

**AACC**

**Advancing Clinical  
Laboratory Science  
Worldwide**

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# Industry Division Newsletter Summer 2005

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## Looking in the Mirror

**Letter from Richard Miller  
Industry Division Chair**

The Industry Division has been issued a challenge. This challenge comes from two sources, the IVD Industry and the AACC.

In March, Richard Park wrote an editorial in **IVD Technology** entitled, *An Industry Makeover*. It discussed an article in the January/February issue by Jim Reid Anderson that pointed out that the IVD industry has an image problem. "The problem is not the result of some controversy that has tarnished the industry's image. On the contrary, the IVD industry's problem is that it lacks an image altogether." Mr. Park went on to discuss the problem and urged a coordinated effort by organizations such as AdvaMed, the Association of Medical Diagnostics Manufacturers and the Industry Division of the AACC to improve this image.

Almost simultaneously, another challenge came from the last AACC's Division Management Group meeting. At that meeting, there was a discussion about the lack of image of the clinical chemist or clinical laboratory practitioner. During that discussion, Tom Burgess related a story about an artist drawing caricatures. The artist asked him what he did. He explained his profession as a clinical chemist and the caricature was drawn. When he received it, Tom noted that there was no face. He asked the artist why and was told, "I don't know what you do."

I think many of us have had similar experiences. One of my examples is my mother, who understands how important monitoring her cholesterol is, and that a high Troponin meant earlier treatment for my father when he was having a heart attack. But she does not relate my profession with providing the ability to perform these tests, or to the laboratories and doctors who use them.

Our image is dependant upon the image of our direct customers, the laboratory scientists and physicians who use our products. Our public does know that cholesterols, PSAs, genetic testing, and all of the other services we make possible are important. They do not know how these happen. We have no *Quincy* or *CSI* to deliver our message. On the contrary, if anyone has seen the television program, *House*, they often will see the physicians in the laboratory running their own tests—an image many of our public shares.

**Letter from Richard Miller (continued)**

One may think this image does not damage us. I disagree! When we hear about federal reimbursement budget cuts, and physicians who believe the IVD industry is weak, it affects our business. Reductions in reimbursements have a direct effect on our ability to provide our products. They also have an effect on the ability of the laboratory to provide services. Although we can continue this way for a while, it will erode our market if it goes on too long.

I agree with Mr. Park. We need an image makeover. We also need that image makeover with our direct customers: clinical laboratory practitioners. I am asking us—the Industry Division of the AACC—to take on Mr. Park's challenge. Some ways we can do this are through partnerships with clinical laboratories to take on joint challenges to our mutual benefit, and by demonstrating that we are addressing areas of significant concern in healthcare today.

We should be partnering with the clinical laboratory to solve our mutual challenges. Our image is but one of the challenges that we can mutually approach. Through collaboration on these challenges, the laboratory practitioners will recognize our value to the healthcare community. By widely publicizing our efforts and solutions, we will be recognized as the strong contributors to the healthcare community that we are.

We have initiated one such partnership already. As you may know, one of the top five priorities that came from the AACC's 2004 needs survey was error proofing. The Industry Division has been approached by clinical chemists with a request to provide training on error proofing and risk management. The idea stemmed from the fact that IVD manufacturers have been dealing with risk management for years and thus understand the technology. As IVD experts in this area, we can help strengthen the laboratories' understanding of these technologies.

As a result of this request, we have been in contact with representatives from the CLIA, CDC, CLSI and the AACC to discuss the possibility of developing a forum to pursue this opportunity. This group has initiated development of a workshop in the area of risk management. The proposed title is, *Improving Patient Safety and Medical Error Reduction Through Risk Management*, and is slated for spring 2006.

It is our hope that a forum such as this will provide us with an opportunity to demonstrate our value to our customers. Additionally, with proper publicity, we will be explaining to the public that we are contributing to solving a significant problem in the healthcare community, namely medical errors.

Another opportunity that has come to my attention is in the area of the application of lean enterprise to cost containment. The 2006 roundtable-organizing committee has suggested that laboratorians are interested in learning about lean. You may have also seen the recent article in **Clinical Chemistry News**, *Getting The Fat Out Of Labs*, or know about the audio conference on June 15th about lean and six sigma. These are areas that many of us have been dealing with for years.

If you have been as involved in lean as I have over the years, you are well aware that lean techniques reduce costs by eliminating waste and poor quality, not renegotiating prices or eliminating services. We need to share our knowledge with our colleagues in the laboratory and with other IVD manufacturers.

I encourage anyone who is an expert on lean to please feel free to submit programs for next year's meetings. The Industry Division would be happy to co-sponsor such programs and to help publicize them.

Returning to Mr. Park's challenge, we also need to work with other organizations to change our image. We will discuss this at the Industry Division's next Executive Board Meeting. I consider this a high priority over the next few years and am asking your help in meeting this challenge.

Please become involved in the Industry Division and submit your ideas on how to put a face in the mirror. You may make your suggestions directly to me at [rrmiller@ix.netcom.com](mailto:rrmiller@ix.netcom.com) or [rick\\_r\\_miller@dadebehring.com](mailto:rick_r_miller@dadebehring.com). Obviously, we may not be able to do everything, but I will take your ideas seriously and the Industry Division will do what it can to make things happen.

This topic will be on the agenda at the Industry Division membership meeting in Orlando, which will be held July 27th at 5:00 pm in the Rosen Centre Hotel, Salon 14. I hope you will join us.

Rick Miller  
Industry Division Chair

## Industry Division Awards Announcement

The Industry Division is pleased to announce two cash awards that will be given at the annual AACC/IFCC meeting in July 2005.

