



# Quality in the Global Pharmaceutical Supply Chain

Pilgrim Software White Paper  
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Supplier quality has been a prime topic at recent industry conferences. Original Equipment Manufacturers (OEM), material suppliers and contract manufacturers are hearing about the implications and driving forces behind the scrutiny of our supply chain. Although regulations and guidelines are already in place in multiple industries, supply chain complexity has grown from simple domestic sourcing, manufacturing and distribution, to a complex evolution of global sourcing, manufacturing and distribution centers around the world.

The great commotion that has caused regulatory agencies to be more focused in their scrutiny stems from the growing level of media exposure to patient health, with issues ranging from Herapin, Baby Formula, Spinach, Beef, Pet Food, Defibrillators and more. Warning letters citing deficiencies in production and process, specifically about purchasing controls, continue to increase. Agencies like the FDA will no longer tolerate long lead times for corrections. FDA's follow-up has revealed the lack of due diligence of supply chains is widespread. Expectations from the FDA commissioner, Dr. Margaret Hamburg, stated companies need to "act swiftly and aggressively to protect public health," and cites that multiple warning letters will no longer be submitted. In addition, Dr. Hamburg is focused on national and international partners to find ways to ensure that global and domestic companies secure their increasingly complex and ever-growing supply chains. Regulations will be tightened with requirements for compulsory audits (US and Europe). What does she expect from companies? "The Solution is a commitment to compliance backed by a strong compliance program. Now is a good time to reassess whether you have such an effort in place."

But the FDA is not the only one scrutinizing supply chain and public safety. Legislation has been passed in Congress and the Senate concerning food safety. The Bills contain specific language and focus on supply chain quality, safety and traceability, and will have impact to supplements such as the growing probiotics demand. Don't think that other U.S.

agencies are not involved in this as well. Organizations such as the Consumer Products Safety Commission (CPSC), U.S. Customs & Border Protection (CBP), Immigration & Customs Enforcement (ICE), Justice Department (DOJ), Security & Exchange Commission (SEC), Bureau of Industry & Science (BIS), and the Department of Commerce & Office of Foreign Assets Control (OFAC) are all watching the implications of our supply chain under export and import laws, foreign corrupt practices act and compliance to international commercial terms (INCOTERMS), a series of standard international sales /trade definitions published by the International Chamber of Commerce. They want to know who, what, where, how, and the potential risk and liability to our country's supplies. The FDA continues to examine opportunities for more effectively using information gained through close interaction with local, state and federal regulatory partners and foreign counterparts, as well as Boards of Pharmacy. Sharing information between regulatory bodies will lead to more cohesive enforcement activities as well as better use of resources through targeted activities. These actions will include the development of risk control and enforcement strategies in the interest of achieving a swift, effective, positive public health outcome that mitigates the risk of harm and achieves both short-term and sustained, longer-term compliance.

With more regulations being handed down by other international agencies (IPEC – International Pharmaceutical Excipients Council) and standards bodies (ICH Q7, ICH Q10, etc.), with emphasis on outsourcing and suppliers, document retention down the supply chain tiers, and clarifications from ISO 9001:2008 concerning the control of outsourced processes, companies need to sit up and pay attention to their supplier quality programs. Companies will need a sharper focus on supply chain issues with a full realization that the full depth of the chain needs scrutiny with renewed impetus for e-pedigree and anti-counterfeit technology. In addition, a broadening focus will be needed for comprehensive auditing of quality, business continuity, Environmental Health & Safety (EH&S) and security.

So what do companies need to do? First, remember that EVERYBODY is a supplier!

- Classic “suppliers” supply your plants and customers.
- Your plants “supply” each other and your distribution centers (DCs).
- Your DC’s “supply” your customers.

