

## **Appendix A**

Memorandum

From Michael Marcarelli, Director, Division of Bioresearch Monitoring, CDRH  
To Linda Kahan, Deputy Center Director, CDRH  
“Enforcement of GLP Regulations for Non-clinical Device Studies”

August 31, 2006



Memorandum

Date: AUG 31 2006

From: Michael Marcarelli, Director, Division of Bioresearch Monitoring

Subject: Enforcement of GLP Regulations for Non-clinical Device Studies

To: Linda Kahan, Deputy Center Director  
Center for Devices and Radiological Health

Through: Tim Ulatowski, Director, Office of Compliance

ISSUE

How should CDRH enforce the Good Laboratory Practice (GLP) regulation of non-clinical safety studies submitted in support of research and marketing applications?

RULES

GLP is the requirement for conducting non-clinical laboratory studies that support FDA-regulated products: FDA promulgated the Good Laboratory Practice (GLP) regulation (21 C.F.R. Part 58) under section 701(a) of the Federal Food, Drug, and Cosmetic Act (the Act) to assure the quality and integrity of safety data in support of FDA-regulated products. The scope of the GLP regulation (21 C.F.R. 58.1(a)) includes non-clinical laboratory studies that support research or marketing permits across medical products including devices under sections 510 (*Registration, e.g., Premarket Notification*), 513 (*Device Classes*), 514 (*Performance Standards*), 515 (*Premarket Approval*), 516 (*Banned Devices*), 518 (*Notification*), 519 (*Records and Reports*), and 520 (*General Provisions, e.g., Custom, Restricted, and Investigational Devices*), and 801 (*Imports and Exports*) of the Act.

There is direct reference of GLP in the Investigational Device Exemption (IDE) regulations: An IDE sponsor is required to submit a statement that all non-clinical laboratory studies were conducted in GLP compliance or if not in GLP compliance, then a statement for the reason of noncompliance. 21 C.F.R. 812.27(b)(3). In addition, failure or inability by an IDE sponsor to comply with the GLP requirement does not justify failure to submit information to FDA on a relevant non-clinical test study.

There is direct reference of GLP in the Premarket Approval (PMA) regulations: A PMA applicant is required to submit a statement that all non-clinical laboratory studies were

conducted in GLP compliance or if not in GLP compliance, then a statement for the reason of noncompliance. 21 C.F.R. 814.20(b)(6)(i). FDA may withdraw PMA approval if a non-clinical laboratory study (1) was not conducted in GLP compliance and the reason for noncompliance was not provided, or (2) if the reason for noncompliance was provided but the differences between GLP and non-GLP do not support the validity of the study. 21 C.F.R. 814.46(a)(3).

GLP is applicable to all classes of medical devices under the promulgated regulation, *supra*; however, there is no direct reference to GLP in the medical device classification regulations. 21 C.F.R. Part 860. The medical device classification regulations describe the kind of data that may be required to determine the safety and effectiveness of a device under sections 513 (Device Classes), 514(b) (Performance Standard), 515(b) (Pre-market Approval Application), and 520(l) (Transitional Provisions for Devices Considered as New Drugs) of the Act. When establishing a reasonable assurance of safety and effectiveness of a device, a sponsor may be required to conduct investigations using laboratory animals and non-clinical investigations including in vitro studies. 21 C.F.R. 860.7(d)(1).

GLP is applicable to 510(k) applications under the promulgated regulation, *supra*; however, there is no direct reference to GLP in the Pre-market Notification regulations. 21 C.F.R. Part 807. The 510(k) submission must contain a statement that describes the similarities and differences of the device with one or more devices in commercial distribution; accompanied by data, which may include non-clinical laboratory data, to support the statement. 21 C.F.R. 807.87(f).

## ANALYSIS

There is no question that non-clinical studies of medical devices are within the scope of the GLP regulations. In the preamble to the final rule, the Commissioner specifically addressed comments which sought language exempting various classes of FDA regulated products, explicitly medical devices, from coverage by the regulations. The response to these comments states (43 F.R. 59989, December 22, 1978): "the Commissioner has generally elected not to permit exemptions based on broad categories of regulated products because no compelling reasons have been presented that would support the contention that assurance of safety is less desirable for one class of regulated products than for another." The preamble further states "the proper safety decisions are important for all these products; accordingly, the processes by which such safety data are collected should be subjected to identical standards of quality and integrity." In addition, in three separate legal opinions, the Office of Chief Counsel opined that the GLP requirement applies to all submissions. Annette Marthaler, March 6, 2001; Beverly Rothstein, January 2, 2001, and Seth Ray, December 29, 2000.

