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A Risk Modeling Framework for the Pharmaceutical Industry

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ABSTRACT

This conceptual paper seeks to advance a theoretical discussion on risk modeling and how it is used within the context of business process modeling. It discusses developments in risk modeling and then shows how they have been applied to the USA pharmaceutical industry. The pharmaceutical industry is a particularly interesting example in that it is bound on one side by stringent USA government mandates, and on the other by a risk adverse consumer population. A third aspect, the expanding cost structure of drug production and compliance, adds to the complexity of the problem. The discussion of risk in this paper applies mainly to regulated industries, and may be less applicable to more unregulated industry sectors. The important lesson for researchers is that a risk framework can play a significant part in business process modeling. The format for this paradigm may very well resemble a process repository, similar to those found in knowledge management systems.

INDUSTRIAL STRENGTH SYSTEMS

One of the principal tasks of business process modeling (BPM) is to develop what Booch broadly calls "industrial strength" systems (Booch, 1994). In complex environments one of the fundamental features of an industrial strength system is that it can manage the forces of internal complexity and external variability throughout the life cycle of the system. To build industrial strength systems researchers and practitioners often turn to the 'best practices' of industry leaders. These best practices are accepted standards which have usually been developed over time and have proven themselves through benchmarking and quality assurance tests. Yet risk analysis has often been an unexamined premise that is fundamental to the development of best practices.

When a technical system fails, a reasonable conclusion is that the system was not stable enough to survive the internal and external forces that caused the system to degrade (Scott, 2000). The failure may be ascribed to an incomplete or faulty process modeling technique, weak implementation, or similar problems. Though when a system fails and a disaster occurs or is narrowly avoided, the business and technical community also belatedly conclude that not enough attention was paid to possibilities outside the predicted range of events. In these instances the industry best practices and other benchmarks are found to be lacking. Based on this failure scenario, the business process model can be modified and a different set of best practices can evolve. The designer's basic objective would be to further minimize and constrain unnecessary risk.

This paper's focus will be to highlight steps taken by the pharmaceutical industry to incorporate risk modeling in their system development. It is important to note that while the U.S. pharmaceutical industry's experience is well documented, these findings may not apply to other similar industrial sectors that are not so rigorously regulated. The pharmaceutical industry in some senses may be considered unique in that it has a fiducial responsibility in management and production functions.

USA PHARMACEUTICAL INDUSTRY

The USA pharmaceutical industry is an excellent example of a business sector that is incorporating risk planning into their BPM. It is particularly useful to study this industry because it faces the complex tasks of developing, testing and manufacturing of drugs, has a rigorous oversight agency in the U.S. Food and Drug Administration (FDA), and serves a marketplace with an exceptionally low tolerance for variability in pharmaceutical products (FDA, 2003a; FDA, 2004).

Yet it is common knowledge that the pharmaceutical industry, like many mature industries, is built around traditional manufacturing processes and legacy information systems. Each is based on rigid work flow patterns that have been optimized for efficiency and cost reductions, rather than for data integration and compliance.

Attaining regulatory compliance within this environment is significant in that the following challenges have to be addressed:

- Isolated work silos exist that have critical information trapped within the manufacturing processes.
- Data redundancies with multiple overlapping reports sometimes confuse and obfuscate further analysis.
- Data communications between processes are missing, and therefore there is no centralized control.
- Process controls are often localized and do not provide corporate-wide problem remediation.
- Fiscal and operational optimization has a higher priority than the need for compliance.
- Attempts at introducing Enterprise Resource Planning (ERP) systems are often a lengthy, time consuming, and expensive undertaking, and results may only partially address the problem of compliance.

In order to meet these issues, the FDA has adopted a new risk-based paradigm for addressing its role as an oversight agency for the pharmaceutical industry. FDA guidelines state that the agency must inspect domestic drug manufacturing establishments at least once every 2 years. But internal reviews show that the agency no longer has the resources to meet this statutory requirement. Simply put, the FDA workload of examining registered human drug establishments keeps increasing, while the number of FDA human drug inspections remains static, causing an increasing backlog. Therefore beginning in fiscal year 2005, as part of the Agency's mandate, the FDA is piloting a new initiative, the Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century (FDA, 2004).

