

Regulatory Update:

GHTF Guidance Ignites Risk Management Concerns for ISO 13485:2003

- Regulatory guidance sparks compliance concerns
- Guidance for ISO 14971:2000 implementation
- Update on ISO 14971:2000 conformity assessments
- Technology assistance for risk management

“This is a ticking time bomb hidden in ISO 13485”

-participant at RAPS annual conference

Risk Management: A Regulatory Time Bomb?

Until recently, quality system regulation and international quality system standards requirements have left the impression that risk-related processes were primarily located in the design and development departments of medical device companies. However, with the advent of ISO 13485:2003, risk management has become a requirement for essentially all product realization activities. In fact, guidance on the implementation of ISO 13485 (ISO/TR 14969) indicates that risk management activities draw from, and can affect the performance of, quality management system activities that are even outside of product realization. Now, guidance developed by the Global Harmonization Task Force (GHTF), along with recent pronouncements by FDA speakers, confirms the broader application of risk management.

Industry anxiety regarding risk management was evident at the 2004 RAPS annual conference. One participant at the session titled *Importance and Impact of ISO 13485:2003* went so far as to term the new risk management requirement, “a ticking time bomb hidden in ISO 13485.”

Industry’s nervousness stems, in part, from the expanded emphasis 13485 places on risk management and the implications for company-wide compliance. According to Section 7.1 (Planning of product realization) of the newly-implemented standard:

“The organization shall establish documented requirements for risk management throughout product realization... Records arising from risk management shall be maintained (sec 4.2.4).”
[italics added for emphasis]

Note 3 of the same section directs the reader to “See ISO 14971 for guidance related to risk management.”

Companies Struggling with Risk Management

Industry veteran and consultant Ed Kimmelman (gpa_ed@msn.com) is the convener of ISO/TC 210 Working Group 1 on Quality Systems and was a chief architect of the new ISO 13485 standard. According to him, many companies are struggling with effective implementation of risk management within their quality management systems (QMS). He notes that areas such as:

- Required competencies of personnel
- Nature and depth of acceptance activities
- Handling of nonconformances
- Customer complaints
- Corrective and preventive actions
- Control of infrastructure

are all affected by risk management activities – and all of them are outside the area of product realization.

In order to raise industry awareness and provide direction, the GHTF has just published an important guidance document (SG3/N15R8). According to Kimmelman, this guidance provides a “roadmap that demonstrates where risk management is recommended by ISO 13485:2003.”

New Guidance for Risk Management

Underscoring the more expansive interpretation of risk management, the GHTF guidance states

“Medical device manufacturers are generally required to have a quality management system as well as processes for addressing device related risks. These processes for managing risk can evolve into a stand-alone management system. While manufacturers may choose to maintain these two management systems separately, it may be advantageous to integrate them as it could reduce costs, eliminate redundancies, and lead to a more effective management system.”

Although only guidance, the GHTF document indicates that risk management should pervade the entire product realization process, including:

Interviews and information from:

Edward R. Kimmelman, JD

Regulatory consultant, past President of National Committee for Clinical Laboratory Standards, former Chairman of HIMA (now AdvaMed) Standards Section and Science and Technology Section, convener of the ISO/TC 210 Working Group 1 on Quality Systems.

Harvey Rudolph, Ph.D

Global Program Manager for Medical Devices with Underwriter’s Laboratories, 25-year FDA veteran (Deputy Director Science and Technology; Chief of Medical Practices Section). Co-chair of US Technical Advisory Group for Risk Management. Distinguished Services Medal recipient (Public Health Service).

Marc H. Miller, MBA

CEO of Crimson Medical Translation (ISO 9001:2000 and ISO 13485:2003 certified, ISO 14971:2000 endorsed translation services), former Sr. Research Fellow with S.I.A.R. (international strategy consultant / medical technology industries).

GHTF Guidance Sparks Compliance Concerns

Management Responsibility:

“Top management has a responsibility to incorporate risk management into the organization. This includes establishing risk management policies to ensure effective implementation of risk management principles and activities.”

Outsourcing:

“A manufacturer may outsource processes (e.g. sterilization, tooling, coating processes, testing, design, manufacturing) or products (components, subassemblies or entire devices) and must maintain control over these outsourced processes and products. The manufacturer is responsible for incorporating appropriate risk management activities for these processes and products by planning and by ensuring risk control measures are appropriately applied.”

Purchasing Controls and Acceptance Activities:

“Risk management activities should identify hazards and evaluate risks, including those potentially introduced by suppliers early in the product realization process.”

“Risk management roles and responsibilities of the manufacturer and supplier should be defined as part of the purchasing requirements. In addition, prescribed risk control measures derived from the risk management process during product realization should be included in the purchasing requirements as part of the purchasing information.”