The Commissioner chose not to exempt broad classes of regulated products; however, as further explained in the preamble to the final rule there are "examples of studies that are not within the scope of these GLP regulations" which include "...[a]ll studies done on

products that do not come in contact with or are not implanted in man.” 43 F.R. 59989, December 22, 1978. In vitro diagnostic devices and certain class I and II devices would fall into this category as being exempt from the GLP regulations.

CDRH staff has speculated whether 510(k) applications are subject to GLP requirements, since there is a lack of specific reference to the GLP regulations in the Premarket Notification regulations (21 C.F.R. Part 807). In addition, the reference to section 510 of the Act in the GLP regulations is limited to section 58.1 Scope; the Definitions under section 58.3(e) describes the various applications for research or marketing permit but fails to list premarket notification applications. This section does list data and information regarding a medical device submitted as part of the procedures for classifying such devices under part 860. The lack of clear applicability has led to inconsistent CDRH application of the GLP requirements to 510(k) applications. Generally, the Program Operations Staff instructs 510(k) applicants that the GLP requirement is not required for 510(k) applications. However, at the review division’s request, FDA inspected two non-clinical laboratories (LaHaye Total Eye Center and University of Louisiana at Lafayette) associated with 510(k) K032400 to assess GLP compliance, and FDA, subsequently issued correspondence to these two firms citing GLP violations.

The preceding two statements by the Commissioner, plus three legal opinions, overwhelming support the presumption that GLP regulations apply to 510(k) applications despite clear applicability in the regulations. The question of what enforcement discretion should be taken with regard to 510(k) applications is a controversial issue since many predicate devices upon which subsequent 510(k) applications may be approved have not been based upon non-clinical studies that have met GLP requirements. The “Recommendations” section of this document attempts to address this controversy by proposing a guidance document and enforcement strategy.

An August 1979 report<sup>1</sup> of Management Briefings of the GLP Regulations specifically indicates that Class I, II and III Devices are regulated products that are within the meaning of the GLPs; however, data contained in a 510(k) notification is not subject to GLP. The Office of Regulatory Affairs (ORA) admits that the report is outdated, the latter statement about a 510(k) notification is antiquated, and does not reflect current regulations and agency policy.

The Center for Biologics Evaluation and Research<sup>2</sup> (CBER), which regulates some medical devices, applies the GLP regulation to all research and marketing applications that come under their purview including BLA, 510(k), IDE, IND, NDA, and PMA. Center for Drug Evaluation and Research (CDER) applies the GLP regulation to all research and marketing applications under their purview including IND and NDA.

Prior to the February 27, 1997 implementation of FDA’s Good Guidance Practices, CDRH used Blue Book Memorandum to implement center-wide policy to staff. The May

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<sup>1</sup> [http://www.fda.gov/ora/compliance\\_ref/bimo/q\\_as.htm](http://www.fda.gov/ora/compliance_ref/bimo/q_as.htm)

<sup>2</sup> Statement made by Leonard Wilson, Special Assistant to the Associate Director, Review Management, regarding CBER’s Premarket Review Program 6/6/2006.

1, 1995 Blue Book Memorandum G95-1 specifies the use of the International Organization for Standardization (ISO) 10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" for the biological evaluation of medical devices submitted in 510(k) or PMA applications and provides direction to CDRH reviewers on how to compare biocompatibility data for a device and select appropriate toxicity tests to evaluate the biocompatibility of component materials. ISO 10993, Part 1, Section 3.6 specifies the GLP requirement for any *in vitro* or *in vivo* test for biological evaluation of medical devices. The acceptance of ISO standards by many countries or regulatory authorities has elevated GLP to be the international prerequisite for the mutual acceptance of data, whereby, these countries will only accept non-clinical laboratory studies from other countries as long as these studies follow GLP standards.