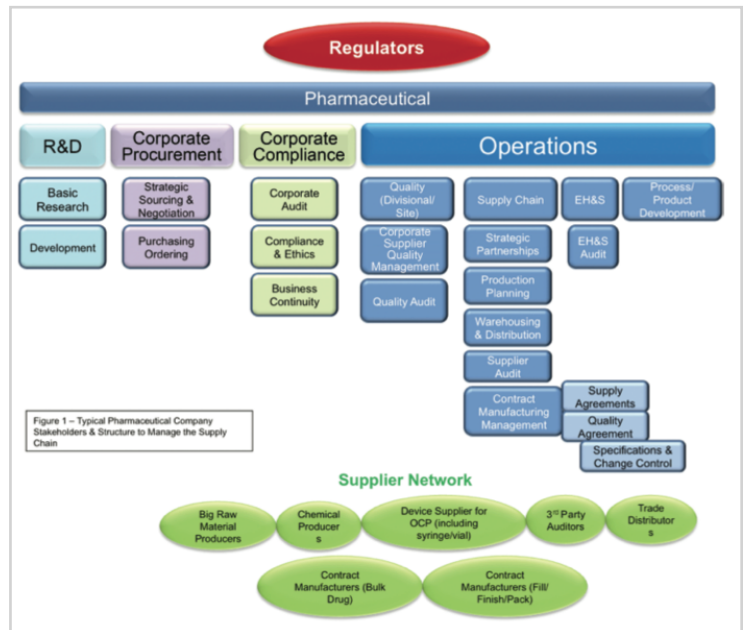
Agencies, like the FDA, are looking at BOTH external and internal suppliers. So does your current supplier quality program include your internal suppliers as if they were external suppliers?

Not an OEM and not feeling the pressure – YET? You WILL. Although an OEM is held accountable, expect more inspections for Tier 1 AND possibly sub-tier suppliers. This is already happening. One conversation with a small contract manufacturer stated the lack of its quality management systems had the FDA on premise for over four months, notified their clients, and shut down their operations. Classically, after focused efforts in putting improved quality and purchasing controls and programs in place, the company is back in operation.

In 2008, Baxter Healthcare Corporation (who made almost half of the Herapin blood thinner used in the U.S.), was forced to halt sales of its multiple-dose injectable Herapin, following about 350 reports of health problems associated with Baxter Herapin. Forty percent were deemed serious. It was later determined that the potentially toxic Baxter Herapin was produced in a Chinese factory that was never properly inspected by the FDA. With the Herapin scandal, the FDA Warning Letter to Changzhou SPL cited many serious cGMP deficiencies, including inadequate evaluation of the effectiveness of critical processing steps to remove impurities and failure to define or control critical process parameters. SPL did not adequately evaluate its suppliers of Herapin crude materials, and did not test incoming crude materials properly or have appropriate specifications for them. Result – disaster in the upstream market. Additionally, the mantra of “Faster, Cheaper, and Better” is no longer a differentiator as supplies and contract services have become commoditized in this global economy. Service and Quality will be the “Key” to a supplier’s on-going success. You will need to make sure you have the RIGHT contracts, communication,

and a comprehensive understanding of roles and responsibilities. Most of all – be prepared.