### First Award - Best Abstract of Interest to the Industry Division

The first \$750 cash award is for the best IVD-related abstract of those accepted for display at the Annual Meeting. This will be awarded in cooperation with the Society of Young Clinical Laboratorians (SYCL), who will assist with the selection of the best abstract. The criteria are:

- The abstract should make a significant contribution to the IVD Industry in one of the following areas: management, regulatory, improved patient care through a new or improved medical device (e.g., diagnostic method, reagent system, or other).
- The abstract should be of interest to a significant portion of the IVD industry.
- The winning abstract will be innovative and contain new information.
- In the case of multiple authored abstracts, the award will be presented to the person presenting the abstract.
- The nominee does not need to be an Industry Division Member.
- The nominator does not need to be an Industry Division Member.
- Self-nominations are welcome.

Nominations must include the name and contact information of the presenter and nominator, a copy of the abstract, and a brief rationale describing why the abstract meets the above criteria. Submissions should be sent to [aaccindustryawards@yahoo.com](mailto:aaccindustryawards@yahoo.com) by June 30, 2005.

### Second Award - Industry Division Service Award:

The second \$750 cash award is the Industry Division Service Award for outstanding accomplishment or effort. The criteria are:

- An outstanding accomplishment evidenced by the initiation or support of a single event or a continuous effort that has served the AACC Industry Division Membership and / or the IVD Industry.
- The effort or accomplishment should be recognized as an "outstanding service" activity by AACC members.
- The activity should help to further the education of awareness of the IVD Industry or the AACC as a whole.

Nominations for this award must include the name and contact information of the nominator and nominee, some background information about the nominee, a description of the contribution(s) to be considered, a brief rationale, if not obvious, stating why the contributions meet the awards criteria. Send nominations to [aaccindustryawards@yahoo.com](mailto:aaccindustryawards@yahoo.com) by June 30, 2005.

The awards will be presented at the AACC Annual Meeting in Orlando, FL:

Joint Mixer of  
The Pediatric and Maternal-Fetal, Molecular Pathology, and Industry Divisions  
Tuesday, July 26th 2005, 6:00 pm – 8:00 pm  
Peabody Hotel

If the recipient is a member of SYCL, the Abstract Award will also be presented at:

SYCL Reception  
5:00 pm - 6:00 pm  
Rosen Centre Hotel  
Signature 1 Room

If you have any questions, please contact one of the Awards Committee members:

<b>Richard Miller</b>	<a href="mailto:rick_r_miller@dadebehring.com">rick_r_miller@dadebehring.com</a>
<b>Catherine (Katie) Smith</b>	<a href="mailto:Katie.M.Smith@Biogenidec.com">Katie.M.Smith@Biogenidec.com</a>
<b>Joan Gordon</b>	<a href="mailto:jgordon@mmqci.com">jgordon@mmqci.com</a>
<b>Steven Goss, SYCL Representative</b>	<a href="mailto:Steven_Goss@dadebehring.com">Steven_Goss@dadebehring.com</a>

## Industry Division Officers

### ***Richard Miller – Division Chair***

Richard Miller received his B.Sc. in Physiological Chemistry from Ohio State University in 1966. After 2 years at Philadelphia Naval Hospital Laboratory, he accepted a position as chief of chemistry at Saratoga County Laboratory in Upstate N.Y. He joined Technicon Instruments (Bayer) as a development scientist in 1978, where he held several middle-management positions in Quality Assurance, Manufacturing and Technical support. In 1996, Rick joined Dade Behring as a Quality Assurance Manager and has since moved to Delaware as a Staff Scientist in the Consumables Manufacturing Organization.

Rick is an ASQ Certified Quality Engineer whose main interests are Quality Systems and Calibration and Traceability systems for clinical laboratory instruments. He has been active in NCCLS and AACC standardization efforts. In addition to being involved with several local sections, Rick has contributed to several working committees on standardization such as the CLSI (formerly NCCLS) Electrolytes Working Group, the National Reference Council, the Area Committee for Clinical Chemistry and the Joint Committee for Traceability in Laboratory Medicine. Rick is the chair of the CLSI Subcommittee on Uncertainty of Measurement.

Rick has been active with the Industry Division of the AACC for 5½ years. During that time he has assisted with the drafting and acceptance of the Division's Bylaws and with several educational programs sponsored or co-sponsored by the Division. He served as the Industry Division Treasurer for the past two years before becoming Division Chair.

### ***Paul D'Orazio, Ph.D. – Chair Elect***

Dr. Paul D'Orazio is Director of Sensor Development at Instrumentation Laboratory, in Lexington, Mass. He received a Ph.D. in Analytical Chemistry from the State University of New York at Buffalo in 1979 and has been employed in the diagnostics industry for over 25 years, including 20 years with Bayer Diagnostics and at Instrumentation Laboratory since 1999. His interests include development and integration of chemical sensors and biosensors into instrumentation for critical care and point of care testing.

Paul is past Chair of the Critical Care Testing Division of the American Association for Clinical Chemistry, and continues as a member of the Critical and Point of Care Testing Division. He has also been active in CLSI (formerly NCCLS) as a member of the Area Committee on Clinical Chemistry and Toxicology and former Chair of the Subcommittee on Electrolytes. He also serves as a member of the IFCC Working Group on Selective Electrodes and Point of Care Testing and editorial board member for the Journal of Point of Care Testing. Paul holds several patents in field of chemical sensing and application of this technology to medical diagnostics.

### ***Joan T. Gordon, B.S., M.T. (ASCP) – Secretary/Treasurer***

Joan Gordon, President of Maine Molecular Quality Controls, Inc., has over 20 years experience in the diagnostic testing field. Joan graduated Summa cum laude from the University of Vermont with a B.S. in Medical Technology. She worked as a generalist in a Boston hospital laboratory and then as a Senior Technologist in Clinical Chemistry with certification for Chemistry Specialist at Maine Medical Center. Subsequently, she transferred to Maine Medical Center Research Institute to work in the Molecular Pathology Laboratory and assist in the implementation of a novel HIV genotyping assay and other molecular-based tests. Joan became involved in a research project begun by Clark Rundell, Ph.D. to develop controls for molecular diagnostic assays. In January 2000, Joan and Clark founded their company, Maine Molecular Quality Controls, Inc., in Scarborough, Maine, to continue the development and manufacture of novel quality controls for the molecular diagnostic community.