The noteworthy points from the 2004 FDA mandates are their focus on working through these challenges, using a risk resolving methodology as the metric for prioritizing reporting and compliance tasks. "The model is based on a risk-ranking and filtering method that is well-recognized, objective, and rigorously systematic. This approach should help the Agency make the best use of its limited surveillance and enforcement resources while maximizing the impact of those resources on the public health" (FDA, 2004). In essence, the functionality for this model may very well resemble a process management repository, where definitions, procedures, and reports are stored and control data is analyzed (FDA, 2003b; Maier, 2004).

FDA Initiative

Clearly, regulatory oversight is a critical component for ensuring pharmaceutical quality and efficacy. During the development and production life cycle of human drugs, vaccines, and other biological products, the FDA acts as the supervisory agency, assuring that industry best practices are followed (GAMP, 2001). Furthermore, the FDA wants oversight to guarantee that industry approved steps are followed for identifying and isolating problems with such issues as contaminants and failed processes. Additional areas of compliance ensure that approved Corrective And Preventive Actions (CAPA) are taken.

In other words, the FDA is using the concept of risk prevention to focus and drive these initiatives. This leads directly to developing and building verifiable processes that identify, control, and reduce risks in the product or services. In brief, the FDA has mandated that the pharmaceutical industry follows the risk methodology outlined below. Each step is verifiable, in that critical data can be captured and reported in a timely fashion to the agency (FDA, 2004).

- The first action of an operational risk based system is to identify a hazard, nonconformity, or source of variability.
- The next step is to prioritize the seriousness of the risk using FDA and industry standards.
- The system then triggers an alert which serves as a marker for remediation.
- In parallel, the integrated system triggers a system-wide alert and begins the risk log.
- The system then searches for the hazard, as well as the root cause(s) of the problem.

- The corrective mechanisms within the system isolate the threat from the process, and address the root cause(s).
- The methodology is iterative, continually searching for and removing remaining residual risks.

These steps provide verifiable oversight and control, without unnecessary complexity. As a minimum the system continuously monitors key processes, highlighting critical measurement of variability. The FDA then uses the risk methodology to filter and prioritize this data and thereby determine the frequency and severity of a risk for different production practices and design changes.

This is accomplished by applying risk management statistics to the oversight and control systems data. The analyzed results in combination with the industries best business practices provide an ongoing evaluation of the severity of each risk against the likelihood of its occurrence. The FDA can then compare this information with its industry risk guidelines and its corporate performance history.

RISK MANAGEMENT

An essential role for business management is to build systems that enhance competitive advantage. While there are different approaches to achieving this, it is fair to say that management seeks on the one had efficiency and effectiveness in its business processes, while on the other hand it looks to minimize and control risk. One of the most important features in total risk management is that it evaluates the changing context within the business process model. The FDA and the pharmaceutical industry have an overlapping functionality. Each knows that efficient and effective processes create a strong environment conducive to best business practices. Yet the FDA does not wish to micro-manage the pharmaceutical industry but rather to monitor and evaluate those identifiable processes that are the foci for risk.

At each phase of the system life cycle, the FDA and the pharmaceutical industry are on the same page, reviewing the context, identifying and prioritizing the threat level of potential hazardous forces within the environment. It is a shared analysis, looking at the same data, though not necessarily in the same time frame. A pharmaceutical company would be monitoring and reviewing critical data in real time, and less critical data in a longer timeframe. The FDA function is more procedural, in that it wants to assure that the pharmaceutical companies have the mechanisms in place to accomplish their tasks in the established timeframe.

Therefore the FDA maintains its oversight of the procedures and evaluative processes, while the pharmaceutical companies are focusing on building and managing iterative systems that search for those factors which may raise the risk level within the system. These factors include the direct causes of the particular threat, as well as the indirect and secondary causes. Following the identification of the hazard, there is a determination of its probability of occurrence as well as the potential damage. This is standard decision making theory where risk is the probability of occurrence of loss multiplied by its respective magnitude. Risk management then uses FDA approved best business practices to establish procedures for preventive or corrective actions. This approach is particularly valuable in an environment where multiple, seemingly negligible risks have the combined potential to cause harm.