“Established criteria for selection, evaluation and re-evaluation of suppliers of purchased products and services should also be based upon the risk associated with identified hazards related to the purchased products and services determined during the risk management process.”

With the advent of ISO 13485:2003 and confirmation through GHTF guidance, application of risk management to all areas of the product realization process is an undisputed requirement. Now, the important question for most companies is “How do I perform risk management?” For that answer, companies are best served by referencing the consensus risk management standard itself: ISO 14971:2000.

ISO 14971: The Basis of Risk Management

Dr. Harvey Rudolph is the Global Program Manager for Underwriters Laboratories’ Medical Devices Business Unit and a 25 year veteran of the U.S. FDA (Harvey.Rudolph@us.ul.com). He is also a primary author of ISO 14971:2000. In Dr. Rudolph’s words, “Why do we need risk management? Because it promotes safer and more cost-effective devices, because regulators in the major world markets (the EU, North America, and Japan) require it, and because risk management makes good business sense.”

Although risk management is a requirement in the world’s major markets, the regulating authorities (much like the companies themselves), are struggling to understand and apply it. In fact, according to Dr. Rudolph, “Many of the Notified

Body auditors don’t have a firm grasp on how risk management should be implemented and, therefore, it is applied unevenly.”

For his own part, Dr. Rudolph looks for specific items in the company’s technical file when auditing in order to demonstrate appropriate levels of risk management including:

- Clearly stated risk management policy;
- A procedure for hazard identification and risk estimation, evaluation, and control;
- Periodic management oversight;
- Postmarket activities; and
- Risk management ties from pertinent departments.

He also points to the GHTF guidance document as an important factor in raising awareness and improving uniformity for risk management application. “Integration of risk management in every aspect of the QMS is the message of the GHTF guidance. For example, training of personnel is a key risk management factor that is often not thoroughly addressed. If an adverse report comes in from the field, all personnel involved need to be aware of the risk management implications. The only way to effectively accomplish this is through appropriate training.”

Proposed Conformity Assessment for ISO 14971:2000

Another important initiative in this area is a proposed conformity assessment to ISO 14971:2000. In an article recently published in *Medical Device and Diagnostic Industry*, Dr. Rudolph laid out the arguments supporting a medical device risk management certification, including the possibility of reduced insurance premiums and ease of assessment by third party certifiers to standards where ISO 14971 is required in part or in whole. Currently, Dr. Rudolph is working to establish just such a certification scheme.

Finally, Dr. Rudolph mentions another upcoming GHTF guidance document on risk management, “The document will be a modification to *Guidelines for Regulatory Auditing of Quality Systems of Medical Device Manufacturers – Part 2: Regulatory Auditing Strategy* and will provide guidance on how to audit risk management activities within the QMS.” At that point, many of the existing questions around risk management implementation will have been answered.

A Technology Fix for Risk Management?

Given the increased focus on risk management, many companies are turning to technology and automation for support. For instance, Pilgrim Software, a firm with experience in other regulated industries, has developed what they call the “SmartSolve Solution” for integrated risk management in the life sciences arena.

Pilgrim’s system enables clients to manage their

CAPA, SOP & Policy documentation, audit, and training functions – primary components of a risk management system – in an integrated manner. For instance, a CAPA event may trigger a documentation update that, in turn, is tied to a training requirement. The net result is a “closed loop” system where events in one area link to required actions in other areas. Since relationships are made explicit through the system’s workflow, there is reduced risk of important outputs being overlooked or neglected as inputs to related areas.

Says Nikki Willet, Director of Products and Corporate Marketing for Pilgrim, “Not only does the system provide you with an integrated method for handling dependencies in a risk management system, but it also provides you with a historical snapshot for use in CAPA and root cause investigations.” Willet explains that since the Pilgrim system maintains a historic record of training and procedures, clients have a window on the training environment at the moment an error might have occurred. “This is especially useful when attempting to determine if previous procedures or training requirements contributed to an issue.”

The Pilgrim system delivers bottom line results, too. One client saw their CAPA steps reduced from 27 to 7 and NCR aging reduced by 97%. Another client saw the labor requirements of their CAPA system reduced by 50%.

Risk Management: Beyond Compliance

All of these efforts support the basic insight that effective risk management is also good business practice. In fact, Dr. Rudolph goes so far as to say, “While ISO 14971 does not explicitly mention business risk, it effectively does. The risk management principles embodied in ISO 14971 can help a company to operate more efficiently and effectively.”

At previous RAPS conferences, senior executives from the aerospace industry have spoken of the positive correlation between quality and profitability. Nikki Willet notes that the device industry is lagging other industries, such as pharmaceuticals or automotive, in applying this fundamental insight. By truly embracing quality system and risk management principles, device companies can realize business benefits beyond basic compliance.

