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Standardizing Patient Safety Risk Management

by Mark Cupryk

This article presents the challenges in patient safety risk management for the Patient, US Food and Drug Administration (FDA), Healthcare Provider, and Sponsor. The article reviews specific risk management tools to show how audits can be leveraged by the Sponsor to provide additional patient safety focus and consistency across the medical product supply chain.

While Sponsors must navigate through multiple challenges in today's competitive environment, keeping their medical products safe always tops their extensive "to do" list. The use of medical products, which include drugs, biological products and medical devices, involves balancing the risks versus the benefits for the patient. From medical product development and testing, through manufacturing to patient delivery and care, the safety risks to the patient must be managed continually.

Patient safety accountability for the numerous medical products can be divided across four primary groups – the US Food and Drug Administration (FDA), the Sponsor, the Healthcare Provider, and the Patient as depicted in Figure 1. Each group's unique objectives and constraints have yielded a non-uniform approach to patient safety risk management. However, a convergence of patient safety is evolving at a rapid pace with each stakeholder increasing patient safety communication through new and established communication channels.

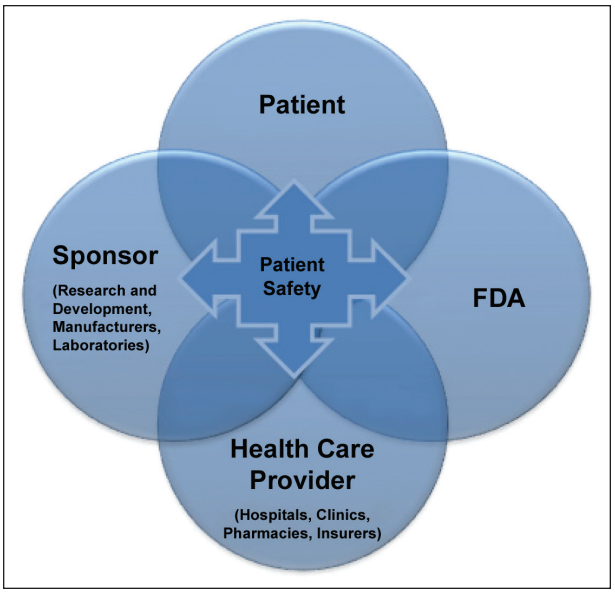


Figure 1. The four key stakeholders in increasing patient safety.

The regulatory audit, a significant process in the Sponsor's quality management strategy, helps extract valuable compliance data to mitigate patient safety risks from day one. The purpose of this article is to contrast the challenges in patient safety risk management for the Patient, Food and Drug Administration, Healthcare Provider, and Sponsor and to review specific risk management tools to show how audits can be leveraged by the Sponsor to provide additional patient safety focus and consistency across the medical product supply chain.

What exactly is patient safety?

The patient safety domain assumes a sensible consensus about the efficacy of a treatment and focuses on whether these treatments have been delivered safely. For example, the definition can include harm to the patient, incidents that may give rise to harm, processes that increase the likelihood of incidents, and the attributes that help protect against harm and enable rapid recovery when risk escalates.[1]

Unfortunately, too many definitions of patient safety exist and these differences also diminish the focus on its principal elements. Even so, risk management has a governing role in providing strategies to protect the patient.

In 2009, a list of 50 research priority areas in developed, transition, and developing countries was compiled by the World Health Organization Patient Safety group.[2] Figure 2 identifies the top six priorities in developed countries, which can be equated to areas requiring significant improvement. For example, leading research priorities like communication, process improvement, clear safety measures, and adverse events are all representative of the current transformational targets in the US. What's

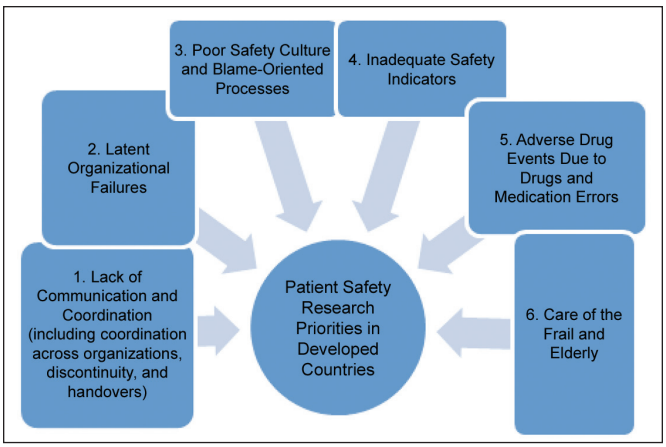


Figure 2. Top global patient safety research priorities in developed countries WHO.[2]

more is that latent organizational failures, such as lacking an adequate risk management strategy for a specific entity perhaps due to deficient procedures and/or training, are high on the research priority and therefore, a opportunity target for improvement.

The question evolves into how best can an organization structure itself to strategically manage the numerous patient safety risk events? A well aligned risk management program can provide the suitable infrastructure by applying continuous monitoring, internal and external audits of varying degrees, and reassessments of its tolerance limits for risk events. An example of such a frame work will be reviewed later.

Currently, each of the four stakeholders is using a number of paper and electronic patient risk communication tools to better manage patient safety as listed in Table A. Because of their unique processes and needs, each group focuses on different aspects of patient safety and they have taken different approaches to reducing and monitoring related risks within their sphere of influence. For example, the FDA and the sponsor evaluate patient safety at the pre-marketing phase through the data reports on the various clinical trial performed. Recently, during the post marketing phase, the communication has expanded into numerous forms of media as well as higher involvement from each of the stakeholders. Social networks, for instance, are driven by each of the four stakeholders and these complex associations are still forming to provide patients with substantial safety data. Higher performing networks will be the patient safety data mines of tomorrow.

Challenges for the Patient

Each of us is personally involved in patient safety. Today, questions like "What is in this medical product? Are the effects really worth the benefits? Will it actually work? How do I know there is no mix up?" are still only partly answered in real time.