An AACC member for over five years, Joan has served as Treasurer of the Molecular Pathology Division, and is currently Treasurer and Secretary of the Industry Division of AACC. She comments: "Now that I am an owner of an IVD company, I'm particularly interested in working with the Industry Division. I hope that my clinical background will provide useful insights for the group. I am certain that I will benefit from interaction with AACC members knowledgeable in industry issues, such as FDA regulation of ASRs and the European IVD directive." Joan is currently the Round Table Coordinator of the Annual Meeting Organizing Committee for the AACC 2006 Annual Meeting to be held in Chicago.

**Industry Division Officers (continued)****James E. Love, Jr., Ph.D., D.A.B.C.C. – Past Chair**

Dr. James Love is an independent consultant with the SAM Group and an Emeritus member of the AACC. He received a B.S. in Medical Technology from Temple University, M.S. in Medical Technology from Wayne State University, M.B.A. from Austin Peay State University, and Ph.D. in Clinical Chemistry from Ohio State University.

Dr. Love has been active in the AACC since 1984, serving on the Awards Committee in the Northern California Section, the Industry Advisory Group, the OEM Lecture Series Coordinator, the Nominating Committee of the Industry Division, and the 2002 Annual Meeting Organizing Committee. He is currently on the Steering Committee of the House of Delegates, Past-Chair of the Industry Division, and is a member of the Program Coordinating Commission.

## Something Funny....



## AACC 2005 Annual Meeting

Orlando, FL  
Orange County Convention Center  
July 24 – 28, 2005

The Industry Division is proud to endorse the following sessions, workshops, roundtables, and activities to be held at the 2005 AACC Annual Meeting in Orlando, FL.

### *Saturday, July 23*

A special satellite workshop produced by the Mayo Medical Laboratories Education Department

8:00 am -5:30 pm

#### **How the Practice of Medicine Informs Technology**

**Registration:** You may download a full version of the brochure along with a registration form at: <http://www.mayo.edu/pmts/mc0600-mc0699/mc0661-48.pdf>

**Location:** **Rosen Centre Hotel**

Decisions regarding laboratory services that contribute to enhanced patient outcomes and physician satisfaction are best made in a local setting in the context of patient care. Performance standards for quality, turnaround time and appropriate test selection relevant to the practice can only be designed and improved through a medically driven decision-making process. This program will present experience gained in a clinical setting with the development and application of emerging technology and disease management strategies. Emphasis will be placed upon test validation that yields true evidence-based results.

For additional information, contact the Mayo Medical Laboratories Education Department at phone 800-533-1710 or 507-538-6253 or e-mail [levell.connie@mayo.edu](mailto:levell.connie@mayo.edu).

## 2005 Annual Meeting (continued)

**Monday, July 25****EduTraks**

All Day

3208

**Quality Management in Clinical Laboratories Through ISO Standards, Six Sigma, and Lean Manufacturing Principles**

Moderator, James E. Love, Jr. Ph.D.

**Registration:** When you sign up for the Annual Meeting.**Location:** Will be printed on your ticket.

Clinical laboratories are looking for ways to increase customer satisfaction with greater efficiency. The implementation of ISO Standards and the use of complimentary tools such as Six Sigma and Lean Principles can help laboratories achieve effective results from both technical and managerial perspectives. The application of these approaches within various clinical laboratory settings will be discussed.

Speakers will include Rogerio Rabelo, MD, Ph.D., Fleury Diagnostics, Sao Paulo, Brazil; Carl Garber, Ph.D., Quest Diagnostics, Lyndhurst, NJ; and Maureen Harte, MT(ASCP), Ortho-Clinical Diagnostics, Raritan, NJ.

At the conclusion of this session, the participant will be able to:

1. Describe the basic principles and requirements of the ISO 9001:2000, 15189:2003 and 14001:1996 standards, and their usefulness to clinical laboratories.
2. Identify the main steps for a successful implementation of these ISO standards in the clinical laboratory, and discuss how it benefits different stakeholders (patients, laboratory staff, and healthcare managers and administrators).
3. Describe the 5 steps of the DMAIC process and explain, by examples, how to apply the DMAIC process in the workplace.
4. List Lean tools and general outcomes of applying Lean Principles to clinical laboratory operations.

**Workshops**

10:30 am -12:30 pm

2203

**Reducing Risk of Lab Errors Using Failure Mode Effects Analysis**

Jan S. Krouwer, Ph.D., FACB, Krouwer Consulting, Sherborn, MA

**Registration:** When you sign up for the Annual Meeting**Location:** Will be printed on your ticket.

This workshop is a tutorial on a combined fault tree – FMEA approach to risk reduction in processes. Whereas diagnostic manufacturers are familiar with FMEAs and fault trees to varying degrees (often for products not processes), the combination of using fault trees and FMEAs in one (software) tool is largely unknown. The advantage of adding a fault tree to a FMEA is that the graphical fault tree adds structure to the FMEA, which is largely an unorganized list.

The difference between FMEA and FRACAS (Failure Review And Corrective Action System) is covered. Emphasis is also placed on the error event / detection / recovery model, which is helpful in mitigation strategies. Ranking choices for prioritization of potential errors are illustrated, as ranking is often more difficult for hospital processes than for product FMEAs, where all severities are often only one variable such as cost. Principles are illustrated with real medical errors taken from the literature.