Additionally, both Kimmelman and Rudolph agree that companies who implement risk management principles now will be better positioned to manage future regulatory developments. According to Kimmelman, “If ISO 13485 changes, it will probably be to apply risk management to processes outside of product realization” – explicitly requiring risk management in every area of the organization’s quality management system.

The Importance of Labeling for Risk Management

If you doubt the importance of labeling (including IFUs, manuals, and other instructional materials) as a risk management tool, consider the recent multi-million dollar Vioxx debacle. Prior to Merck's voluntary recall, a simple label change kept the popular pain killer on the market.

According to the most recent guidance (SG3/N15R8) from the GHTF, effective labeling is the minimum that must be done within "a fixed hierarchy of risk control measures" to help mitigate product risk. This important, just-published guidance specifically states:

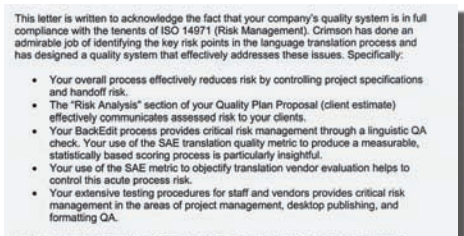
"External communications methods such as warning labels, user manuals, advisory notices, etc. should also be utilized to communicate necessary risk information."

In practice and by definition, product labeling is a vital risk management tool. Therefore, the accuracy of this information is essential.

Labeling Translation and Responsibility

Most medical technology companies produce their own English-language labeling and documentation. Here, risk management is implicit since the company that developed the product is the clear choice to author the labeling. Still, product labeling receives close scrutiny from regulators and auditors even after thorough vetting within the company.

When producing translated documentation, companies face a new risk: how to ensure that their translated labeling is accurate and fulfills the same risk management function as the original? Panelists at the 2004 RAPS annual conference highlighted this risk when they noted that inaccurate translation may jeopardize conformance to ISO 14971 in overseas markets.



KEMA Endorsement Letter

Since most companies employ a vendor for labeling translation services, insight into the vendor's risk management processes is essential to ensure that the manufacturer is meeting their responsibility under the standard. According to the GHTF guidance:

"Processes required by the quality management system [e.g. labeling] and performed by suppliers to the manufacturer are the responsibility of the manufacturer. Risk management activities [e.g. translation of product labeling] relating to any process within the quality management system are ultimately the responsibility of the manufacturer."

In other words, labeling is a key risk management tool and you are responsible for ensuring that it is accurate.

Labeling Translation Risk Defined

With responsibility assigned to the manufacturer, the importance of vendor selection is clear. According to the GHTF guidance:

"Established criteria for selection, evaluation and re-evaluation of suppliers of purchased products and services should also be based upon the risk associated with identified hazards related to the purchased products and services determined during the risk management process."

Translated labeling is both a potential hazard and a specified risk management tool. Therefore, evaluation criteria are clearly required for translation vendors. The first step in defining appropriate criteria for translation vendors is to understand the risks associated with the activity.

In March, 2005, Crimson Medical Translation filed a provisional patent entitled, "A Method for Analyzing and Managing Risk within the Translation Activity." This first-ever translation risk management patent outlines the key risks associated with labeling translation and details-mitigation methods.

Translation Risk: Sources and Mitigations

Labeling translation involves two basic risks: Resource Risk and Process Risk. As embodied by Crimson's patent-pending process (within an ISO 9001:2000 certified quality system), translation resource risk is mitigated through screening, testing, and audit. Screening involves predetermined criteria, such as an advanced degree in the subject area or minimum years of professional experience in the subject area. Testing and audit are best carried out using controlled materials and with the help of an objective standard – Crimson employs a Notified Body-approved version of the SAE J2450 translation quality metric appropriately modified for use in a medical context.

Process risk is managed using classic risk management techniques, such as redundancy and diversity. For instance, traditional translation risk management relies on a single redundant review – translation and edit. However, this basic process is inadequate for the requirements of medical translation. The Crimson patent specifies three separate, redundant reviews (in addition to translation/edit) to ensure effective risk management.

Along with redundant review, risk management effectiveness can be improved through process diversity. For instance, Crimson's Linguistic Optimization step resolves ambiguities in the source text that can lead to poor translation results. Also, a proprietary QC step (BackEditing™) solves the "native speaker dilemma" and verifies semantic accuracy.