Since the inception of the GLP regulations, FDA has been actively involved in the development of international GLP standards and has influenced the development and adoption of GLP principles and compliance programs through the Organization for Economic Cooperation and Development (OECD). OECD is a treaty organization of 30 member countries, including the U.S., plus nearly 100 other countries with observer status who have harmonized GLP standards internationally to promote the mutual acceptance of data among participating member countries. The OECD GLP standards and compliance programs are fully compatible with FDA GLP regulations and have served as the common standard for memorandum of understandings with nine countries. Many countries including Australia, Austria, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Japan, Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Slovenia, South Africa, Spain, Sweden, United Kingdom, and the United States, regularly share GLP status reports of the inspection of non-clinical laboratories.

Under the IDE and PMA regulations, FDA gives sponsors and applicants an opportunity to explain reasons for GLP non-compliance. Acceptable reasons for non-compliance include universally accepted principles of good laboratory practice found in formal lateral agreements (i.e., Memorandum of Understanding) between FDA and other countries or more commonly through OECD GLP standards. Basic exploratory studies, device functionality studies, field trials in animals, or *in vitro* tests of diagnostic devices are exempt from the GLP requirement. [21 CFR 58.3(d); 43 F.R. 59989, December 22, 1978]

The Bioresearch Monitoring: Good Laboratory Practice Program (Compliance Program Guidance Manual: Chapter 48) is an agency-wide program covering diverse medical products including chemical contaminants, food additives, biologics (therapeutics, blood, and vaccines), human drugs, animal drugs, and medical and radiological devices. To ensure a uniform and harmonized approach for GLP implementation for all FDA regulated products, FDA established an intra-agency steering committee that directs compliance and enforcement policy across the agency. The success of the agency's GLP program in meeting the agency's objectives of ensuring data quality and integrity of non-clinical studies depends upon the participatory role of each Center, working collaboratively with the Office of Regulatory Affairs (ORA), to plan and conduct inspections of non-clinical studies, and implement corrective enforcement actions when

appropriate. Any proposed changes in regulations, program implementation, or procedures must be coordinated, collaboratively and accepted agency-wide.

Through established intra-agency collaboration, the results of non-clinical inspections that targeted specific product lines are frequently extended to other medical product areas. These results provide other Centers a representation of the non-clinical laboratory's capabilities to comply with applicable GLP requirements and are used to judge the acceptability of safety data submitted in support of research and marketing applications in other Centers.

FDA has established inter-center agreements for review and oversight of certain categories of combination products (drug-device, drug-biologic, and biologic-device combinations). In these agreements, the centers collaborate, administer, and, as appropriate, enforce various activities associated with these products, including their respective components, according to provisions of the FD&C Act. Differences in GLP policies could complicate the consistency and uniformity of reviews and approvals.<sup>3, 4</sup>

Similar collaboration exists with foreign regulatory bodies. FDA receives requests from these entities to perform data audits of medical products or to release their inspectional findings of specific sites. For example, on May 24, 2006, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) requested an inspection of Texas Heart Institute and a data audit of medical device studies supporting an application under review.

In most situations when serious problems of GLP non-compliance are identified during FDA inspections, the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research reject the non-clinical study data, request the sponsor to conduct the study over again following GLP standards, and pursue a compliance action such as a Warning Letter. As described below, CDRH has taken similar actions when serious problems are found.

Some have argued that the GLP requirement is an economic burden to sponsors. The preamble to the GLP regulation (52 F.R. 33770, September 4, 1987, Comment #8) stated that the implementation of these regulations will increase the cost of non-clinical laboratory studies; however, such costs are justified because of the improved assurance of the quality and integrity of the safety data submitted to the Agency. In addition, FDA concluded (41 F.R. 51220, November 19, 1976) that the GLP regulations do not require preparation of an inflation impact statement under Executive Orders 11821 and 11929, Office of Management and Budget Circular A-107 and the guidelines issued by the Department. During a Device GLP Course on November 29, 2005, Linda Palagi Lynn, an industry compliance expert, stated that frequently the difference between a non-GLP study and a GLP study is a quality assurance unit which represents 5-10% of the cost of the entire study.

