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Pharmaceutical Risk Control Systems

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ABSTRACT

This paper outlines an initial investigation of the bio-pharmaceutical industry (BPI) and the steps it is taking to meet the new FDA risk mandate. It reviews the industry's' current strategy of improving its quality management systems that are central to achieving best practices within its operations. In addition the paper also reviews the strategy for upgrading to the next generation manufacturing execution systems which will control the enterprise facilities through full data integration and actionable intelligence.

U.S. PHARMACEUTICAL INDUSTRY

The U.S. life science industry is a business sector with high visibility which faces the significant task of developing, testing and manufacturing of pharmaceuticals. Within the complex environments in which bio-pharmaceuticals are developed, there is a strong need for IS systems that monitor, control and manage the production processes. These industrial strength systems (Booch, 1994) can drive each of the steps within the product life cycle and are critical for guaranteeing that quality standards are met. The internal standards are set through quality assurance techniques developed from 'best practices,' while the external standards are set by the U.S. Food and Drug Administration (FDA).

At the basis for FDA endorsement of industrial practices is the knowledge that system developers use standards that have been developed over time and have proven themselves through benchmarking and production experience (de Neufville, 2004). Now the FDA has added to this traditional approach an additional criterion -- a risk analysis methodology (FDA, 2004). Risk analysis has always been an informal part of monitoring and controlling the production life cycle, as well as a part of business process modeling, quality management, and continuous improvement. In fact business process modeling and best practices are strengthened by the formal acknowledgement of risk, and procedures for corrective and preventative actions (CAPA).

This paper outlines an initial investigation of the bio-pharmaceutical industry (BPI) and the steps it is taking to meet the new FDA risk mandate. It is based on a review of pharmaceutical systems and discussions with technical staff at a large BP company about the role of information technology and system development. The outcome is a review of various IT systems and BPI plans for future development to meet this new risk criteria. This research phase will serve as the basis for developing a more formal research proposal to study in-depth changes in the BP industry.

U.S. FDA and RISK METHODOLOGY

The FDA's task is to apply rigorous oversight to the BPI to ensure the high standards, efficacy, and safety that the public demands. Throughout the research, development and manufacturing life cycle of drugs, vaccines, and other biological products, the FDA role is that of principal supervisory agency, assuring that industry best practices are followed (GAMP, 2001). In addition, the FDA uses its oversight to guarantee that such issues as problems with contaminants and failed processes are identified and isolated. Following compliance guidelines, the FDA tracks and confirms that approved corrective and preventive actions (CAPA) are implemented. This results in an exceptionally low tolerance for variability or deviation in quality pharmaceutical products (FDA, 2003a; FDA, 2004).

In order to meet its mandate, the FDA has chosen a new risk-based paradigm for achieving its objectives as the principal oversight agency for the U.S. pharmaceutical industry. The rationale for this new risk model is the fact that its own internal guidelines state that the agency must follow a 2 year cycle in inspecting domestic BP facilities. Yet, its own internal review board has determined that the agency's lack of staff, funds, and other resources prevent it from meeting its statutory responsibilities. The number of registered BP research and production sites keeps increasing, while the number of FDA visits and inspections have not kept up with the demand. This backlog is well established and has forced the FDA to consider alternative approaches. Therefore in 2005 the Agency began piloting its risk methodology, outlined in part by the Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century (FDA, 2004).

In essence, the risk resolving methodology is the metric for managing, controlling and 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).
Risk management has become one the FDA's principal tools in identifying, controlling, and reducing risks in pharmaceutical products and services. Each of the steps in the FDA's methodology is objective and verifiable, in that necessary critical data can be defined, captured and key performance indicators reported to the agency in a timely fashion (FDA, 2004).

- Management pre-defines and identifies hazards, nonconformities, or sources of variability in the working environment. It then prioritizes the seriousness of the potential risk using FDA and industry standards.
- The monitoring system triggers an operational alert when the pre-defined boundaries are exceeded. This serves as a marker for remediation.
- In parallel, the integrated enterprise system triggers a system-wide alert and begins the risk log. This is necessary because the problem may affect a range of processes from raw materials to finished product.
- 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 until the operation conforms to the established industry standards.

This methodology is straightforward, providing verifiable oversight throughout the phases of hazard definition, monitoring key performance indicators and system remediation (ICH, 2005). The FDA then has the ability to use this feedback from the BPI to update its risk library concerning the frequency and severity of risk hazards for different production practices and design changes. Therefore both the BPI and the FDA have additional tools for capturing and controlling critical measurement of variability (FDA, 21CFR 820).

In addition the FDA applies a comprehensive set of risk management statistics to the oversight and control data it evaluates. This information, combined with the BPI's best business practices, permits an ongoing re-evaluation and reassessment of its working library of hazards (in terms of severity of each risk and the probability of occurrence). The FDA can build a corporate performance history and then schedule site visits and evaluations focusing on those key risk indicators (ICH, 2007).