These factors can be summarized in the following formulas. The first deals with risk estimation, the mapping of the probability of the event against the severity of harm. The basic formulation for risk estimation is the probability (P) of the identified event evaluated by its consequence (C):

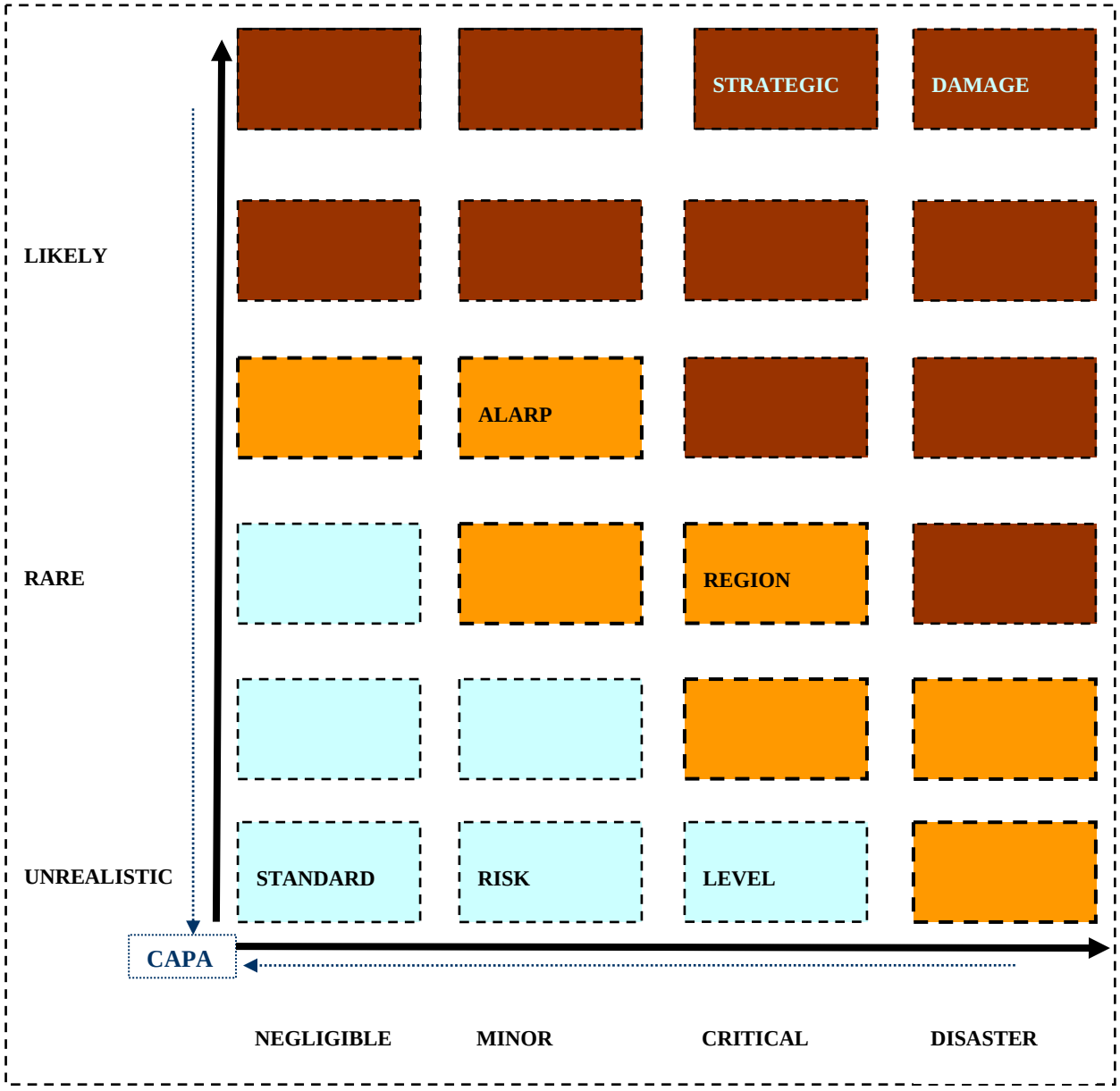
$$R = \{P, C\}$$

Once the initial risk level has been evaluated, then decisions can be made on the FDA acceptance level associated with the hazard. This risk acceptance level would take into consideration any corrective and preventative actions (CAPA) which would act as mitigating forces. CAPA would act to reduce the probability of occurrence as well as to limit and control the overall damage. Therefore in the next formula corrective and preventative actions (CAPA) are introduced to the function.