The patient plays an active role in monitoring their own safety. The internet is the preferred communication vehicle for current safety information from the FDA, Sponsor, and Healthcare Provider. Each group has broadened its reach through diverse virtual hubs due to the realization that communication efforts, such as virtual patient forums for instance, apart from educating about treatment access, reimbursement options, disease complexities, may also provide a positive influence on dealing with the medical condition itself.

On the other hand, to gain more safety information from the patient is still the chief issue. If a patient experiences an effect while being treated, there is always the possibility of playing the symptoms down and relating other causes for the effect such as stress, fatigue, diet, etc. In fact, one in six Americans who have ever taken a prescription drug experienced a side effect serious enough to send them to a doctor or hospital, but only 35 percent were aware that they can report these side effects to the FDA and only seven percent indicated they

Marketing Phase	Medical Product Safety Data Communication	Patient Safety Data Description	FDA	Health Provider	Sponsor	Patient
Pre-Marketing	Pre-Clinical	Data demonstrating that the product is safe for clinical research on human subjects.	✓		✓	
	Clinical Trials Phase I, II, III	Data demonstrating that the product is safe and effective for market.	✓		✓	
Post-Marketing	Phase IV Studies	Data demontrating that the product is still safe and effective while on market; may also include additional patient types.	✓	✓	✓	
	MedWatch	FDA volunteer safety information and adverse reporting program. Patients can use direct mail, fax, phone, or internet to report an adverse event. Uses form 3500 to capture data.	✓	✓	✓	✓
	AERS and VAERS	Systems containing all medical product adverse events. Vaccines Adverse Events are reported into their own database.	✓	✓	✓	✓
	MAUDE	Manufacturer and User Facility Device Experience Database for Adverse reports involving medical devices. Part of Medwatch, i.e., also uses form 3500 to capture events.	✓	✓	✓	✓
	Sentinel System	System designed to link additional data sources to enable queries on deidentified patient safety datasets of interest to the FDA.	✓			
	Periodic Safety Updates	Medwatch alerts, Drug Safety Podcasts, Quarterly Safety Newsletter, Recalls, Market Withdrawals, and Safety Alerts.	✓	✓	✓	✓
	Safety Announcements	Public Health Advisories, Letters to Health Care Professionals, Information Sheets.	✓	✓		✓
	CMS Data Bases	Centers for Medicare and Medicaid Databases have national coverage of patient safety information.	✓	✓		✓
	Commercial Data Bases	FDA works with commercial organizations to further understand patient safety trends and patterns.	✓			
	Patient Safety News	Televised Series for healthcare professionals regarding safety information on new drugs, biologics, and medical devices.	✓	✓		
	Drugs@FDA	Information on approved medical products.	✓	✓	✓	✓
	Social Networks	Facebook, Twitter, Flickr, etc. are being leveraged to share information to various groups.	✓	✓	✓	✓
	DailyMed	Web site giving physicians and patients electronic access to FDA approved drug labels.	✓	✓		✓
	Collaborative Agreements	FDA collaborates with various institutions to further research patient safety trends and patterns.	✓	✓	✓	

Table A. Stakeholders and patient safety risk communication.

would inform the Agency.[3] With soundly designed technological improvements and effective educational campaigns, such reporting statistics will certainly get healthier. However, the main challenge within the Patient Group is securing their safety effect and event communication in a standard and thorough manner so that the other stakeholders as well as themselves reap more benefits. Barriers originating from confidentiality, motivation, and education of the patient will need to be removed.

Challenges for the Healthcare Provider

In the last decade, healthcare activity focused on understanding the deeper patient safety pains by seeking the root causes and remedying with strategic and tactical countermeasures. In 1999, the "To Err is Human" publication served as the catalyst in highlighting the untold risks of the healthcare system.[4] The frightening numbers echoed – "Almost 100,000 people die in hospitals from preventable medical errors per year." The visible analogy of a large aircraft crashing every other day loomed. One of the identified key root causes was poor information management practices, such as unconfirmed verbal orders, illegible prescriptions, unanswered telephone calls, and lost medical records.

In contrast, a March 2010 article indicated that the patient safety incidents had not yet declined from 1 million over 2006 to 2008 and that as a result, 10 percent of these incidents resulted in death.[5] Even with the many initiatives undertaken to reduce errors, clearly, opportunity for improvement still exists. To compound the burden, healthcare faces a lack of available nursing and medical expertise, and increasing regulations such as HIPAA.

These challenges have demanded continual improvement by standardizing healthcare data information systems across the nation. For the Healthcare Provider, patient safety information technology has evolved in three main areas.

First, in terms of vocabulary, although there is no single standard, the International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM), Current Procedural Terminology (CPT) and diagnosis groups are the most widely used for classifying diagnoses and procedures.[6] Second, data interchange standards – how and when healthcare applications exchange and integrate their data – has been led by the Health Level Seven (HL7) Standards. Finally, Health record content standards also progressed by HL7 Electronic Health Record (EHR) Functional Model and ASTM Healthcare Informatics subcommittee's Continuity of Care Record (CCR) standard.

Also identified by the WHO in Figure 1, determining the right patient safety indicators for proper detection and observation is one of the developed countries' top research priorities. By carefully transforming its past qualitative culture into quantitative system with measureable patient safety metrics, healthcare evolution albeit slower than desired, persists forward.[7,8] According to McGlynn, there are six challenges for measuring the quality of healthcare – balancing perspectives, defining accountability, establishing criteria, identifying reporting requirements, minimizing conflict between financial and quality goals, and developing information systems.[9]

An example of 21 indicators in Table B for patient safety was derived from a project, undertaken as part of the Organization for Economic Cooperation and Development (OECD).[1] The indicators are important patient safety events perceived as lapse of care in procedural complications, child birth trauma and medication error. At the healthcare level, patient safety indicators have been less about minimizing risk coming from the medical product itself like defects, but more attentive on reducing preventable errors. The Agency for Healthcare Research and Quality (AHRQ), also part of the OECD project, is performing significant patient safety indicator research including using composite measures.[10] However, the defect indicators are still low priority and a barrier to an overall view of the patient safety risk continuum. One additional data challenge is reconciling the hospital diagnosis data with the billing data to get patient safety indicators that reliably identify adverse hospital events.[11]

Many Lean Six Sigma initiatives are focused on the Healthcare Provider's priority of reducing preventable errors and providing better communication. Using a data driven approach to better understand the issues has reduced blame-oriented processes. Cycling the event information back to the public is also not being taken lightly by the government. For example, California has already implemented penalty clauses for not making adverse event information available to the public in required time.[12]

Challenges for the Sponsor

While delivering quality medical products meeting its established specifications, the Sponsor is facing its own obstacles in reducing patient safety risks.