People interested in previewing the presentation should go to:

[http://krouwerconsulting.com/IFTFTraining\\_files/frame.htm](http://krouwerconsulting.com/IFTFTraining_files/frame.htm)

## 2005 Annual Meeting (continued)

**Tuesday, July 26****Workshops**

2:00 pm – 5:45 pm    **2311    Understanding Method Accuracy by Establishing Traceability**

**Registration:**    When you sign up for the Annual Meeting

**Location:**        Will be printed on your ticket

The IVD Directive has required IVD manufacturers establish the traceability of values assigned to their calibrators to reference materials and methods of higher order. The ISO and Committee of European Nations have published standards explaining how to do this. There is still confusion, however, amongst some manufacturers about the details of establishing traceability. Additionally, the impact of these standards on the clinical laboratory is that they may experience changes to values assigned to calibrators to meet these standards.

This workshop is intended for IVD manufacturers and for clinical laboratories to explain the implementation of the ISO standards and their impact on the clinical laboratory. The attendee of the workshop will, upon completing it, learn and be able to apply the following to their practices as either a manufacturer or a clinical laboratory scientist:

- The need for traceability in the clinical laboratory.
- A description of ISO standards for both manufacturers and clinical laboratories.
- What is Commutability and how does it apply to calibrators and controls?
- What criteria should a manufacturer use to select higher order reference materials and reference laboratories?
- What is uncertainty and how do you estimate the uncertainty of a calibrator value and a patient result?
- How will traceability improve the accuracy and harmonization of test results?

The workshop is presented by a hospital-based clinical chemist, an IVD manufacturer, a reference methods expert and a metrology expert from NIST to provide a balanced view of the issues and benefits of establishing traceability.

**Mixer**

6:00 pm – 8:00 pm    **AACC Joint Mixer: Pediatric and Maternal-Fetal, Molecular Pathology and Industry Divisions**

**Registration:**    Not necessary

**Location:**        **Peabody Hotel**

Come meet your colleagues in the Industry Division. All members invited.

Industry Division awards will be presented (see page 3).

**Wednesday, July 27**

5:00 pm – 6:00 pm    **Annual Industry Division Membership Meeting**

**Registration:**    Not necessary

**Location:**        **Rosen Centre Hotel**

All members are invited to the annual meeting.

Come and help us plan our activities for the next few years. We have some exciting programs in mind but also want to hear from each of you to assure that we are meeting your needs. Come join us and tell us what you want to see from the division and learn more about what we are doing.

## 2005 Annual Meeting (continued)

**Thursday, July 28****Discussion**

8:00 am – Noon    **4424 Strategies for Credentialing Clinical Reference Procedure Laboratories in North America**

**Registration:** Not needed.

**Location:** Rosen Centre Hotel

The purpose of this forum is to identify options for Reference Measurement Procedure Laboratories in North America for demonstrating compliance to ISO 15195 that will be technically sound and still cost effective.

**Background:**

In June 2002, the Joint Committee for Traceability in Laboratory Medicine (JCTLM) was created to meet the need for a worldwide platform to promote and give guidance on internationally recognized and accepted equivalence of measurements in Laboratory Medicine and traceability to appropriate measurement standards. These are embodied in ISO 17511 and 18153. The JCTLM created two working groups: **WG1**, Reference Materials and Reference Procedures, and **WG2**, Reference Laboratory Networks

**JCTLM WG1** was charged with establishing a process for identifying, reviewing against agreed upon criteria, and publishing List(s) of Higher Order Certified Reference Materials and Reference Measurement Procedures required for industry compliance with the EC IVDD regarding in vitro diagnostic medical devices. Nominated reference materials and measurement procedures have categorized according to the criteria described in ISO 15194 and ISO 15193. Two Lists of Higher Order Reference Materials and Reference Measurement Procedures have been published:

Additional details concerning the JCTLM, the Database of Higher Order Reference Materials and Reference Measurement Procedures and the general procedures by which reference materials and reference measurement procedures have been evaluated for listing and are provided can be found at: <http://www.bipm.org/en/committees/jc/jctlm/jctlm-db/> and <http://www.ifcc.org>.

**JCTLM WG2** is establishing criteria and processes for assessing the competencies required by ISO 15195 for Reference Measurement Laboratories to be included on the JCTLM lists.

A very important issue that is currently under discussion by WG2 is how to assure compliance of Reference Measurement Procedure Laboratories to ISO 15195. The current proposal is for them to be required to have accreditation according to ISO 15195 or as a calibration laboratory under ISO 17025. Although accreditation is an acceptable mechanism for recognizing and eliminating laboratories that are not meeting the proper ISO requirements, another result may well be to eliminate laboratories that are already providing acceptable services, but feel they cannot afford the cost of accreditation.

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The purpose of the NIST/AACC Industrial Division forum is to discuss and agree on various rigorous and metrologically-sound approaches for addressing this issue in a cost effective manner.

## 2005 OEM Lecture Series

### *An AACC Annual Meeting Special Event*

The AACC Annual Meeting Clinical Laboratory Exposition features a large number of companies supplying components and subsystems for research, product development and the manufacturing of in vitro diagnostic products. In addition to the OEM (Original Equipment Manufacturer) exhibits at the exposition, the AACC, in cooperation with the Industry Division, created the OEM Lecture Series as an additional opportunity for OEM vendors to present the latest innovations in technology and services to a targeted audience.

The 21 presentations listed below will be given covering topics ranging from services, new tools for R&D and potential new products to take to market on Tuesday, July 26 and Wednesday, July 27, from 8 am to noon. The presentations will be held at the Orange County Convention Center in Orlando. Make the OEM Lecture Series a part of your program while attending the AACC Annual Meeting.

Registration is not necessary.