$$R = \{P, C, CAPA\}$$

This formula is then fine-tuned by actual design and production experiences as well as industry best practice standards. A risk matrix is a useful tool for conceptualizing this approach (Figure 1). The vertical axis shows the probability of an event occurring, while the horizontal axis shows levels of severity. The vertical axis displays a range of probabilities from rare to frequent, while the horizontal axis has multiple outcomes from negligible to catastrophic. In this matrix, each hazard entity is located within a specific X,Y region, ranging from standard acceptable risk level, "As Low as Reasonably Practical" (ALARP), to strategic damage. The traditional matrix has been expanded to show the effect of CAPA procedures and protocols which can drive down and contain the potential hazards. This mitigating effect is indicated by the dotted line pushing back the probability and magnitude of the threat. Lastly surrounding each of the entities is a dotted black border to indicate a series of alarms, stored procedures and methods aimed at containing a particular hazard from escalating into a significant threat.

Figure 1: Risk Matrix.



Risk Modeling in Pharmaceutical Manufacturing

The stated goals of the pharmaceutical industry are to manufacture products with the highest quality, safety and efficacy, at the lowest responsible cost. In order to achieve these goals the industry has to focus on process design in manufacturing, supply chain management, and overall system security. Over time, hazards and variability have been reduced, and manufactured products have achieved a very safe tolerance level. Much of this has been accomplished using traditional design methodologies that focus on building systems that meet fixed specifications. These improvements come from best practices and regulatory guidelines that address problems with quality, variability in processes, time induced degradations, and the like.

So in theory "good designs do not fail", because in part the system specifications are often based on some risk analysis. Manufacturing systems take into consideration the mean time between failure of components, and frequently sample production runs for quality. These are unstated acknowledgements of production risks (de Neufville, 2004).

Even without the existence of this new FDA risk mandate, corporations in the pharmaceutical industry would have eventually realized the advantages of this methodology in providing quality performance, as well as intelligent management of compliance. Both must be accomplished cost effectively with minimal expenditure of resources. Risk methodology provides additional tools to accomplish these objectives.
In fact BPM and best practices are strengthened by the formal acknowledgement of risk, and procedures for CAPA mitigation. These can act as an overall catalyst for the elimination of system stoppages and failures on one hand, and on the other be the basis for cost effective management and production. In this way managers can guarantee system and product integrity, and provide compliance in real time reports. This is the needed assurance that companies are meeting both their internal objectives as well as the necessary regulatory inspection standards for pharmaceutical products.

Yet the question remains as to how BPM design methodology can best incorporate risk management. In complex organizations such as those found in the pharmaceutical industry, there is also the practical question of how to transmit, integrate and manage best practices and compliance reporting. This is taken up in the next sector which discusses the concept of a BPM/process repository. This may very well serve as part of the organizational "intelligence", assuring that the best practices are actively taken up.

PROCESS MANAGEMENT REPOSITORY

So far the discussion has focused on the concept of risk management through best practices. Yet the strength of risk management is its potential for straight forward implementation within the corporate structure. One of the newer BPM approaches is the development of a process management repository that employs risk management functions.

A process management repository would contain data and methods which underpin best practices, risk management and compliance with the FDA. The Enterprise Risk Management (ERM) framework described by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) and those of IT Governance Institute's (ITGI) COBIT 4.0 methodology partially outline this approach. With the ERM framework, corporations are building a broad enterprise-wide system of internal controls and management practices. The ITGI's framework is also broad but more focused on developing a roadmap for IT best practices. In fact part of the ITGI best practices comes from the Enterprise Risk Management (ERM) framework. The overall result is that both the ERM and COBIT frameworks address building an overall philosophy, as well as infrastructure to manage both risk and performance.

These functional aspects of ERM and COBIT can be implemented using knowledge management systems, and in particular its process management repository (PMR). This implementation would use such tools as data dictionaries describing risk classes, repositories for storing critical compliance information, best practices, CAPA methods/procedures, and performance measurements (Tiwana, 2000). Using the same logic, a PMR could very well be the basis for a future FDA infrastructure focusing on the immediate need for oversight and the reduction of risk. This infrastructure would actively manage best practice and verifiable compliance. Therefore a critical element in moving to the FDA model, or to any risk centered model, is the successful conceptualizing and implementation of a process repository (Alavi, 2001).