First, the relentless increase in medical product counterfeiting is estimated globally at $75 billion to $200 billion.[13] The countermeasures include remarkable attention to the protection of each step in the medical product supply chain

Domain	Domain Name	Patient Safety Event
1	Hospital-acquired infections	1. Ventilator pneumonia 2. Wound infection 3. Infection due to medical care 4. Decubitus ulcer
2	Operative and post operative complications	5. Complications of anaesthesia 6. Post-operative hip fracture 7. Post operative pulmonary embolism or deep vein thrombosis 8. Post-operative sepsis 9. Technical difficulty with procedure
3	Sentinel Events	10. Transfusion reaction 11. Wrong blood type 12. Wrong-site surgery 13. Foreign body left in during procedure 14. Medical equipment-related adverse events 15. Medication errors
4	Obstetrics	16. Birth trauma - injury to neonate 17. Obstetric trauma - vaginal delivery 18. Obstetric trauma - Caesarean section 19. Problems with childbirth
5	Other care-related adverse events	20. Patient falls 21. In-hospital hip fracture or fall

Table B. Patient safety indicators from OECD project.[10]

from "factory to finger." Database software cleverly coupled with radio frequency devices lead as the mainstream solution. Such innovative technology not only reduces the risk of counterfeiting, but it enables data transfer from each supply chain participant including the collection of patient's safety information.

Manufacturing and design defects leading to lawsuits is another concern, especially in hard economic times. In 2009, the top five verdicts of the U.S. market rose 52 percent in total value to $620 million, indicating a trend toward more favorable outcomes to the plaintiffs.[14]

From a survey of 538 life science companies, the major problem for pharmaceutical manufacturing is accessing and analyzing the process data. Forty-six percent of records are still in paper formats. Variability, also identified as a high risk ailment in manufacturing by 60 percent of participants, is now under aggressive treatment.[15]

In the past five years, one of the contributors for better risk management has been the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use with ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Quality Systems. ICH Q9 provides the scientific tools and guidance for continual improvement to diminish potential patient risks coming from manufacturing, and development, both of which are also supported by ICH Q10 and ICH Q8, respectively, as shown in Figure 3.

In particular, the ICH Q9 provides a solid framework on the "what" of the quality risk management process.[16] It establishes a defined process through risk assessment in terms of identification, analysis, and evaluation; risk control in terms of reduction, acceptance; risk review, risk communication, and risk tools. Annex I provides the "how," that is, Risk Management Methods and Tools, which in fact embrace the Lean Six Sigma toolset and methodologies including examples. Annex II, Potential Applications for Quality Risk Management, offers consideration on "where" to focus the risk management efforts. ICH Q10's guidance, based on ISO norms quality system, runs across the entire medical product cycle. ICH Q8 supports the science behind pharmaceutical development.

Sponsor driven technology changes from paper to electronic

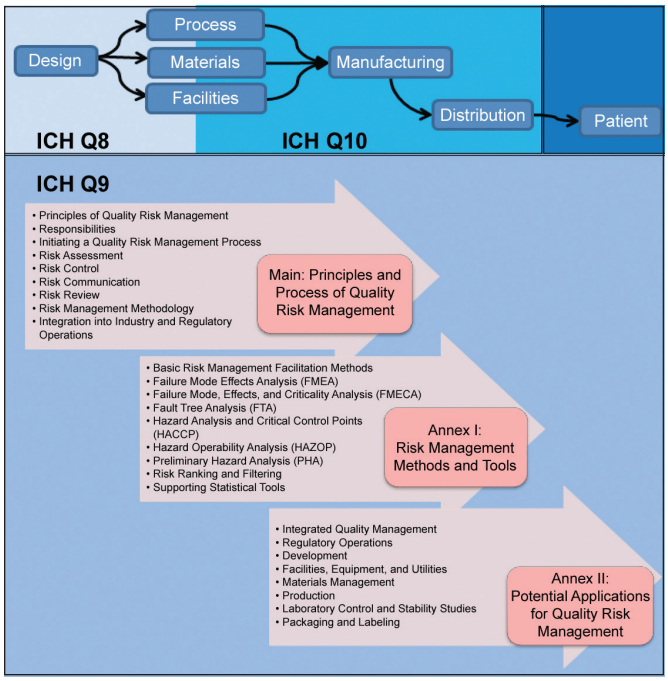


Figure 3. ICH Q9 guidance for risk management.

submissions have led to the Study Data Tabulation Model (SDTM) developed by the Clinical Interchange Standards Consortium (CDISC). The content of SDTM is typically exchanged by ASCII, HL7 v3 and SAS Transport files to the FDA.[17] Hence, the adverse events during pre-marketing also can be cataloged and analyzed electronically by the Sponsor and submitted to the FDA.