In the new FDA paradigm, BP companies are accountable for the success or failure of data integration and CAPA activities (FDA, 1999). For instance, if the supply chain system does not trigger an enterprise alert about a contamination failure, then this problem is both a production breakdown, as well as a failure in system integration and intelligence. This situation when analyzed from a risk perspective shows that the system did not have the necessary level of data integration and CAPA procedures to meet the internal quality assurance standard and the external FDA risk review (Scott, 2002).

This example shows the close relationship between risk and data integration in older legacy control systems. The pharmaceutical industry, like many older manufacturing environments, uses traditional production processes and has legacy information systems. The work flow has been optimized for straightforward production and cost reductions, rather than for transparent information delivery and compliance. Furthermore, even though certain BP companies have begun to incorporate enterprise systems, their level of sophistication is such that it does not provide automated actionable intelligence or integrated CAPA functionality (Alavi, 2001).

Therefore a BP corporation has to address the following IT challenges to attain regulatory compliance:

- Non-integrated production silos that trap critical information within their manufacturing processes.
- Redundant and conflicting data that obfuscates analysis.
- Incomplete CAPA communications and control.
- Inability of process controls to trigger enterprise-wide problem remediation.
- Legacy systems that inhibit compliance with the new mandate.

Additional factors working against compliance include the need to invest significant capital, time and manpower to change over to the new system.

LEGACY SYSTEMS

The BPI's legacy sub-systems, developed for specific functional activities, lack complete connectivity with other enterprise systems. This should not be much of a surprise since these sub-systems were developed for specialized isolated tasks at a time when communication protocol standards were lacking and necessary hardware and software were deemed too expensive.

But the situation is different today with the FDA, as well as BPI's management, calling for integrated systems that work transparently. BP companies now face tactical and strategic choices on how to achieve this integration, since a wrong or even poor choice may over the long term negatively impact the corporate mission and FDA compliance. For instance, many large BP corporations have the following systems for their processes:

Table 1: BPI Vendor Systems.

Functions	Vendor Systems
Document Management	GxPharma
Laboratory and Production Maintenance	Maximo
Quality Assurance Management: Investigations & Laboratory Testing	Trackwise
Laboratory Information Reporting	Multiple LIMS Systems
Process Controls & Management	Multiple Process Maintenance Systems
Customer Complaints and Product Quarantines & Recalls	Trackwise
Training	ISOTrain
Change Control/Management	Trackwise
Internal and Regulatory Reporting	Trackwise

Table 1 lists the functions commonly found in large BP corporations and some of the most popular vendors of those systems. The first thing that is evident in the table is that there are multiple vendor systems. Yet in a general survey of the industry, Trackwise (TW) is one of the dominant players.

Table 2: SAP R/3.

SAP Enterprise Sub Systems
Supply Chain Management System (SCMS)
Supplier Relationship Management (SRM)
Customer Relationship Management (CRM)
Materials Management (MM)
Quality Management (QM)
Corrective and Preventive Actions (QM-CAPA)
Laboratory Information Management System (LIMS) –
Advanced Planner and Optimizer (APO)
Plant Maintenance (PM)
Environmental Health & Product Safety (EH&S)

Table 2 shows an alternative system design whose modules are being evaluated or currently installed by many large BP companies. It is one based on enterprise integration using the SAP R/3 system. These two tables represent the choices faced by large BP corporations: to either upgrade their current legacy systems or move to a new enterprise platform. In other words, the question is whether the best, most cost effective and straightforward path is to upgrade their legacy software to newer versions with communication services; or choose to move to a comprehensive enterprise system whose strong point is current and future data integration.

Part of the answer and certainly one of the criteria in any evaluation is the ability of an enterprise system to achieve electronic enforcement of processes, where the manufacturing system executes established business rules to manage, control and enforce each step of the development and manufacturing process. These newer manufacturing execution systems (MES) like SAP QM and 2nd generation TW are replacing legacy software in providing the necessary integration fabric to meet quality production and the FDA mandate. These are in fact the first generation of MES that begin to offer some automated electronic enforcement and intelligent CAPA responses (FDA, 21CFR 820), as well as more integrated supply chain management. Their reporting and control systems can also form the basis for documenting and demonstrating FDA compliance (FDA, 2003b).

Similarly, this type of system would ensure that corporate standard operating procedures (SOPs) and best practices are followed using FDA guidelines. When a rule is not followed, or data readings are missing or exceeding specifications, the system triggers an alarm, alerting appropriate personnel and recording the event and automatically implementing CAPA responses to contain and resolve the problem. In this manner the system documents the workflow, tracking key performance indicators, and building an audit trail for FDA reporting. Part of this audit trail consists of tracking production and drilling down to data by product line, specific batches, serial number and ingredients, irrespective of data sub system or platform. The audit trail meets FDA guidelines by reporting the hazard, CAPA activity timeframe, and the outcome in reducing or eliminating the threat.