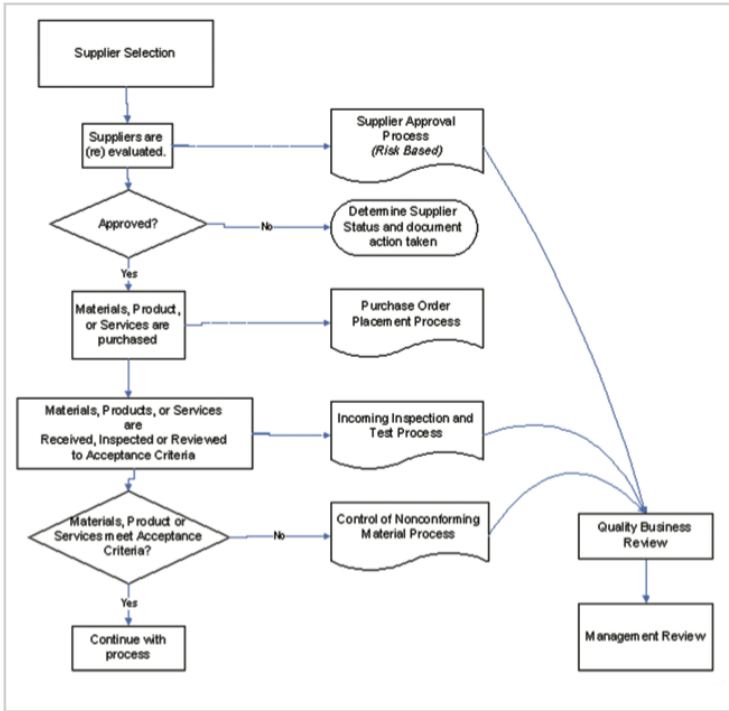
## Improving Your Supply Chain Program



Companies need to develop, implement, and maintain a Supplier Management Program that “integrates compliance,” “oversight,” and “strong supplier relationships” into business practices and quality systems. Yet in many cases today, not all suppliers are selected, evaluated, or maintained according to the type of product or service provided. Supplier questionnaires or audits are not always consistent with the selected supplier. Trending and data is not always analyzed and/or visible to the appropriate level in the organization. Employees at both the manufacturer and/or the supplier don’t always know or understand their responsibility or authority. The industry spends a high proportion of revenues on Research and Development (15-30%) and relatively little on raw materials and manufacturing. These numbers strongly influence the way supply chains are managed and the subsequent risks that can emerge. Although raw materials and services may be low in cost compared to the prices of the pharmaceuticals that are produced from them, the risks to supply chain can have devastating quality and financial consequences well beyond that value measure.

Using your Supplier Management Program can help improve profitability by decreasing the cost of quality. Additional emphasis should be placed on the control/oversight of suppliers as outsourcing

activities increase. Remember, poor cost of quality results in rework, waste, delays in product approval, resource inefficiencies, corrections and removals, enforcement actions, etc. which impacts the bottom line (profitability).



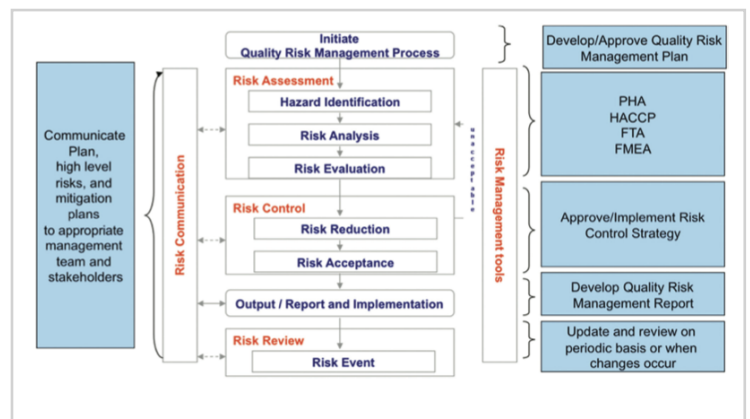
A good Supplier Management Process should include:

- Supplier selection, evaluation, and approval to determine the appropriate supplier level (risk) for products, materials and services/consultants; the appropriate contracts and agreements meeting the needs of the business; good rationalization of the supplier base with segmentation based on strategic importance, people, information sharing, competitive factors, quality, ethics, culture, stability, longevity, and history; and sound quality and business/financial systems. Such processes will secure access to more/better sources of supply and reduce the cost of procurement.
- Monitoring/Maintenance that will include the initial review, on-going reviews and annual evaluations (audits, internal & external nonconformance data, on-time delivery data, etc.); and keeping suppliers on-track by communicating company strategy, performing quarterly business reviews, having annual supplier conferences and keeping supplier scorecards. Such processes will increase compliance and decrease risk.

- Appropriate Removal/Inactivation controls for noncompliance and inactivity. Such processes will reduce the cost of quality.
- Real-time data that demonstrate control over suppliers – metrics, data analysis, and action items. Such systems will provide better control over the supplier base with increased collaboration, resulting in standardized practices and processes and improved transparency and auditability.

## Risk Management

To ensure that quality is maintained, there must be a risk management process that covers the entire lifecycle. This requires strong supporting audit processes, and an improved quality of internal and 3rd party audit resources and information management systems that allow in-company resources and external supply chain partners and auditors to share information. The risk assessment process needs to include an execution of pre-qualification processes for new suppliers and accompanying follow-up audits. Given the limited resources available for numerous audits, a risk-based approach is essential. In addition, the issue of visibility of the supply chain has become a key issue. The Herapin problem revealed the complexity of a multi-tiered and global supply chain. While companies may be less concerned with their supplier's suppliers, when it come to business risk this visibility becomes essential.



