sponsors if evidence of scientific misconduct is sufficient to justify FDA intervention.

Although it is premature to specify what actions may be merited, FDA generally acknowledges the apparent need to enhance the training of clinical investigators and local institutional review boards to ensure they have a clear understanding of their regulatory and ethical obligations. In addition, the agency may consider other measures to ensure the integrity of clinical investigators and the investigational studies they perform, particularly with respect to accountability of investigational medical devices.

David A. Kessler, M.D.

cc: Assistant Secretary for Health