In manufacturing, process parameters are typically monitored using Programmable Logic Controllers (PLC) and Distributed Control Systems (DCS). ISPE's GAMP 5 provides guiding principles and practices on ensuring product quality. These plant floor control systems are usually developed and configured with ANSI/ISA-88 (S88) standard and IEC 61131. S88 provides the models, terminology, data structures, and guidelines for language, recipes, production records and unit states. Also, ISA-95 and IEC 62264 are both international standards for enterprise control system integration, which provide consistent terminology for communications,

No.	Risk Identification	Risk Description	Potential Risk Impact
1	Product Defects	Product defects have been an important source of medical product-associated injuries. In pharmaceuticals, product defects are usually a lack of potency and lack of purity of drugs.	Preventable Adverse Events
2	Medication or Device Error	Medication or device errors involve the incorrect administration of the prescribed product or incorrect operation or placement of a medical device. Errors also can involve the unintended substitution of the wrong product for the prescribed product. These errors are often a result of a sequence of errors within the health care system.	Preventable Adverse Events
3	Known Side Effects: 1. Avoidable 2. Unavoidable	When using a drug or medical device, a patient has the risk of potential reactions from the medical product. These known side effects usually have been identified and are indicated as possible risks in a product's labeling. Unavoidable known side effects are the source of the majority of injuries and deaths resulting from product use. Unavoidable known side effects are the price for the benefits of the medical product. Some known side effects are predictable and avoidable.	Preventable Adverse Events and/or death
4	Remaining Uncertainties	A degree of uncertainty always exists about both benefits and risks from medical products. Several types of uncertainties exist - unexpected side effects, long term effects, off label use effects, and unstudied populations.	Death and/or Unexpected Adverse Events

Table C. Categories of risk from medical products.[20]

information and operational models between enterprise and manufacturing systems. Manufacturers have been joining their internal disparate information systems, in order to provide real-time capabilities to effectively manage product defects through traceability of lots to raw materials, equipment utilized, personnel involved, and distribution points.[18]

Challenges for the Food and Drug Administration

In the US, the FDA conducts monitoring of the patient safety risks associated with medical products through an extensive premarketing review and a series of post marketing programs.[19] Sources of risk related to medical product have been traditionally identified in four categories: product defects; known side effects, both avoidable and unavoidable; medication or device errors, and remaining uncertainties are shown in Table C.[20]

The FDA relies heavily on the Healthcare Provider, Sponsor, and Patient to communicate events associated with developed, manufactured, prescribed, dispensed, and/or used medical products. The patient safety risk monitoring challenge for the FDA has been the fragmented data systems providing partial visibility of the numerous medical products. The FDA is currently focusing on various medical product safety initiatives with adverse events leading the roll as shown in Table D.

In 2009, the FDA entered 490,835 AEs in their Adverse Event Reporting System (AERS). The AERS is designated to support all post marketing safety surveillance for approved drug and therapeutic biologic products. Various obstacles are preventing the capture related to adverse events.[21] Such "near miss" data is instrumental in detecting causes leading to more serious and/or even catastrophic conditions. The FDA driven MedWatch program has improved the capability of post-marketing reporting with the Adverse Event Reporting System (AERS) and the use of Form 3500 (FDA-regulated drugs, biologics, medical devices), while the Vaccine Adverse Event Report System (VAERS) maintains the vaccine adverse event information. These systems are leveraged by both Patient and Healthcare Providers so that both the FDA and the Sponsor can take the required action to protect other patient populations in a timely manner.

No.	FDA 2010 Medical Product Safety Objectives
1	Increase the proportion of healthcare organizations that are linked in an integrated system that monitors and reports adverse events.
2	Increase the use of linked, automated systems to share information.
3	Increase the proportion of primary care providers, pharmacists, and other healthcare professionals who routinely review with their patients aged 65 years and older and patients with chronic illnesses or disabilities all new prescribed and over-the-counter medicines.
4	Increase the proportion of patients receiving information that meets guidelines for usefulness when their new prescriptions are dispensed.
5	Increase the proportion of patients who receive verbal counseling from prescribers and pharmacists on the appropriate use and potential risks of medications.
6	Increase the proportion of persons who donate blood, and in doing so ensure an adequate supply of safe blood.

Table D. Medical product safety objectives of FDA for 2010.

Standardizing Patient Safety Risk Management

Quality by Design (QbD) is envisioned as the Sponsor's next scientific game changer. Understanding how quantitatively the ranges of each process parameter correlates to the quality attributes of medical products will enhance the boundaries of development, i.e., the design space.

The Sponsors are refining their understanding of these relationships with a vision of greater manufacturing flexibility.[22-25] Case in point, multivariate predictive distribution using process parameters as inputs can help quantify the