Key issues for supplier risk management include:

- Aligning multiple stakeholders
- Applying risk management through the entire supply chain

- Pre-qualifying suppliers
- Having audit standards
- Visibility across the entire supply chain (primary and sub-tiers)
- Implementing the right systems for data collection

The first requirement is to unify the goals and objectives across all functional groups with regards to suppliers and contractors. Cross-functional collaboration is necessary to reduce the risk to the corporation. A failure of quality or significant disruption of supply has a major impact on a company. Hidden costs of manufacturing failures, which can be attributable to suppliers or contractors, can become significant.

A comprehensive risk management system, extending over the complete product lifecycle, needs to start in the early phases of product development with a rough risk assessment based on the immediate data available, including the evaluation of raw materials and services, and appropriate functions involved such as quality, EH&S and procurement. With the appropriate follow through on actions identified, the risk assessment will help ensure cross-functional alignment occurs.

Given the scarce resources typically available for all audits, there must be an agreement across functions on how to best deploy the audit resource including the use of 3rd party and shared audits. Since such resources can be a severe constraint, it requires a rigorous risk assessment before deployment.

Information and data management is another essential component of how manage the risk process over a lengthy product lifecycle. Without access to a cross-functional and collaborative supplier system, it will be almost impossible to manage across multiple stakeholders and achieve a unified approach to managing the risks.

## Supplier Sourcing and Qualification

Each manufacturer establishes and maintains requirements, including quality requirements that must be met by suppliers, contractors, and consultants. It is the responsibility of the OEM to ensure that the materials used in products are of acceptable quality, regardless of the geographical and

logistical challenges in evaluating manufacturers and suppliers in remote countries. Supplier qualification needs to be performed for each material and supplier combination. These expectations are explicitly stated for pharmaceutical components at risk for melamine contamination (August 2009, FDA cGMP Guidance) which goes beyond CFR Part 211, saying that manufacturers need to know and monitor their supply chain for any at-risk components.

The Selection process should occur as early as possible in the product lifecycle process and include cross-functional team members from Purchasing, Quality Assurance, Engineering, and Manufacturing (as applicable). Evaluations should be conducted based upon the type and extent of control needed over the product, material, or service to be provided, and take into account Risk Management Principles. Use risk management principles to determine supplier risk during the selection process.

- Supplier level (type and extent of control)
- Sole source
- Single source

Develop different audit types: On-site audits, Quality Assessment questionnaires, Business/ Financial assessments (stability of the supplier) such as ability to deliver, potential for growth, safety stock for product/ materials and cost and volume. Determine the extent: frequency, each facility location, training, volume, cost, ability to meet acceptance criteria. Finally, determine the results of the evaluation and approval status of the supplier - Accept/ Reject.

Choose a potential supplier based upon the ability to provide consistent product, material, and/or services. Determine the stability of the potential supplier by establishing and/or reviewing:

- Quality systems and data
  - Compliance
  - Contracts
  - Quality Agreements
- Develop Contracts/Quality Agreements with clear expectations and well-defined Acceptance Criteria which should include Quality System requirements such as:
  - Control of material, audits (by the manufacturer and/or by external agency), notification of changes to location, process,

or materials, nonconformance control, complaint handling, correction & removals, etc.

- Finalize an Approved Supplier List (ASL) = A formal controlled listing of suppliers with pertinent information including name, location, type, level, and current status should be available for use.

As companies are looking for ways to improve procurement cost and lead times, the focus in supplier partnerships is shifting from one of price reduction to relationship value and total cost of management.

Examples	Documentation
<b>Level 1:</b> <ul style="list-style-type: none"> <li>• Original Equipment Manufacturer</li> <li>• Sterilization Services</li> <li>• Testing Services</li> </ul>	<ul style="list-style-type: none"> <li>• Approval Checklist</li> <li>• On Site Audit/ Questionnaire</li> <li>• Notification of Change Agreement</li> <li>• Contract/ Quality Agreement</li> <li>• Applicable Certifications (Sterilization, ISO)</li> </ul>
<b>Level 2:</b> <ul style="list-style-type: none"> <li>• Material, Manufacturer specified</li> <li>• Sub-contract Manufacturer</li> </ul>	<ul style="list-style-type: none"> <li>• Approval Checklist</li> <li>• Assessment Questionnaire</li> <li>• Notification of Change Agreement</li> <li>• Purchasing Agreement</li> </ul>
<b>Level 3:</b> <ul style="list-style-type: none"> <li>• "Off the Shelf" Supplies</li> <li>• Independent Consultant (directly impacts quality system)</li> </ul>	<ul style="list-style-type: none"> <li>• Approval Checklist</li> <li>• CV/ qualifications (consultant)</li> <li>• Notification of Change Agreement</li> </ul>