MANUFACTURING EXECUTION SYSTEMS

Many BP companies are currently using a combination of a legacy system with SAP R/3 components. (See Tables 1 and 2.) The critical question facing the BPI is whether they upgrade their current legacy systems or take the step of switching to a SAP enterprise system. This paper reviews the problem comparing two systems which have MES features: 2nd generation Trackwise (TW), which is a multi-functioning quality management (QM) system and its competitor QM (CAPA) from SAP R/3.

It is important to understand that 1st generation TW version 6.0 is being used in many large BP corporations, which means that upgrading to 2nd generation TW is a much easier step than switching to SAP. The TW 2004 version 6.0 has as its main module quality management (QM), with additional modules for governance risk and compliance, change control, environmental health / safety, action tracking / reporting, IT integration and other support applications. It has customers among the largest in the field of life sciences, and is considered one of the premier

products in the industry. In this investigation of a large BP corporation it was found that TW was used in four of the major functional areas mentioned. Most users interviewed were impressed with TW's ability to highlight manufacturing deviations and trap problems. TW's QM sub-system has the capability to capture a variance in a given standard or production process, call a system wide alert and place a system wide injunction on all related processes, while maintaining supervision until a successful outcome is reached. Therefore TW has been used for a range of services from nonconformance and customer complaints to supplier quality issues, internal / FDA external audits and preventive maintenance.

These are noteworthy features, though they do not meet the future criteria of automatic execution of MES activities. The standard that BP corporations are aiming for in their operations is full, complete and automatic electronic enforcement, where the QM system can execute a series of risk management activities, rather than just sounding an alert and recording the manual activities of staff. The TW 2004 version 6.0 described above is a release that lacks full cross functional communications with the other systems shown in Table 1 or SAP functions in Table 2. The reason for this has to do with telecommunication linkages, the legacy nature of some of the other functioning sub-systems, and the different product naming conventions found in SAP R/3.

Therefore BP companies, if they intend to keep TW as one of their principal systems, must upgrade to gain a higher level of electronic enforcement, integration, and a naming convention that is parallel to SAP R/3. This last factor is important, since SAP is dominant in BP supply chain management, and therefore any future MES platform needs to interact with it to resolve issues such as contamination and quality of raw materials.

Furthermore, TW faces the future problem of always trying to maintain compatibility with SAP's modules, as well as with other vendors that are publishing new releases of software. Using the legacy TW version 6.0 software can illustrate this problem. Let us assume that there is a production problem resulting from contaminated raw materials. TW would highlight the problem and alert staff and issue an injunction on activities. Much of the investigation data would be manually collected and analyzed. Table 3 illustrates TW 6.0's level of data integration at a typical pharmaceutical company in the 2007 timeframe for working through the investigation and problem resolution. Since it is limited, much of the work in determining the source of the contamination would be done manually. For instance, a typical question that staff must resolve about a contamination problem: is it from raw materials and therefore a part of supply chain issue, or is it caused by a machine miscalibration on the manufacturing floor, or finally a misplaced SOP update.

Table 3: TW and SAP QM integration comparison.

Data Integration Across Systems	TrackWise 6.0	SAP QM
Bill-Of-Materials Integration	No	Yes
Supply Chain Management System	Partial	Yes
Human Resources personnel	No	Yes
Lot hierarchy and batch search and analysis	No	Yes
Event tracking and trending	Yes	Yes
Assigning and tracking Investigation	Partial	Yes
Compliance with FDA's 21 CFR Part 11	Yes	Yes
Compliance with Internal conformance standards	Yes	Yes

Table 3 also compares the ability of TW and the SAP Quality Management (QM) system to receive or transfer data between different functional areas. The table shows that data is trapped within TW and can not fully cross systems, whether it is to SAP, or to other tasking software such as that found in Table 1. It is not surprising that SAP QM comes off as more integrated since for the most part it was designed to integrate with its other SAP software modules. Furthermore since SAP has become one of the major ERP standards in the BP industry, many smaller vendors have adopted its naming conventions and communication protocols.

The TW system is well regarded in the industry and was widely adopted when it first entered the market place, since it effectively tracked and managed problems, while documenting compliance issues. So initially there was strong justification for its adoption, as it was the best fit for managing and controlling production at the time. In addition, there were few competitors, since SAP QM with integrated CAPA was only introduced in the marketplace in 2005.