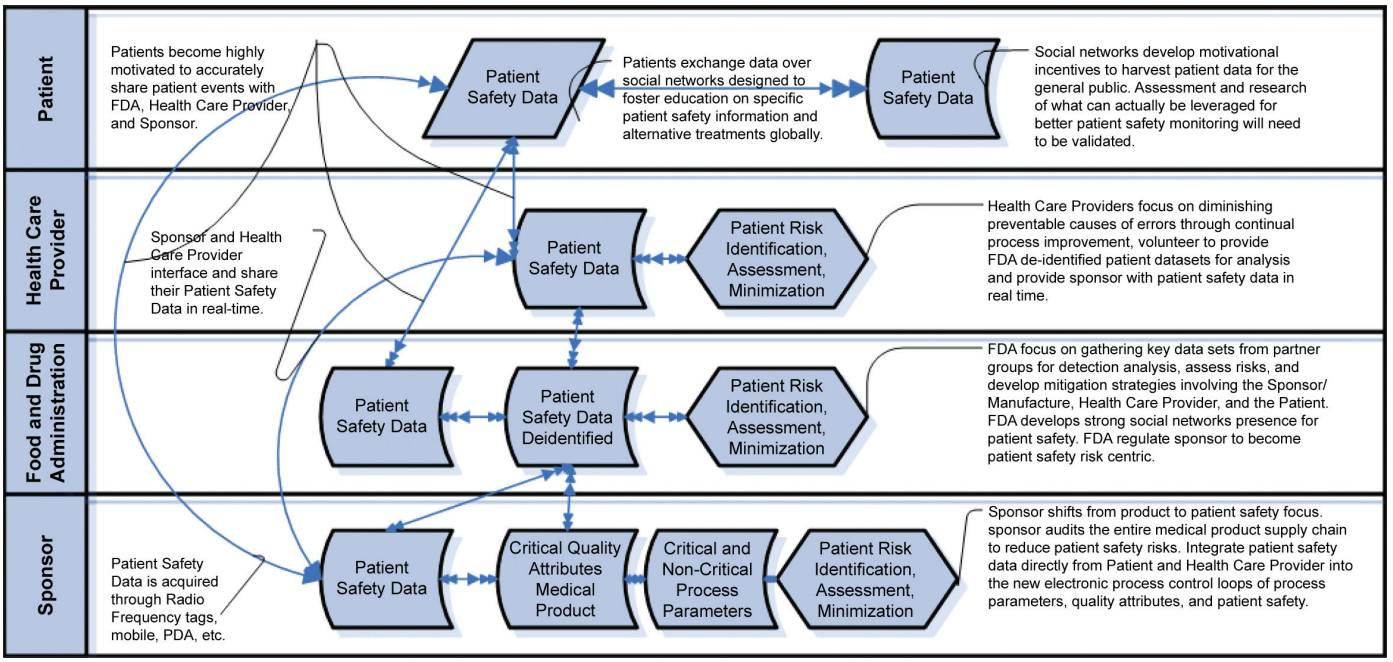


Figure 4. Patient safety risk management.

multiple quality responses so that the manufacturer has a broader band in which to manipulate their processes.[26,27]

In their next revolutionary leap, the Sponsor must expand the design space to incorporate the monitoring and correlating with actual patient effects and events in real time during both marketing phases. Such a tremendous enlargement of the design space will provide a safety process control model for patient safety awareness from product creation to treatment as depicted in Figure 4.

Much of the infrastructure is already work in progress at the stakeholder level, nevertheless, such a transformation will require the design build interface plan for secure real-time communication between Sponsor and their supply chain Healthcare Providers' information systems, including a consensus on vocabulary and data interchange standards on patient safety information.

Patient Safety Risk Management Audits

Much like the results of FDA inspections, the data points detected and collected from regulatory audits performed by the Sponsor at specific phases of the medical product supply chain provide insight on the performance of their internal and partner clinical studies, laboratories, and manufacturing. Not only is the compliance level of each Sponsor partner vis-à-vis the pertinent regulatory requirements gauged; but the retrieved audit data helps forecast events for future medical product development and manufacturing. As mentioned, the current focus must shift to patient safety risk management.

Various challenging questions confront the Sponsor organization when optimizing the yields of their regulatory audit efforts:

- What strategy and tactics to implement at the enterprise and regulatory levels?
- To what degree and how should resources be allocated horizontally and vertically across the different risk areas?
- Where and when in the supply chain should the emphasis be placed?
- What document content details should be emphasized and to what depth of verification?
- What methods should be used to execute and report the verifications?

Coarse Adjustment to Enterprise Risk Management

Before focusing the audit lens onto patient safety risk management, the coarse adjustment knob must be turned to sharpen the image of the entire enterprise risk management process. According to the Committee of Sponsoring Organizations of the Treadway Commission (COSO), enterprise risk management is a process, ongoing and flowing through an entity, applied in a strategy setting across the enterprise at every level and unit, designed to identify potential events that may affect the entity, and manage risk to be within its risk tolerance, to provide reasonable assurance regarding the achievement of entity objectives.[28]

The COSO framework for achieving the objectives of enterprise risk management is broken down into:

- **Strategic:** high level goals, aligned with and supporting enterprise's mission.
- **Operations:** effective and efficient use of its resources.
- **Reporting:** reliability of reporting in both financial and non-financial information.
- **Compliance:** compliance with the applicable laws and regulations.

An effective audit program will identify the targeted patient safety risk areas, but a step back to frame the big picture will ensure alignment and clarity of its objectives. Alignment is accomplished through periodic evaluations of audit plans against business objectives and risks, as well as a clear mission and role definition communicated throughout the organization.

To the enterprise, risk is the probability for loss, damage injury caused by an error, fraud, inefficiency, non compliance, or other type actions. The organization must perform an overall enterprise risk assessment to prioritize its auditing efforts and achieve a shared understanding among the various stakeholders. Annex II[1] of the ICH Q9 Quality Risk Management includes factors for consideration listed in Table E. Additional factors from the Healthcare Provider and the Patient also must be taken into consideration.

Fine Adjustment to Patient Safety Risk Management

Once enterprise risk management is aligned and focused, the Sponsor can adjust its sights onto the patient safety risk targets. Audits are not only a regulatory requirement, but they make business sense, and should be carefully planned in terms of effort and method to derive decision making information from the medical product supply chains.[29] Moreover, the audit costs compound quickly, hence, planning will allow for efficient patient safety risk reduction.

Recent technology, increasing partnering, additional regulatory guidance, and commercial economic pressures have

No.	Factors for Determining Frequency and Scope of Audits
1	Existing legal requirements
2	Overall compliance status and history of the company or facility
3	Robustness of a company's quality risk management activities
4	Complexity of the site
5	Complexity of the manufacturing process
6	Complexity of the product and its therapeutic significance
7	Number and significance of quality defects (e.g. recalls)
8	Results of previous audits/inspections
9	Major changes of building, equipment, processes, key personnel
10	Experience with manufacturing of a product (e.g. frequency, volume, number of batches)
11	Test results of official control laboratories

Table E. ICH Q9 factors for determining audit scope and frequencies.[16]

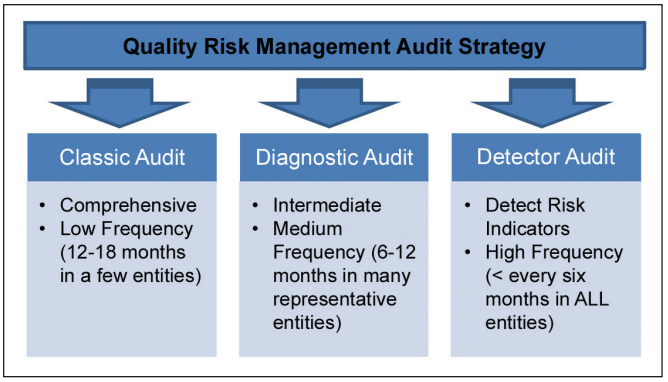


Figure 5. Three prong audit data collection, analysis, and detection strategy.

promoted risk management into the regulatory compliance limelight. Auditing expectations have leaped from traditional sampling of typical GxP risk areas and Corrective Action/Preventive Action plans to sophisticated approaches, partly real time monitoring in nature, combined with predictive analytics, continuous improvement, pattern assessments, and risk priority numbers. Combining the classic, diagnostic, and detector audit to balance cost and benefit efforts in risk management, results in a structured audit strategy using the right tools with the right timing as depicted in Figure 5.