### *Tuesday, July 26*

Orange County Convention Center – No registration required

8:00 am	<b>Polymer microfluidic devices with integrated electrodes</b>	N.P. Kreutter <b>3M</b>
8:20 am	<b>OEM Fluid Level Sensor That Detects The Presence Or Absence Of Fluid From Outside A Container Eliminating The Need To Touch The Fluid.</b>	Jessica Light <b>Gems Sensors Inc.</b>
8:40 am	<b>A research tool for inflammatory diseases- 15-epi-lipoxin A4 ELISA</b>	Paul S. Satoh <b>Neogen Corporation</b>
9:00 am	<b>Holotranscobalamin enzyme immunoassay for vitamin B12 status</b>	Edward Valente <b>Axis-Shield Diagnostics</b>
9:20 am	<b>Enzyme immunoassay for detection of SIV or unusual form of HIV</b>	Suzanne Shope <b>Centers for Disease Control and Prevention</b>
9:40 am	<b>A new lateral flow matrix enables high performance, quantitative, point-of-care tests for cardiac markers</b>	I. Mendel-Hartvig <b>Amic AB</b>
10:00 am	<b>Whole blood rapid tests</b>	N.K. Gupta & A. Gupta <b>Advanced Microdevices Pvt. Ltd.</b>
10:20 am	<b>Stabilization of white blood cells and Immunologic markers for extended analysis using flow cytometry</b>	D.E. Warrino <b>Streck</b>
10:40 am	<b>Stabilization of protein-based in vitro diagnostic products</b>	J.V. Wall, M.A. Lodhi, P.J. Reed, & D.E. Averill <b>SurModics, Inc.</b>
11:00 am	<b>Electronic manufacturing and quality management system</b>	Ron Jellison <b>KMC Systems, Inc.</b>
11:20 am	<b>Utilization of a Common Process Role in OEM Product Development</b>	Mary Wojtas <b>Abbott</b>

## The 2005 OEM Lecture Series (continued)

***Wednesday, July 27***

Orange County Convention Center – No registration required

8:00 am	<b>DS2 – A Completely Open Automated 2-Plate Clinical ELISA Processing Workstation</b>	Adrian Bunce & Allen Bickel <b><i>DYNEX Technologies Inc.</i></b>
8:20 am	<b>A unique, electronic, multi-channel pipettor that simplifies sample preparation, prompts the user in natural language, and interfaces to other laboratory instruments</b>	R.E. Scordato & J. Calhoun <b><i>VistaLab Technologies, Inc.</i></b>
8:40 am	<b>Innovative ISE Module for OEM Applications</b>	Frédéric Furrer <b><i>Roche Diagnostics / Roche Instrument Center</i></b>
9:00 am	<b>FullVelocity™: a novel technology for QPCR and QRT-PCR-based diagnostics</b>	S. Happe, M. Simmons, G. Padmabandu, R. Mueller & J. Sorge <b><i>Stratagene Corporation</i></b>
9:20 am	<b>FullVelocity™ reagents for fast clinical quantitative PCR assays</b>	R. Mueller, G. Padmabandu & J. Sorge <b><i>Stratagene</i></b>
9:40 am	<b>Reliable molecular diagnosis of septicaemic bacteria, a novel procedure of differential nucleic acid preparation</b>	Michael G. Lorenz, Molzym GmbH & Co.KG, and Jack Ramsay <b><i>Filtrona Fibertec Inc.</i></b>
10:00 am	<b>Unique and Innovative OEM Immunoassays at Seradyn, Inc.</b>	Bruce Shull <b><i>Seradyn</i></b>
10:20 am	<b>Diagnostic membrane properties linked to test performance</b>	M. Hollas, V. Thom, H. Beer, & K. Pflanz <b><i>Sartorius AG</i></b>
10:40 am	<b>Assay performance and cost savings in Corning Stripwell™ low volume microplates</b>	J.K. Veilleux <b><i>Corning Incorporated</i></b>
11:00 am	<b>Requirements Management as a Corporate Asset</b>	Timothy M. DeFrench <b><i>The RND Group, Inc.</i></b>

# Application of Risk Management to In Vitro Diagnostics Medical Devices: Part 1

Feature Article by  
Donald M. Powers, PhD

## From Risk Analysis to Risk Management

While *risk analysis* is the term chosen by FDA to describe one of the design control requirements of the Quality System Regulation (the QSR)<sup>1</sup>, the buzz in regulatory and quality circles today is all about *risk management*. According to ISO 14971, *Application of Risk Management to Medical Devices*<sup>2</sup>, risk analysis is only the first step in a total product life cycle risk management process. Risk management is a much broader concept.

The difference between the *risk analysis* required in 1996 and the *risk management* expectations of today is more an evolution of terminology than an escalation of requirements. When the QSR was written, *risk analysis* and *risk assessment* were the terms used—often interchangeably—to describe all of the activities manufacturers undertake to minimize the risk of using their products. In the meantime, the International Organization for Standardization (ISO) defined risk terminology more precisely. The true regulatory intent of the QSR is revealed in its preamble, which clearly indicates that the FDA intended manufacturers to do much more than implement the beginning of a risk management process.

The risk management requirements in the European IVD Directive<sup>3</sup> are often viewed as more demanding, but in reality they are not that different from the expectations laid out in the QSR preamble. Yet many IVD manufacturers, when their risk management program is audited, will still pull out an Failure Mode and Effects Analysis (FMEA) summary written long ago by product design engineers as their only evidence of compliance.

Now that nearly 10 years have elapsed since the QSR was first published, the next revision to ISO 14971 is nearing completion, and the Global Harmonization Task Force (GHTF) is developing guidance on integrating risk management into the quality system<sup>4</sup>, a review of the basic requirements of a risk management program for in vitro diagnostics is timely. This will also be a good opportunity to highlight some common compliance issues that medical device companies face with respect to risk management.