Therefore many BP companies made the correct decision in choosing TW as the best available in the time period between 1995 and 2005.
Now there still remains a strong rationale for choosing the TW upgrade:

- BP user community familiarity with the TW system,
- Proven as a strong performer with quality management functions,
- Expanded data integration and interconnectivity with other programs, particularly with SAP.

TW upgrade claims still need to be verified in terms of the interoperability and functionality of its new version of QM software. They also need to be verified with every new TW software release to determine that the data integration and interconnectivity functions still work. Furthermore TW software needs to be retested against any new SAP product release, as well as GxPharma and other products that are installed, for there is always a risk of a connectivity failure. In addition to the telecommunications link, there are questions about future data dictionary integration. The TW upgrade must be checked against every new release of SAP, to be sure that the entity naming conventions found in the database and data dictionary have not changed. This logic holds true with future releases of other vendors, for they too must be tested for data dictionary consistency to catch divergent names for products, materials, and equipment.

It is up to the BP companies to fully test and evaluate the compatibility claims of TW and other vendors, though it is clearly realized that some claims can only be evaluated through actual use. Alternatively some claims can be verified by the shared experience of the BPI, assuming that they have the same set of vendor software.

Those that are against the TW upgrade prefer to focus on the SAP integrated platform for the pharmaceutical industry. Some Quality Assurance and IT staff that were interviewed argue that with the new FDA risk initiative, and with the continual growth and expansion of SAP R/3 in marketplace, their corporation should take the step in switching to this unified platform. This argument has merit since SAP-QM / CAPA software integrates fully into the enterprise SAP/R3 modules and with MySAP work portal. This allows for data to flow across boundaries for production purposes as well as for defining work roles, passing information and assigning tasks within MySAP.

Since pharmaceutical companies are at a crossroads, it makes sense to do this type of evaluation before upgrading vendor software or replacing it with SAP R/3 modules which provide the same type of functionality, with potentially superior integration and communications. Lastly, these firms must weigh the long term potential of SAP R/3 to develop into a fully functioning MES platform, with close integration, transparency and electronic enforcement.

DECISION MAKING CRITERIA

To reach resolution on the best way for BP corporations to proceed, there are several helpful IT methodologies that inform the decision making process. These are spelled out by 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. The idea of an MES platform fits within the ERM framework, as corporations are building a broad enterprise-wide system for internal controls and quality assurance. Similarly, the ITGI's framework develops a roadmap for data integration and transparency. In fact the Enterprise Risk Management (ERM) framework includes the ITGI best practices. Therefore it is fair to say that both the ERM and COBIT support the development of an infrastructure to manage risk and performance.
These functional processes that ERM and COBIT describe are in fact comparable in nature and function to an MES which provides analytics and integration for production.
Some of the characteristics of this type of system for the pharmaceutical industry are its ability to incorporate actionable activity from:

- 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

MES analytics and integration are described more fully in Table 4. The more sophisticated and encompassing the MES outlined in this table the greater the chance that this will be a knowledge management system that meets the compliance mandate of the FDA (Maier, 2004). 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, and can be used to assess the choice between upgrading disparate systems or choosing an integrated system such as SAP (Adis, 2007).

The next stage of research will be to see if the COBIT / ERM methodology can be specifically tailored for use in the decision making process for the BPI (Grover, 2001).

CONCLUSIONS

Much of the initial findings from this exploration of the BP industry concern the new FDA risk mandate and how it drives the change to new systems. Parallel with these internal technological steps, the BPI is tracking new developments from software vendors, initiatives by the FDA, changes in hardware, SOA software and communications protocols. This is because the BPI realizes that only through new IT platforms can corporations achieve the necessary level of best practices and compliance.

At the center of the planned development will be an MES platform, with functionality to provide integration, enforceable intelligence and FDA risk tracking. The initial findings indicate that an enterprise IT platform from a leading vendor such as SAP will likely provide the most pragmatic, integrated approach to risk management, compliance, analytics, and control.

Table 4: MES Functionality.

Repository Management	**Risk Component**
Regulatory database	Data repository of regulatory standards and critical measurements
Best Practices database	Industry standard procedures
Compensatory Services	CAPA programs and procedures with triggers
Process 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	Modifying process using CAPA

reconfiguration	
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

The consensus is that this is superior to multiple platforms using various linking protocols and matching data dictionaries. This latter option introduces a layer of complexity that IT staff would prefer to avoid (Tiwana, 2000). The criteria therefore in choosing SAP over its competitors come down to this: its platform has the greater likelihood of achieving data integration, transparency and electronic enforcement as well as provide verifiable FDA compliance. The rationale is to use SAP as the principal platform, leveraging its integration and analytics, and link it temporarily to other vendor software until that point in time when SAP develops the same corresponding modules. This step takes advantage of the SAP infrastructure, its portal MySAP for dashboard analytics, and its NetWeaver integration services with its Service Oriented Architecture.

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