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<sup>3</sup> <http://www.fda.gov/oc/ombudsman/bio-dev.htm>

<sup>4</sup> <http://www.fda.gov/oc/ombudsman/drug-dev.htm>

Some have questioned the value-added in requiring a non-clinical laboratory study to follow GLP. GLP provides a scientific quality standard for designing, conducting, recording, and reporting of non-clinical laboratory studies and assures the quality and integrity of study data. Medical device use in humans is frequently based upon the results of these non-clinical laboratory studies. If we follow the Center's mission and vision of total product life cycle then it is important that we hold the same standard, i.e., GLP requirement, for all medical devices, especially when our regulatory decisions that affect public health are based upon these non-clinical laboratory studies. However, since FDA follows a risk-based classification scheme for medical devices then maybe the GLP requirement should only be applied to high-risk or class III devices. Devices which are made of materials that have been well-characterized chemically and physically in the published literature and have a long history of safe use may not need to be supported by non-clinical laboratory studies that follow the GLP requirement, or even have non-clinical laboratory studies conducted to support marketing clearance. For these reasons, the "Recommendations" section proposes to focus our enforcement discretion on class III devices.

Whenever study data is in question there should be the ability to reconstruct the study to validate the study data. Agency policy is that the safety data submitted in support of a research or marketing application be based on appropriate standards of conduct at the non-clinical laboratory to assure accurate data reporting. There have been instances that support these assumptions.

- Abbott Laboratories notified CDRH of an internal audit that revealed GLP noncompliance and study-specific issues relating to critical aspects of their non-clinical laboratory studies conducted at Atlanta Cardiovascular Research Institute in support of IDE G020169. The studies were not in GLP compliance, could not be reconstructed to demonstrate the integrity of the study, and the data was deemed unsuitable for submission to FDA. Abbott Laboratories withdrew their submission. An FDA inspection confirmed these findings.
- Boston Scientific Corporation's TAXUS™ EXPRESS2™ Paclitaxel-Eluting Coronary Stent System (IDE G010274, PMA P030025) was similarly affected by inspection results that questioned the validity of the non-clinical studies. CDRH could not adequately assess the safety of the device from histopathology reports in non-clinical studies and issued a major deficiency letter requesting an independent third party audit to address unexplained and inadequate conclusions.
- After an FDA inspection of non-clinical studies supporting Medtronic AVE's Driver Over-the-Wire (OTW) Coronary Stent System (IDE G010301, PMA P030009), Medtronic AVE reported GLP noncompliance of a 180-day animal study. Medtronic reported significant deficiencies in the completeness of the study and lack of quality assurance measures during the critical phases of the study. CDRH rejected the study based on the severity of the noncompliance.

- In February 2004, FDA received an allegation of research misconduct that St. Jude Medical withheld critical biocompatibility data of their Silzone heart valve that showed five animals were tested; not four animals as reported in their submission. The fifth animal died of endocarditis, a life-threatening complication. In addition, the results of a rabbit hemolysis study showed that the coating on the valve was leaching, despite the sponsor's contention that the product did not leach. A number of class action lawsuits against St. Jude Medical made evident results of the non-clinical animal studies. Despite the relevant significance of this finding, the statutory requirements for the retention of laboratory records had expired and FDA inspections were not conducted.
- In fiscal year 2005, bioresearch monitoring inspections revealed egregious noncompliance by non-clinical laboratories where safety studies were conducted. We found that laboratories conducting non-clinical laboratory safety studies in support of IDE and PMA applications were not aware of the GLP requirements. In two cases, IDE sponsors (EndoVia Medical and Spineology) had made misleading statements within their submissions by stating the non-clinical studies were conducted in GLP compliance, when in fact they were not. CDRH's relaxed enforcement posture led to minimal enforcement of regulatory requirements which begs to question whether there needs to be better efforts to educate the regulated industry and reviewers.

Several CDRH officials have requested concrete examples of situations in which GLP noncompliance of non-clinical laboratory studies led to serious post-marketing problems. Some of the devices highlighted above have been wrought with post-marketing problems. Unfortunately, a thorough analysis to determine whether there truly is a link has not been conducted.

The failure of medical devices to fulfill their intended purpose of reasonable safety and reliability have been investigated and linked to several device factors, two of which are design error and manufacturing errors. A report published by ECRI, a non-profit agency, entitled "Medical Device Adverse Event Recognition and Investigation," Health Risk Control (HRC) Volume 2, Risk Analysis, May 2004, stated that device error includes inadequate testing of the design before use on humans and inadequate evaluation of the device and its safety and performance in the hands of the typical users as part of its design, evaluation, and development process. The report describes manufacturing errors as the easiest device factor to prevent because they are based on the failure to devote sufficient priority to purchasing, inspection, and testing of raw materials and components or on failures in inspection, testing, and related documentation and quality control analysis.