## The Risk Management Process

The basic requirements of a risk management process are laid out systematically in ISO 14971, an international risk management standard that is recognized and promoted by most major governments around the world. The well-known flow chart that outlines the ISO risk management process is shown in **Figure 1**.

For the purpose of risk management in medical devices, please note that risk is defined as the probability of harm resulting from a hazardous situation combined with the severity of that harm. Other types of risk are not addressed in the ISO risk management process.

But what is the relevance of ISO 14971 to regulatory requirements? Although the standard is voluntary in the US, it is mandatory for certain IVD products in Australia, Canada, Europe and Japan because it is required by ISO 13485, a quality system standard integral to regulatory schemes based on conformity assessment. Since the QSR is also based on ISO 13485, and since FDA strongly endorses the risk management concepts in ISO 14971 and has been an active participant in the ISO technical committee that developed it, attempting to justify a different risk management approach doesn't make good sense.

Risk management for IVD manufacturers involves four stages:

1. Analyzing the hazards inherent in the use of IVD products and estimating the risks of harm to patients, laboratory workers and the environment;
2. Evaluating the acceptability of the risks against criteria established by company management;
3. Reducing unacceptable risks to an level commensurate with the company's risk acceptability policy, and controlling them so they remain acceptable; and
4. Monitoring internal and external product experience for the possibility of new hazards, as well as the possibility that society's tolerance for a previously accepted risk could change.

**Feature Article by Donald M. Powers (continued)**

The first three stages integrate nicely into the design and development process, as described by Snow in an excellent review article.<sup>5</sup> The last stage of risk management is ongoing throughout the life of a product, and the vigilance required to sustain it will necessarily involve every organization in the company. Risk management is a never-ending process.

The GHTF views risk management as an integral part of a company's quality management system. In its recent draft guidance document, GHTF takes the position that integration into the quality management system is necessary so that risk management efforts will be coordinated and all identified issues will be brought to closure. An excellent panel discussion on practical ways to integrate risk management into the quality system was held at the annual AAMI-FDA standards conference in March and is available on CD ROM.<sup>6</sup>

Because of its close association with the design and development process, some companies mistakenly delegate the entire risk management responsibility to R&D. This is not appropriate. *Risk management is a top management responsibility!*

**Communicating Risk Concepts**

Both the ISO standard and the GHTF make a strong case that organizations need to use a common vocabulary to communicate risk concepts effectively within the organization. Needless to say, it also helps immensely when explaining the company's risk management program to external auditors or FDA investigators. Failures to identify and control risks are often attributable to lack of understanding basic concepts and miscommunication. Please see **Table 1** for definitions of common terms.

Care should also be taken that risk assessments are documented in clear and explicit language. It is often difficult to determine what the risk assessment team concluded. For example, risk analysis tables usually have a column headed, "Probability of occurrence," or simply "Occurrence." But of occurrence what? Failures? Hazardous situations? Harm? These terms are not synonymous – not every failure leads to a hazardous situation, and not every hazardous situation leads to harm. The documentation must clearly convey how the risk analysis team estimated the probability of actual harm from the frequency of specific product failures.

**Risk Management Planning**

Risk management activities, like all quality management activities, must be planned, and the plan must encompass the entire life cycle of the product. Yet, despite this explicit requirement of ISO 14971, few companies that claim to have adopted the ISO risk management process can produce a satisfactory plan during an audit. Many regard their FMEA documentation as the plan, even though it does not have all the essential elements of a plan. FMEAs represent just one deliverable of a life-cycle plan.

In planning the risk management activities, it helps to begin with the end in mind – by defining the information that needed to show that all potential hazards have been identified and assessed, that all unacceptable risks have been mitigated to an acceptable level, and that the effectiveness of all risk controls has been verified. ISO 14971 requires this in a risk management report.

The GHTF guidance includes an example of a summary table that captures the hazards and risk evaluation results and provides traceability of risk control measures to product design requirements and verification/validation activities. The content and format of the risk management documentation should be designed to facilitate its use in change control decisions, complaint and failure investigations, and CAPA. Once the information required for the risk management file is defined, an efficient strategy can be developed and the individual's risk management activities can be planned to ensure they are comprehensive and traceable.

According to the GHTF guidance, the risk management plan should address the following:

- Approach(es) to be used in determining acceptable levels of risk.
- Roles and responsibilities for risk management activities.
- Review of risk management results at appropriate intervals.
- Risk management input to the quality management review process.

While a formal risk management plan is not an explicit FDA requirement, it makes good business sense. GHTF recommends incorporating risk management planning into design and development planning by including the specific risk management tasks, identifying the necessary resources, defining the relationship between tasks, and defining roles and responsibilities for each task. A risk management plan should be a logical part of each new product development plan.

**Feature Article by Donald M. Powers (continued)****Hazard Identification And Risk Analysis**

As early as possible in the design phase, manufacturers are expected to identify potential hazards to patients, users and the environment. This provides the best opportunity to avoid or at least minimize their occurrence through design improvements. The most serious IVD hazards are generally incorrect test results, which create a hazardous situation for the patient if (1) the incorrect results are believable and (2) are reported to the physician. The severity of possible harm depends on the particular analyte.

Hazardous test results are identified from the medical uses of the results. Every test has performance requirements derived from its clinical utility, generally including accuracy, precision and specificity for qualitative assays, and diagnostic sensitivity and specificity for quantitative assays. The risk model for a laboratory-use IVD assay is illustrated in **Figure 2**, which is taken from ISO/DIS 14971:200x.<sup>7</sup> This draft second edition of ISO 14971 contains expanded guidelines for application of risk management to IVD medical devices and is currently undergoing balloting by the ISO membership.