Some of the characteristics of the repository for the pharmaceutical industry could be:

- FDA regulations
- Corporate policies and procedures
- Corporate environment for risk management with supporting surveys
- Industry best practice mandates with supporting evidence
- Test plans with test outcomes
- Business process flows, theoretical and actual
- Risk libraries with stored CAPA plans and self activated procedures

- Control libraries documenting control history
- Evidence for compliance in a transparent electronic format

This is spelled out in greater detail in Table 1. The process repository outlined in this table becomes part of the overall knowledge management system that meets the compliance mandate of the FDA. Its functionality permits on one hand the codifying and storing of best practices and critical data. On the other hand it provides active management of risk accounting and fault management (Scott, 2002). It is direct and focused for FDA oversight, and provides the foundation for further steps as the FDA matures and adopts specifications similar to ERM and COBIT.

Table 1: Process Repository.

Repository Management	**Risk Component**
Regulatory database	Data repository of regulatory standards and critical measurements
Best Practice database	Industry standard procedures
Compensatory Services	CAPA programs and procedures with triggers
Accounting Management	
Mapping of processes	Detailed description of processes and risks
Logistic tracking	Tracking of resources, products, processes
Data comparison	Analysis of critical measurements and variability
Change tracking	Monitoring change in the process
Design optimization	Planning for performance upgrades
Audit	Audit trail showing data creation, modification, deletion
Plug and play configuration	Incorporating new systems
Fault Management	
Alarm notification	Alerting staff and control hardware of faults
Alarm correction	Switching, and isolating supplies, processes and products
Disaster recovery	Isolating and recovering from disasters; logging activities, switching over to redundant systems
Remote process reconfiguration	Modifying process using CAPA
Performance Management	
Capacity planning	Tracking production growth
Event scheduling	Balancing production loads of scheduled processes
Process analysis	Analyzing for errors and faults, using best practices
Test monitoring	Testing samples for quality and performance
Trouble ticketing	Resolving known problems and replacing defects
Information Management	
Data backup	Securing data and configuration information
Monitoring and testing control mechanisms	Checking system controls with test data
Creating transparency for internal usage and for Regulatory Agency	Shared protocols for transferring information internally and externally
Developing dashboards to quantify risks	Straightforward visual metering of risk and performance levels
Firewall filtering services	Screening the information repository and monitoring against foreign activity

CONCLUSION

Pharmaceutical companies are complex organizations that best respond to pragmatic, simple approaches to risk management—ideally through a single integrated system that controls all risks. Best practices and compliance mandates dictate that these organizations leverage their multiple systems through integration and centralized process management.

Information technology plays a critical role in linking and controlling disparate systems in a transparent fashion. Furthermore, IT analytics can handle the necessary risk analysis, mediation and compliance to meet the industry mandate.

There are many lessons that can be learned from the pharmaceutical industry and the FDA's adoption of a risk methodology. The first is that risk analysis is going to play an ever greater role in meeting compliance standards of regulatory agencies. The logical outcome is that risk methodologies will assume a more active part in process modeling.

At the center of these systems will be process repositories, which may very well have a similar look, feel and functionality to the process repository chart outlined earlier. Much more work needs to be done to conceptualize the detailed functionalities of different process repositories and to evaluate which approach best fits within the organizational structure of the industry. This includes the organizational behavior framework and institutional "intelligence".

From a very practical and focused perspective, it will be the role of researchers to evaluate and judge the success of compliance through risk modeling in the pharmaceutical industry. The resulting data will show the strengths and weaknesses of the initial FDA approach.

A broader question about risk management is whether other industrial sectors have enough similar attributes to the pharmaceutical industry to make risk management an important research tool. While the initial answer may be no, increasingly more industrial sectors are facing similar constraints, such as more stringent government oversight and risk adverse consumers, and may find it advantageous to incorporate risk management in their planning methodologies. For instance sectors as diverse as financial services, the defense industries and automotive industries may well become candidates for risk management techniques and process management repositories in the near future. Yet other industries may simply improve their best practices by more formally incorporating the concepts found in risk management.

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