To audit for patient safety risks of every medical product, at every step of each process at each location is unrealistic. Therefore, an up-to-date view of the patient safety risks for each entity according to geography, relevant processes, and medical product as shown in Figure 6 is more pragmatic. The Failure Mode and Effects Criticality Analysis Risk Priority Number (FMECA RPN) is an excellent quantitative method for establishing such prioritization. Sponsor groups are already engaging in such activities, but their center of attention is still on the risks of their medical products. They will need to extend their bandwidth to extract and assess the Healthcare Provider and Patient safety event data to gather indicators and/or other type of patient safety data to strengthen their own internal patient safety risk knowledge base. For example, some errors identified as preventable at the Healthcare Provider stage could possibly be redesigned by the Sponsor with a Poka-yoke or mistake proofing capabilities. Eventually, even real-time adjustments could be made to the manufacturing processes from event and effect data received from the patients.

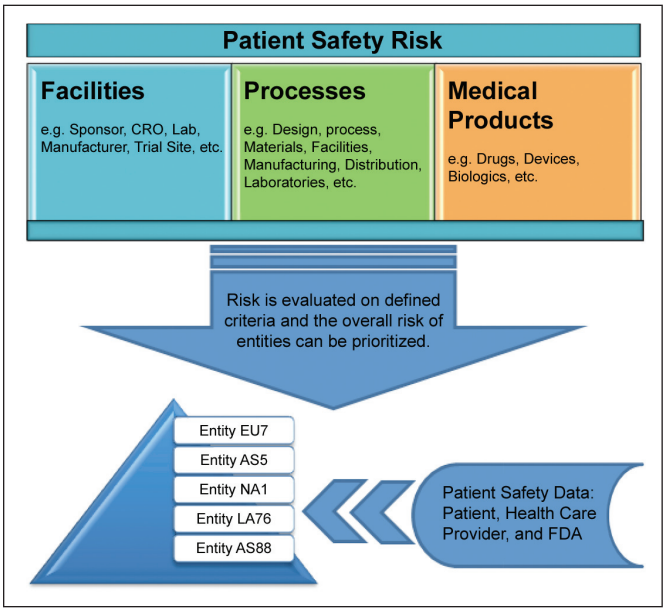


Figure 6. Entity patient safety risk prioritization.

Determining Patient Safety Risk Criticality of a Patient Safety Risk Event

Risk criticality is determined by the likelihood of a patient safety risk event occurring and the severity of its impact. Figure 6 illustrates an example of a tool used for assigning a patient safety risk criticality value of Extreme, High, Medium, and Low for a particular risk event.

Numerous variations for assessing risk criticality exist and it would be essential that a standard for severity of impact be developed and used for patient safety risk criticality across the medical product supply chain. MedWatch Form 3500 criteria could be revised slightly to a standard scale of outcome and effect capture. By means of a check box, the current form captures adverse events outcomes that are serious in nature such as death, life-threatening, hospitalization, etc.[30] Establishing a 10 point severity of impact scale would help standardize the approach and allow the risk managers to automatically integrate the data into both their risk criticality assessments and their Risk Priority Number assignment.

Let's consider an example of the patient safety risk event of informed consent failure, i.e., informed consent not being executed to the regulations at a specific investigating site (entity) for a study of 1,000 patients over two sites in two countries. Table F provides a number of different guides that the risk manager could use to evaluate risk likelihood for the particular event.[31] These can be description based, time or probability based. Such practical guidance leads to a consistent assessment of likelihood across the various entities by different risk managers. Otherwise, the risk management process will lose its equilibrium and efforts will not be distributed

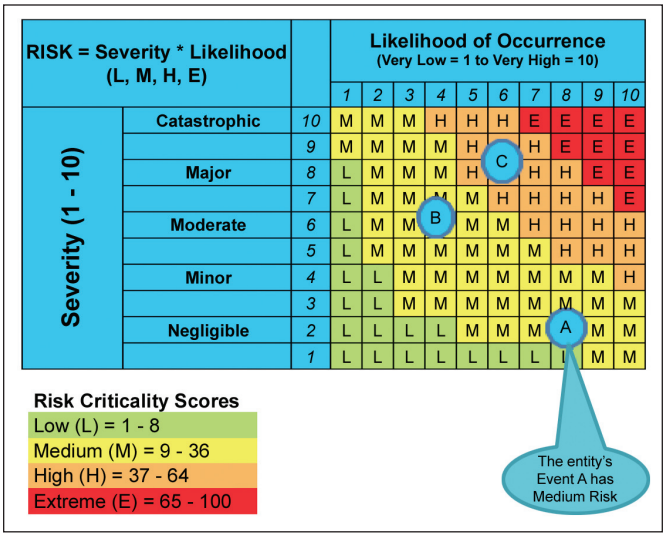


Figure 7. Patient safety risk criticality assessment.

Rating	Description	General Conditions	Time Based Conditions	Probability Conditions	Informed Consent Failure
1					
2	Rare	Will probably never happen/recur.	Not expected to occur for years.	< 0.1 %	Consent not necessary/ special case complies with regulations.
3					
4	Unlikely	Do not expect it to happen/recur, but it is possible it may do so.	Expected to occur at least annually.	0.1 - 1 %	Clearly defined and documented informed consent process with responsibilities identified by individuals/roles.
5					
6	Possible	May happen/recur occassionally.	Expected to occur at least monthly.	1 - 10 %	Unclear process i.e. not documented. Responsibilities of who does consent is not documented. Risks to patient/subject not documented. Unclear areas on informed consent form.
7					
8	Likely	Will probably happen/recur, but it is not a persisting issue.	Expected to occur at least weekly.	10 - 50%	Consent does not cover all aspects of the study/research. Inexperienced/ inappropriate staff delegated to informed consent process. No explanation of recruitment process. No identification of potential risks or hazards. Subject/Patient required to consent the same day.
9					
10	Almost Certain	Will undoubtedly happen/recur, possibly frequently.	Expected to occur at least daily.	> 50 %	Prior instances of poor consenting process, execution and procedures. Documented in 483s or other finding sources - internal audits.