**Table 1:** Example of applying risk management principles to evaluation by taking into account - Cost, Volume, Type and Extent of Supplier.

## Supplier Audits and Testing

Auditing your suppliers is a key part of your quality and compliance improvement. A pharmaceutical company need to insist on a confidential in-depth audit of every part of the facility, operations and quality systems relating to the material it wants to purchase, including manufacturing and testing details. In addition to regular thorough manufacturing facility audits, the company should actively ensure that it or its brokers have very reliable, up-to-date knowledge and verification of the drug substance upstream to ensure that materials really do come from approved sources. If manufacturing and supply chain integrity cannot be verified regularly, the initial cost savings from a cheaper source cannot compensate for increased risk.

Companies need to determine the frequency of re-evaluation of suppliers and to what extent. Risk based measurements should be determined for data analysis in reviewing suppliers including:

- Assuring meaningful data is captured
- Configuring data such that problems can be identified
- Identifying data-driven Status Changes

Audits must be done by skilled, experienced auditors, technically expert and preferably fluent in the local language, with enough time to look carefully at the supplier's operations and records. With the complexity of the supply chain – geographic locations, numerous partners – industry is responding by developing a consortium approach to audit execution and information collaboration. Rx-360, a nonprofit international pharmaceutical supply-chain consortium seeking efficient and effective approaches to supplier risk management, has combined the efforts of leading pharmaceutical companies to implement audit standards, auditor training and auditor certification providing an the capability to support over 1,000 audits. With the goal of a consortium supplier certification program, suppliers can start sharing critical data with transparency to the manufacturer and the distribution channel. In addition, the consortium expects to implement additional standards for:

- Good Distribution Practices
- Good Importer Practices

- Good Storage Practices
- Quality Agreements
- Certificate of Analysis (COA)
- Tamper Evident Packaging
- Pre-Audit Questionnaires

Traditionally, manufacturers get inspection records once the material physically arrives at the manufacturers' premises. A good inspection system will allow for creation of different types of sampling plans (ANS/ASQ such as C=0 and 21.9), and Acceptable Quality Level (AQL), and other characteristics, outlining the criteria to inspect supplied materials. The receiving inspection system, through inspection capabilities and based on inspection results, allows companies to prevent out-of-spec supplied materials from entering the production environment.

However, even if the tests are made more specific, the risk of contamination for materials can be significant. Even third-party testing is certainly not enough to assure the quality of pharmaceuticals. It is not possible to test quality into a pharmaceutical product, because good quality must be built into the product by using appropriate materials and validated processes to ensure the product's safety and efficacy. There is a risk that modification of even a single processing step can change the by-products or impurities of even materials. As with a final drug substance or API, testing is a confirmation of a material quality, but may not be enough on its own without manufacturing records that each batch was made according to a validated process and complied with the final product specifications.

The best suppliers will accept the new reality of increased transparency, and brokers and distributors who can establish and guarantee the level of quality assurance associated with more rigorous auditing and supply chain verification, will be invaluable.