The General Accounting Office (GAO) found that FDA is not receiving information necessary to regulate the safety of medical devices. In a December 1986, report entitled "Medical Devices: Early Warning of Problems is Hampered by Severe Underreporting (GAO/PEMD-87-1)" to the Senate Committee on Governmental Affairs, the GAO reported that the FDA is only aware of approximately 1 percent of the problems

associated with medical devices.<sup>5</sup> Although the report primarily focused on postmarketing surveillance, it frequently cited defective components, design flaws, and deterioration of devices among the major causes of problems. The report underscores the need for a thoughtfully executed approach to the review and verification of the testing of device materials and components before the device is marketed and released in commercial distribution.

There are many classic examples in other product areas that support the conclusion that GLP compliance is essential to determine whether a product should be introduced into humans, and subsequently, whether there is adequate information to assess the product's safety prior to marketing. CDRH relies upon non-clinical laboratory studies to establish some measure of safety to allow the device to be tested in humans and to pre-identify safety problems or device failures that could lead to serious adverse events and device-related pathology. It is extremely important for non-clinical study data to be of sound quality and integrity to base our regulatory decisions of permitting a device to be introduced into humans during clinical studies or before wide-spread human use after approval. In the above situations, the integrity of non-clinical study data was questioned.

There is confusion among CDRH staff and industry regarding the meaning and application of GLP. This has been evidenced by situations in which the sponsor has indicated that the non-clinical laboratory study was conducted in GLP compliance, but a simple review of the summary report and results reveals that the non-clinical study could not have been conducted in GLP compliance. Examples: 3F Therapeutics' PMA M050022 for Aortic Bioprosthesis; Giotto's PMA P050005 for Full Field Digital Mammography System; or Radiant Medical's PMA M020017 for Setpoint Endovascular Temperature Management System. As described at the end of this memorandum, in the Recommendations section, a guidance document for FDA Staff and Industry would be beneficial for educational purposes.

An argument has been made that GLP compliance of non-clinical studies is not always necessary, because all PMAs and many 510(k)s include clinical data, making the non-clinical data of lesser importance. As experts in medical product development, we know that serious adverse events commonly do not materialize until after a product has been introduced for marketing and used widely in the general population. Specific non-clinical studies, e.g., biocompatibility studies that incorporate histopathology, scanning electron microscopy, and morphometric analyses, may identify potential harmful effects on critical organ systems and help better characterize the safety profile of medical products. Animals, unlike human subjects, can be sacrificed at various intervals during a study for analysis of excised vessels and organ samples. Non-clinical testing is a fundamental piece of the medical device development and testing.

## CONCLUSION

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<sup>5</sup> Med Liability Adv's Serv 1987; 12(3): 1-2.

GLP, like good manufacturing practices and good clinical practice, is an international standard that promotes a comprehensive system of quality management for the safe and effective development of all medical products.

GLP is a requirement for non-clinical studies that support all types of medical devices. In research and marketing applications, sponsors and applicants have an opportunity to explain reasons for GLP non-compliance. Acceptable reasons for non-compliance have been described, *supra*. The serious problems with GLP compliance described above highlight a major problem in the medical device industry that is based upon the lack of communication with industry and FDA reviewers that GLP is FDA's accepted standard of conduct for non-clinical laboratory studies that support device research or marketing applications. In addition, training for FDA reviewers would compliment their skills to recognize when a non-clinical study is GLP non-compliant, to convey expectations during pre-IDE and IDE discussions with sponsors that non-clinical studies should follow GLP requirements, and acceptable reasons for noncompliance. CDRH is indirectly promoting non-compliance throughout the medical device industry by not communicating to the industry that GLP is the accepted standard for non-clinical laboratory studies of medical devices.

An applicant should be advised they are required to state whether the study complies with GLP and, if not, describe the noncompliance in the application. The review scientist should be encouraged to evaluate the effects of the noncompliance on the validity of the study in all device submissions. If the noncompliance is so severe to question the quality and integrity of the study, and make it difficult for the sponsor to reconstruct the study, then the onus is on the applicant to validate the study.