Table F. Various examples for assigning likelihood score.

according to the appropriate priorities. Using Figure 7, the risk manager would assign a rating of "Negligible" or "2" as the informed consent failure risk severity to the safety of the patient. If the likelihood of the informed consent failure would be described as "8" per the "Informed Consent Failure" guidance example provided in Table F, then the patient safety risk criticality ranking would be Medium (M) with an overall score of 2 × 8 = 16.

Determining the Risk Priority Number (RPN)

Once criticality for a patient risk event has been determined, the next step is to establish its detectability as shown in Figure 8. Higher detection by controls and/or indicators will lower the detection score, i.e., a score of "1" is equal to almost certain that the event will be detected by some kind of key indicators to a score of "10" where the event cannot or will not be detected as shown in Table G. For the informed consent failure example, if in our informed consent activity is paper based, then the Sponsor cannot detect the event. The informed consent failure will not be detected so its detectability would be a ranked as "10." The overall RPN for the particular event would be equal to 16 × 10 or 160.

The various risk events RPNs are combined and analyzed by entity, by process, by product, entity type, stakeholder, etc. Analogous to process control systems with critical process parameters, alarms also should be associated with the Risk Priority Numbers to ensure that the priorities remain up to date. Improvements in detection also will help reduce the priorities of certain activities such as the more expensive classic audits. Such an RPN structure should not only be ap-

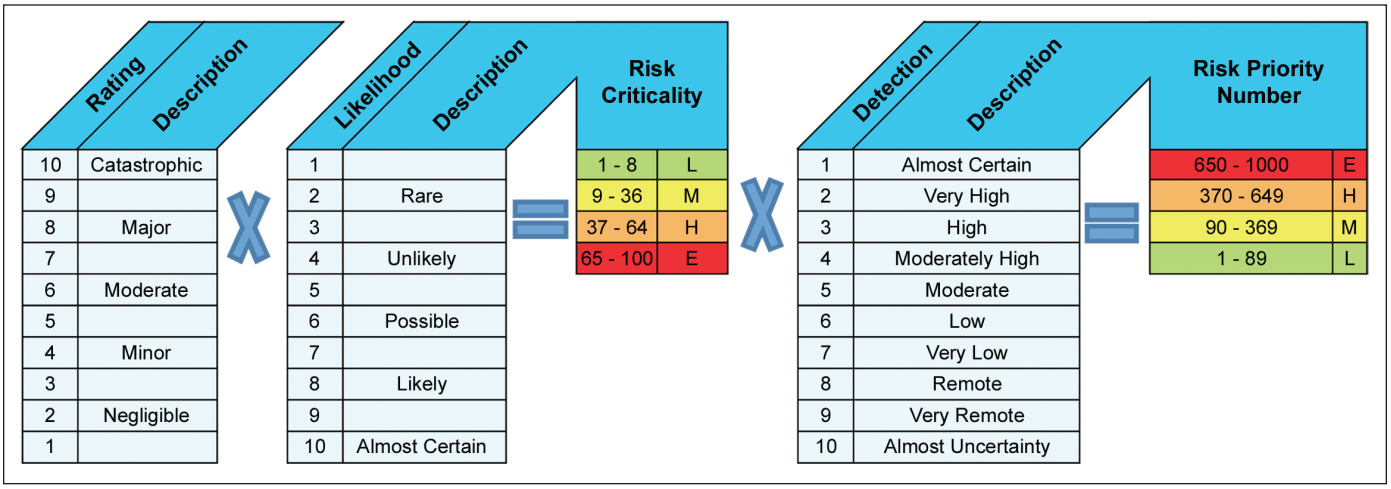


Figure 8. Patient safety risk priority number (FMECA RPN).

Rank	Detection	Likelihood of Detection by Indicators and Other Controls
1	Almost Certain	Controls will almost certainly detect a potential cause/mechanism and subsequent failure mode.
2	Very High	Very high chance the controls will detect a potential cause/mechanism and subsequent failure mode.
3	High	High chance the controls will detect a potential cause/mechanism and subsequent failure mode.
4	Moderately High	Moderately high chance the controls will detect a potential cause/mechanism and subsequent failure mode.
5	Moderate	Moderate chance the controls will detect a potential cause/mechanism and subsequent failure mode.
6	Low	Low chance the controls will detect a potential cause/mechanism and subsequent failure mode.
7	Very Low	Very low chance the controls will detect a potential cause/mechanism and subsequent failure mode.
8	Remote	Remote chance the controls will detect a potential cause/mechanism and subsequent failure mode.
9	Very Remote	Very remote chance the controls will detect a potential cause/mechanism and subsequent failure mode.
10	Absolute Uncertainty	Controls will not or cannot detect a potential cause/mechanism and subsequent failure mode.

Table G. Likelihood of detection ranking.

plied to the Sponsor, but extend to the Healthcare Provider and Patient.

Conclusion

With modern technology, the medical product stakeholder's information boundaries are slowly eroding and enabling a convergence on patient safety communication. The patient safety data will be harnessed effectively and the next steps will be to ensure consistency in risk management across the medical product supply chain. The Patient along with the FDA, Healthcare Provider, and Sponsor, each have a critical role in increasing the strength of patient safety information.