## Operational and IT Challenges

Technology is critical to securing the global supply chain because it is the only way to have visibility into products and assets across the extended supply networks, and the ability to immediately take action. Senior management should be informed and updated regularly as to the security and integrity of critical supply chains. Overall reports usually include:

- Metric and Data Analysis Review
- Inspection Results (Incoming, Production/ Manufacturing, Source Inspections)
- Nonconformance Control/CAPA Oversight
- Complaint Handling/Corrections/Removals
- Business Metrics (Delivery Lead Time, Technical Support, Cost Strategic Initiatives)
- Supplier Scorecard
- Adherence to Contracts/Quality/Purchasing Agreements
- Audit Results and Responsiveness
- Cost of Quality

However, current manual processes can limit the integration of applications and data for adequate analysis to effectively understand your state of supply chain quality, compliance, and potential risks. While supply chain data may be maintained within a certain quality system, departments, or other manufacturing and procurement automated solutions, in many cases different elements of an organization's product supply, quality, regulatory and commercial functions are disconnected. An integrated quality approach needs to be embedded into the core business. Ask yourself, how many systems contain some supplier quality data throughout the product lifecycle? How much time is spent navigating the maze of data versus using and focusing on problem solving? How much time is spent on the duplication of data entry or searching for data entry errors across different supplier quality systems? Can people at all points in the chain create data that are recognized from end to end? SCARs – do they signal not only discrete performance issues (e.g., a failed batch) but overall degradation to the whole company? CAPAs – are all sites aware of the issues that affect them and are they actively looking to make connections? Holds – are they instantaneous throughout the entire chain? Nonconformances – does the information get passed along forward and backward? Have you truly leveraged technology to enable effectiveness, efficiency, and closed-loop processes?

Although these systems provide automation that helps organizations reap the benefits of repeatability and sustainability, are they truly complementing your overall supplier quality investments? Integration allows real-time access to data stored within each

system, enabling your organization to make informed decisions based on current information. But it's not just about technology and automation. Automation of inefficient processes, by default, will simply make your inefficiencies happen faster. A comprehensive supplier quality management system helps companies understand the significant impact that poor quality, service and delivery has on sales and profits. Take what you've learned from your process inefficiencies, and your understanding of best practices, and architect them into an integrated supplier quality platform across your organization value chain.

With such technology enablers in place, reporting and analysis becomes easier for management and all stakeholders to understand the supply chain state of risk, quality and compliance.

## Conclusion

Make the Supplier Management System flexible, simple, risk-based, and easily integrated throughout the organization. Assure that sufficient mechanisms are in place so that all suppliers are managed according to the type of product, materials, or service provided --this includes 'consultant' services. Have a selection, maintenance, and reporting process that includes materials, products, and services throughout the product life cycle. Make sure the appropriate functional partnerships are established – Engineering, Manufacturing, Purchasing, Quality and the supplier's representative functions. Invest in resources to support the internal partnerships between Quality, Purchasing, Engineering, and Manufacturing to drive for successful oversight and management of suppliers. Build supplier relationships.

Integrate risk management throughout the supplier selection, maintenance, and data reporting processes. Implement measurement, data analysis tools, and processes for different levels of the organization. Configure data such that problems related to product, process, or quality systems can be identified. Results of the analysis and/or any further decision to take action are identified and communicated to the supplier. Drive for the development and ownership of supplier relationships (accountability).

A good Supply Chain Management Program with effective Quality Processes will help pharmaceutical companies:

- Reduce cost of goods purchased
  - Improved market access
  - More effective price negotiations (company leverage)
- Reduce risk due to increased compliance
  - More thorough specs and better communication to supplier
  - More rigorous testing and reporting
- Improved supplier performance
  - ON-TIME, ON-QUALITY, "NO SURPRISES"
  - Standardized contracts that are easier to monitor
- Sustainable competitive advantage
  - Consolidation and visibility into entire supply chain

So now what?

- Be Concerned? **Yes!**
- Get Better Contracts & Qualifications? **Yes!**
- Be Diligent? **Yes!**
- Be Compliant? **Absolutely!**

HOW? By putting (or re-assessing) the controls and programs in place for your supply chain NOW! In fact you're almost too late!

## About Pilgrim Software

Pilgrim Software, the world leader of cloud and on-premise enterprise solutions for quality and compliance management, delivers integrated applications for pre- through post-market operations of Life Sciences companies. For more than a decade, Pilgrim's tightly integrated 21 CFR Part 11-compliant system has enabled its clients to proactively manage documents, audits, complaints, nonconformances, corrective/preventive actions, supplier quality, and training, helping ensure product safety and regulatory compliance, reduce manufacturing costs, and improve customer satisfaction.

For more information, visit Pilgrim Software's website at [www.pilgrimsoftware.com](http://www.pilgrimsoftware.com).