The success of the agency's GLP program in meeting the agency's objectives of ensuring data quality and integrity of non-clinical studies depends upon the participatory role of each Center, working collaboratively with ORA, to plan and conduct inspections of non-clinical studies, and implement corrective enforcement actions when appropriate.

Enforcement of the agency regulation must be consistently applied across all FDA regulated products, particularly, medical devices; especially, when the problems are extensive enough to affect the validity of the study to support the application and studies upon which FDA makes critical safety decisions. Regularly inspecting non-clinical testing facilities and conducting data audits is essential to maintaining public confidence in the agency's systematic method for ensuring non-clinical safety data that, it relies on to make regulatory decisions of broad public health significance. Regular inspections of non-clinical laboratories maintain the credibility of our program to our international regulatory counterparts, facilitating the acceptance of U. S. data abroad. FDA inspection history on non-clinical laboratories is shared annually with foreign GLP monitoring authorities through FDA's participation in the OECD GLP working group.

Managers, scientists, and other professionals within the Agency and the regulated industry have an obligation to promote the importance of quality and reliable data generated from non-clinical laboratory studies as an essential first step in protecting the

safety of human research subjects. Our efforts should strive to achieve the common goal of safe and effective products in the marketplace for U.S. consumers.

## RECOMMENDATIONS

- Office of Compliance believes that the issuance of a guidance document that reflects current policy should be issued to educate industry and CDRH staff regarding the significance of GLP in the conduct of non-clinical laboratory studies and the review of applications including requirements for 510(k) applications. This guidance document, developed through good guidance practices, entitled, *Guidance for Industry and FDA Staff: Good Laboratory Practice for Non-clinical Laboratory Studies of Devices*, was completed in February 2005 following review and endorsement by FDA staff and the Office of Chief Counsel, but needs to be revised to address current thinking, and released as a Level 1 guidance with appropriate notice and comment rule-making.
- Due to limited resources, FDA has discretion to enforce regulations that have the greatest impact on public health. Office of Compliance believes that it should primarily focus routine inspection resources on non-clinical laboratory studies involving class III devices. These inspections are to be conducted soon after submission, early in a product's development, prior to introduction or wide-spread use of the device in humans. Marketing applications (i.e., humanitarian device exemptions) for which clinical testing is minimal and greater reliance is placed on non-clinical studies to support human use will also be prioritized. Generally, routine surveillance inspections of non-clinical studies that support Premarket Notification (510(k)) applications will not be issued, unless specifically requested by the review division.
- "For cause" inspections would be utilized to address allegations of research misconduct from the review division or other creditable sources. For cause inspections would not be limited to Class III devices, but could involve other device classes, including 510(k) applications, to address questions of data validity and to promote the reliability and integrity of safety data submitted to support the approval of human studies or pre-market clearance and approval.
- ODE and OC will have to continue to work collaboratively to develop consistent enforcement policy including when certain regulatory or compliance actions will be taken as a result of significant findings of GLP non-compliance. Marketing clearance may not be limited based upon GLP non-compliance, if safety and effectiveness information is substantially based upon clinical data.
- When serious or repeated problems of regulatory significance are identified during FDA inspections of non-clinical laboratories, the Office of Compliance follows established procedures to promote compliance with the regulated industry. Compliance actions that may be taken against non-clinical laboratories include, based

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upon increasing severity of non-compliance, information letter, untitled letter, warning letter, formal disqualification, or referral to the Office of Criminal Investigations.

Draft/Edited: Kevin Hopson 1/31/06, 4/26/06, 6/8/06

Edited: Matthew Tarosky 2/3/06, 2/6/06, 2/9/06, 2/10/06, 3/9/06, 5/11/06, 6/9/06

Edited: Stan Woollen 2/9/06

Reviewed: Michael Marcarelli 3/8/06

Reviewed: Tim Ulatowski 3/9/06, 6/5/06

Reviewed: Miriam Provost 3/29/06

Reviewed: Thinh Nguyen 3/23/06

Reviewed: Elisa Harvey 3/21/06

Reviewed: Heather Rosecrans 3/29/06

Finalized: Matthew Tarosky 8/31/06