If a failure of a glucose analyzer led to a falsely high result, for example, the incorrect result could cause a physician to administer insulin, which could be dangerous if the patient were actually hypoglycemic. In a typical risk analysis, using a FMEA technique, teams of scientists, engineers and clinical experts would analyze the various ways a glucose assay can fail to cause such hazardous results, and assign probabilities that each failure mode would occur. A Design FMEA identifies failure modes in the analyzer design itself, whereas Process FMEAs are performed to identify failures in the manufacturing, distribution, servicing or other processes that can affect product quality. Other risk analysis tools, such as Fault Tree Analysis (FTA) and Hazard Analysis and Critical Control Points (HACCP), may be employed to ensure a comprehensive risk analysis.

Obviously, every failure of an IVD analyzer does not necessarily cause harm to a patient. Many quality control safeguards have evolved in laboratory medicine to discover incorrect results before they are reported, and physicians have learned to cope with occasional erroneous results, most of which emanate from the pre- and post-analytic errors. Systems to detect incorrect results can be conservatively factored into the probabilities that an erroneous result will (1) be reported from the lab, and (2) will be believed by the physician. In the parlance of the risk management, a hazard must develop into a hazardous situation before a patient is exposed to harm.

That being said, manufacturers must err on the side of caution when estimating the probability that a lab will detect a believable incorrect result. While some laboratories have implemented sophisticated QC systems, others simply do not have the capability. Except perhaps for systematic errors that develop slowly over time (such as a reagent stability failure), or a result incompatible with life (such as potassium of 10 mmol/L), manufacturers must generally assume that an incorrect result will be reported by the laboratory and could influence a physician's decision.

With IVD assays, a percentage of medically incorrect results occur in normal use—results that could potentially indicate the wrong diagnosis or treatment. Westgard points out that few assays operate at the 6-sigma level, which represents approximately 3.4 “errors” per million test results.<sup>8</sup> Based on CLIA criteria and PT data, he calculates that analytes such as cholesterol, calcium, glucose and prothrombin time (INR) operate at the 3 – 4 sigma level (6210–233 “errors” per million test results), while analytes such as glycohemoglobin and PSA operate at less than a 3 sigma level.<sup>9</sup> The risk associated with these incorrect results must be evaluated.

A greater percentage of incorrect results occur from IVD assay or device failures, in which performance claims are not met. This includes anticipated use errors and any foreseeable misuse of the device or its results. A common approach is to consider each failure to meet a performance claim as a potential hazard.

Failures to perform a proper risk analysis often stem from the lack of a systematic approach to identifying potential hazards, neglecting to consider alternative uses of the product or the results, and incorrect assumptions about the medical requirements. These failures frequently reflect a lack of training in the specific risk management techniques being used.

Not documenting the risk assessments in a way that facilitates their use throughout the product life cycle is another common problem. Risk assessments must be continuously reviewed and updated with inputs from other processes, such as change control and CAPA.

As development progresses and the design improves, new information is accumulated in the risk management file. Risk analyses are repeated and risk estimates are updated. Process FMEAs are conducted to analyze the effects of manufacturing failures on the product and ultimately on its safety.

Failure to keep the risk analysis up to date creates a major compliance risk. Therefore it is essential that risk analysis documentation be developed as a living document with future uses in mind.

**Feature Article by Donald M. Powers (continued)**

Discontinuities between design and process FMEAs are generally symptomatic of a firm's failure to integrate development of its manufacturing processes into the overall design and development process. Misunderstanding of the role of a process FMEA in the risk management program is a frequent source of confusion. Process risk analyses cannot be done solely by manufacturing personnel in a vacuum; they must be linked to the product intended uses and safety characteristics. Although the hazards originate in process failures, it is the effect on product performance (i.e., diagnostic results) that leads to patient harm. To the extent that process failures can lead to incorrect results, they must be added to the list of potential hazards, addressed as part of the risk management plan and documented in the risk management file.

Of course, FMEAs can also be conducted to improve the process itself, but that is over and above the basic duty to minimize risk to users and patients. Separate FMEAs should be done for process optimization.

**Risk Evaluation**

Once the hazards are understood and the probabilities of occurrence estimated, the risks have to be evaluated against the company's policy for acceptable risk. This is why risk management cannot be placed on R&D's shoulders alone. Establishing criteria for the risk the company is willing to accept and deciding when medical benefits outweigh the risks is a management responsibility.

The most common deficiencies at this stage of the risk management process are lack of a management policy on how acceptable risks will be determined, failure to establish criteria for acceptable risk, lack of top management's involvement in risk decisions, and confusion between product safety risk and other types of risk, such as the project schedule, liability exposure or financial return.

**Risk Assessment Reviews**

GHTF recommends that design and development reviews include risk assessment results (i.e., risk analysis and risk evaluation). Therefore, design review procedures need to define the risk review tasks that will be performed at the different stages of design and development. Reviewers with the breadth and depth of experience to assess design decisions concerning risk acceptability are needed for these design reviews.

For example:

- Early design and development reviews will focus on hazard identification, risk estimation, and the needs and requirements for risk control measures.
- Later stages of design and development reviews will shift focus to the implementation of risk control measures and evaluation of residual risk. During the verification and validation stages, the effectiveness of risk control measures would be reviewed.
- The final design review will include evaluation of overall residual risk after evaluation of all single identified hazards has been completed. If the residual risk is still too high, a risk/benefit analysis can be performed at that time to determine if the medical benefits outweigh the remaining risks.

Feature Article by Donald M. Powers (continued)

Conclusion of Part One

This discussion introduced the current concepts of risk management, described the application of ISO 14971 risk management process to in vitro medical devices, and discussed the integration of the Risk Analysis and Risk Evaluation stages of risk management into the quality management system.

Part 2 will continue the discussion and explain how the Risk Control and Post-Production Monitoring stages of the risk management process can be integrated into the quality management system.