The following actions must materialize for a uniform Patient Safety Risk Management paradigm to take shape:

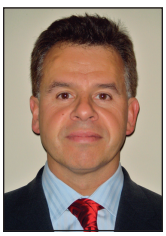
1. The patient must be motivated to report timely and accurate adverse event related to the use of their medical products.
2. The FDA must regulate the shift from product to patient centric for the Sponsor.
3. The Sponsor must motivate sharing of patient safety data inputs from both the patient and Healthcare Provider. To make it possible, the Healthcare Provider, and Sponsor must establish a standard for communication of patient safety information across their different types of information networks.
4. The sprawling social type networks must be harvested to create a customer driven model and drive more reliable patient safety communication.
5. The Sponsor should extend and leverage various types of strategic regulatory audits to monitor the reduction of patient safety risks from the development of their products through to their intended use.
6. A standard methodology should be mandated for the collection of patient safety data indicators and events so that patient safety risks are managed uniformly in terms of severity impact, likelihood, and detectability, potentially, using the Risk Priority Number as a basis for comparison.

References

1. McLoughlin, V., Millar, J., Mattke, S., Franca, M., Johnson M.P., Somekh, D., Bates, D., "Selecting Indicators for Patient Safety at the Health System Level in OECD Countries," *International Journal for Quality in Health Care,* Volume 18, Aug 2010, pp. 14-20.
2. Who Patient Safety Research, World Health Organization 2009.
3. Silverman, E., "You Can Report Side Effects to the FDA," *Pharmalot,* 2 April 2008.
4. Kohn, L.T., Corrigan, J.M., Donaldson, M.S., "To Err is Human – Building a Safer Health System," *Institute of Medicine,* Nov 1999.
5. www.medicalnewstoday, "Patients Safety Incidents at U.S. Hospitals Show No Decline, Cost 9$ Billion," 31 March 2010.
6. Wager, K.A., Lee, F.W., Glaser, J.P., "Managing Health Care Information Systems – A Practical Approach for Health Care Executives," John Wiley & Sons, 2005.
7. Leape, L., Berwick, D., "Five Years After To Err Is Human: What Have We Learned?" *Journal of the American Medical Association,* 18 May 2005.
8. "To Err Is Human – To Delay is Deadly," SafePatientProject.org, May 2009.
9. McGlynn, E.A., "Sic Challenges in Measuring the Quality of Health Care," Health Affairs, Vol. 16, Issue 3, 7-21, 1997.
10. AHRQ, "Patient Safety Indicators (PSI) Composite Measure," http://www.qualityindicators.ahrq.gov, 2006.
11. Naessens, J.M., Campbell, C.R., Berg, B., Williams, A.R., Culbertson, R., "Impact of Diagnosis-Timing Indicators on Measures of Safety, Comorbidity, and Case Mix Groupings from Administrative Data Sources," *Med Care,* Aug 2007 pp. 781-8.
12. SafePatientProjec.org, "Preventable Harm: California Fails to Follow Through With Patient Safety Laws," March 2010.
13. "Fake Drugs – Poison Pills," *Economist Business,* 4 September 2010.
14. Fisk, M.C., "Jurors Turned Against Companies in 2009 Product-Defect Cases," Bloomberg.com, 7 January 2010.
15. Shanley, A., "Data Access Still a Top Challenge," *Pharmaceutical Manufacturing,* July/August 2009.
16. "Guidance For Industry, Q9 Quality Risk Management," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), June 2006, ICH

17. "Introducing the CDISC Standards – New Efficiencies for Medical Research," CDISC, 2009.
18. Danese, J.E., Constantinou, D., "Pharmaceutical Manufacturers – Embracing Lean Six Sigma," *Pharmafocusasia*.
19. "Managing The Risks from Medical Product Use – Creating A risk Management Framework," Report to the FDA Commissioner From the Task Force on Risk Management. May 1999.
20. "Report to the FDA Commissioner From the Task Force on Risk Management," U.S. Department of Health and Human Services, FDA May 1999.
21. Dudzinski, D.M., Hebert, P., Foglia, M.B., Gallagher, T.H., "The Disclosure Dilemma – Large-Scale Adverse Events," Health Law, Ethics and Human Rights, *The New England Journal of Medicine,* Sept 2010.
22. Lionberger, R.A., Lee, S.L., Lee, L., Raw, A., Yu, L.X., "Quality by Design: Concepts for ANDAs," *AAPS Journal,* June 2008, pp. 268-276.
23. Bush, L., "Determining Critical Quality Attributes From the Foundation for QbD Implementation," *Biopharm,* Aug 12, 2008.
24. Anurag, S.R., Winkle, H., "Quality by Design for biopharmaceutical," *Nature Biotechnology,* 27, 2009, pp. 26-34.
25. Schmidt, B., "Implementing Quality by Design: Are You Ready, or Not?" Pharmaqbd.com, 4 Aug 2010.
26. Peterson, J.J., "What your ICH Q8 Design Space Needs: A Multivariate Predictive Distribution," Pharma Manufacturing.com, 2010, Article 097.
27. Bush, L., "Determining Critical Quality Attributes Forms the Foundation for QbD Implementation," *BioPharm Bulletin,* 12 Aug 2008.
28. Steinberg, R.M., Martens, F.J., "Enterprise Risk Management Framework," COSO – The Committee of Sponsoring Organizations of the Treadway Commission, 2004
29. "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance," ICH, April 1996, p. 36.
30. https://www.accessdata.fda.gov/scripts/medwatch/
31. National Patient Safety Agency, "A Risk Matrix for Risk Managers," January 2008.

About the Author



Mark Cupryk is a principal partner of Biovalorem, a regulatory compliance consulting firm, which specializes in lean six sigma, project management, and GxP audits. Cupryk has more than 20 years of experience working with multinationals, small/midsize businesses, academia, not-for-profit in technology related compliance projects in clinical, manufacturing, and healthcare. He is a chemical engineer with a Master's degree in business administration and a Master's degree in project management. He is a certified Project Management Professional (PMP) and Master Black Belt in Six Sigma. He can be contacted by email: mark.cupryk@biovalorem.com.

Biovalorem, 11732 Admirals Ln., Indianapolis, Indiana 46236, USA.