Criteria for Choosing Your Labeling Translation Vendor

Given the importance of labeling as a risk management tool and the responsibility of the manufacturer to control the outsourced translation activity, established vendor selection criteria (based on Resource and Process risks) are essential. Based on regulatory requirements, your criteria should include:

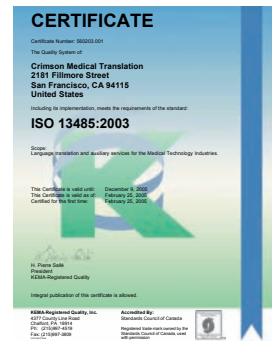
- **Audited quality system** – Third-party certification helps to ensure compliance with generic (ISO 9001:2000) or medical-specific (ISO 13485:2003) quality system requirements.
- **Resource Screening, Testing, Audit** – What is the vendor's process for ensuring that resources are qualified? Can they provide evidence of testing and qualification? Monitoring and (when appropriate) dismissal? Do they use an objective standard, such as SAE J2450?
- **Control of Process Risk** – Does the vendor employ process redundancy and diversity? How does the vendor address the "native speaker dilemma" (i.e. verify semantic accuracy)?
- **Process Documentation** – Can the vendor provide in-process documentation as evidence that all specified steps were carried out as required?
- **Client Feedback/References/Endorsements** – Can the vendor provide references from medical clients, Notified Bodies, or other regulators to demonstrate the effectiveness of their process? What is their process for gathering client feedback? Results?

Conclusion

Just-published GHTF guidance directs companies to exercise risk management in their critical outsourced activities. One of the most commonly outsourced activities, translation, may have critical implications for your risk management strategy (through labeling) in overseas markets. According to the GHTF guidance, established criteria are required for selection, evaluation, and re-evaluation of labeling translation suppliers. These criteria should take into account the known risks associated with the translation activity.



Marc H. Miller is CEO of Crimson Medical Translation. Crimson is the only translation company in the world to be certified to ISO 9001:2000 and ISO 13485:2003 and hold an official endorsement to ISO 14971:2000.



Valuable MDD, IVD, ISO, and Other Regulatory Resources Available at www.medical.crimsonlanguage.com

Finding reliable, up-to-date regulatory information can be a challenge. Now, there's help. Valuable information on worldwide labeling requirements, an electronic IFU Labeling Symbols Library, Ed Kimmelman's QS Matrix, updates on regulatory requirements for vendor outsourcing and much more are available – free of charge – at www.medical.crimsonlanguage.com.

A password is required to access certain items. Password requests can be emailed to hhutchison@crimsonlanguage.com.

Free Online Library of 350 Labeling Symbols

In order to create their professionally designed electronic library of 350 labeling symbols (63 different families representing 83 discreet meanings), Crimson Medical Translation invested hundreds of hours of research and development. The symbols are font-free vector graphics, available for download in Mac or PC format. Importantly, the Crimson library already includes many of the non-harmonized symbols contained in the new, soon-to-be-published, EN 980 standard. Current EN 980 symbols have been validated by E.U. Notified Body, KEMA (www.krqusa.com).

Regulatory & Labeling Requirements for the EU, EU Accession, and Asian Countries

Detailed descriptions including labeling language requirements, Competent Authorities, Notified Body designations, and clinical trial registration requirements for the world's major markets.

Risk Management & Vendor Outsourcing Requirements

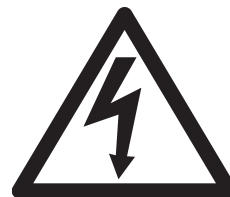
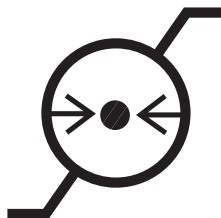
Vendor outsourcing and risk management requirements as specified by ISO 14971:2000 and ISO 13485:2003 – including risk management guidance for professional services.

Secrets of an E.U. Notified Body

An interview with Dr. Jeff Schakenraad, head of KEMA's Western U.S. Notified Body Division, details the little-known, but critical, differences between "Process Audit with Partnership" and traditional "Compliance" audit for CE Marking. This little-known difference in Notified Body audit style can save you tens of thousands of dollars.

Quality System Matrix Untangles Relationship between ISO 13485:2003, ISO 9001:2000, and 21 CFR part 820

Ed Kimmelman's QS Matrix: AdvaMed charges for this valuable resource; Crimson gives it to you for FREE. All the information you need to design a single quality system to satisfy the requirements of ISO 13485:2003, ISO 9001:2000 and 21 CFR part 820.



Legal Guidance for E.U. Language Requirements

Authored by industry veteran Larry Pilot, this legal memorandum from the law firm of McKenna & Cuneo provides definitive guidance for MDD language requirements. The memo, commissioned by Crimson Medical Translation, includes a discussion of the Regulatory Framework, Labeling Requirements, National Implementing Legislation, and specific penalties for non-compliance.



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