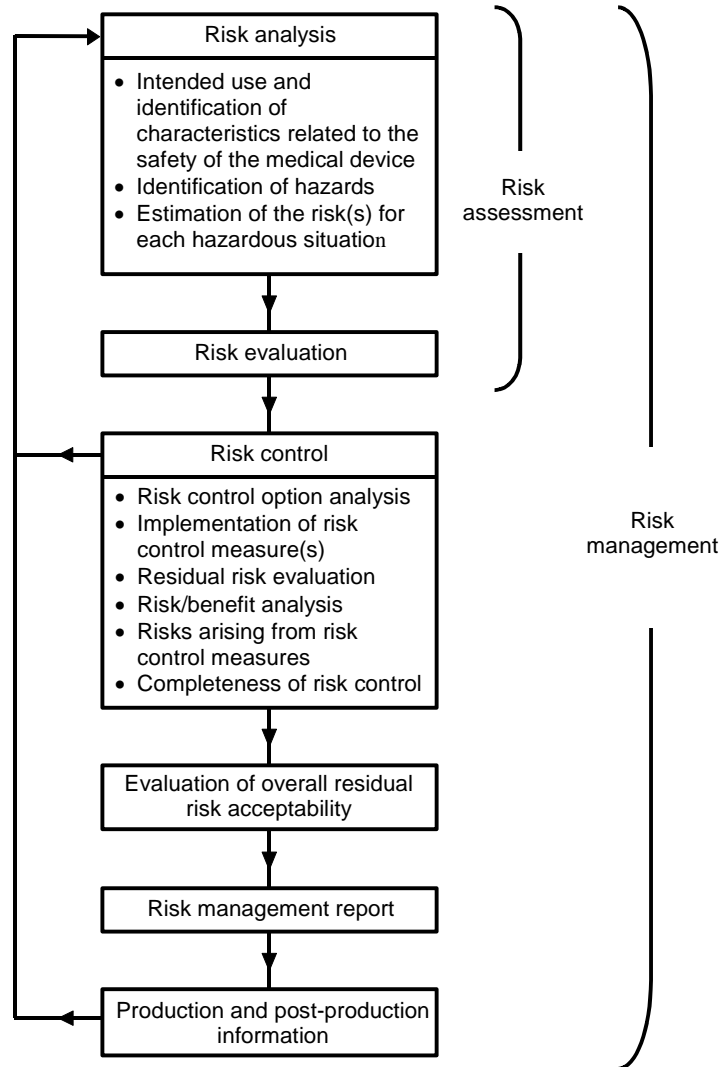
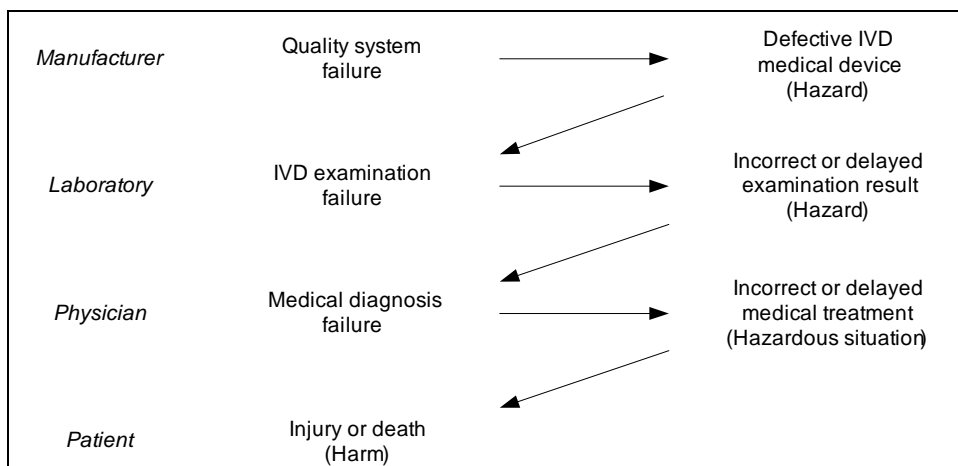


Figure 1 – A schematic representation of the risk management process

Source: ISO/DIS 14971:200x

**Feature Article by Donald M. Powers (continued)**



**Figure 2** – A risk model for laboratory use IVD medical devices

Source: ISO/DIS 14971:200x

**Table 1 – Definition of Risk Terms**

<b>Term</b>	<b>Definition</b>
<b>Hazard</b>	Potential source of harm
<b>Harm</b>	Physical injury or damage to the health of people, or damage to property or the environment
<b>Hazardous situation</b>	Circumstance in which people, property, or the environment are exposed to one or more hazards
<b>Residual risk</b>	Risk remaining after risk control measures have been taken
<b>Risk</b>	Combination of the probability of occurrence of harm and the severity of that harm
<b>Risk analysis</b>	Systematic use of available information to identify hazards and to estimate the risk.
<b>Risk assessment</b>	Overall process comprising a risk analysis and a risk evaluation
<b>Risk control</b>	Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels
<b>Risk estimation</b>	Process used to assign values to the probability of occurrence of harm and the severity of that harm
<b>Risk evaluation</b>	Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk
<b>Safety</b>	Freedom from unacceptable risk
<b>Severity (of harm)</b>	Measure of the possible consequences of a hazard

Source: ISO 14971:2000

**Feature Article by Donald M. Powers (continued)****References**

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- <sup>6</sup> Kim Trautman, Ed Kimmelman, Ken Kopesky and Paul Brooks, *Quality Systems and Risk Management Integration: An update on ANSI/AAMI/ISO 13485:2003 and related guidance documents*, March 23, 2005. Presentation available on CD ROM from Association for the Advancement of Medical Instrumentation (AAMI), 1110 North Glebe Road, Suite 220, Arlington, VA 22201-4795.
- <sup>7</sup> *Medical Devices: Application of Risk Management to Medical Devices*, 2nd Edition. ISO/DIS 14971:200x (Geneva: International Organization for Standardization).
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