IBM Business Consulting Services

The metamorphosis of manufacturing

From art to science

An IBM Institute for Business Value executive brief

IBM Business Consulting Services, through the IBM Institute for Business Value, develops fact-based strategic insights for senior business executives around critical industry-specific and cross-industry issues. This executive brief is based on an in-depth study by the Institute's research team. It is part of an ongoing commitment by IBM Business Consulting Services to provide analysis and viewpoints that help companies realize business value. You may contact the authors or send an e-mail to iibv@us.ibm.com for more information.

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Introduction

Pharmaceutical manufacturing has traditionally been regarded as the "Cinderella" function in the value chain,[1] with a "cause no problems" mentality focused on getting enough manufactured product through extensive quality controls to meet market demand. Manufacturing techniques have not kept up with advances in science and technology. Until recently the economic climate did not demand it, product complexity did not require it and the regulatory framework actively discouraged it.[2] But that has all changed.

Pressure on margins intensifies

The pharmaceutical and biotech industry (Pharma) must contend with an increasingly difficult economic climate. Profit warnings have become the industry standard. "Since June [2004] the sector, measured by the FTSE US pharma index, has been 11 percent lower than the S&P 500."[3] This is not surprising given that:

- 56 products have been lost in phase III of development over the last three years with an estimated potential peak sales value of over US$20 billion.[4]
- Between 1997 and 2004, safety-based withdrawals eliminated peak sales potential of over US$13.5 billion.[5]
- US$35.5 billion worth of products will lose blockbuster status by 2008.[6]

So late-stage failures, safety withdrawals and patent expiry have intensified pressure on profit margins and sharpened the focus on operational efficiencies. Highly visible safety issues have resulted in a loss of both investor and patient confidence.

Complexity of products increases

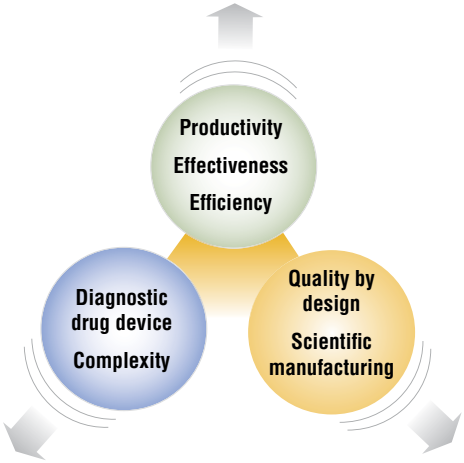
A better understanding of the molecular sciences and significant advances in technology are enabling Pharma to develop hybrid drug/device/diagnostic combination products, healthcare packages for patients with specific disease subtypes, and targeted treatment solutions. These products are complex, delicate and difficult to manufacture. They require collaboration across component suppliers and may require wide-ranging formulation and packaging configurations. Manufacturing today's traditional products is already problematic. Developing and producing the new products requires completely novel techniques – techniques which the industry is still trying to master, as witnessed by recent product recalls.[7]

Modernization of quality regulation accelerates

The U.S. Food and Drug Administration (FDA) has raised the bar. Its rationale for change, the approach it has taken and the progress achieved are all well documented.[8] In September 2003, *The Wall Street Journal* published a front-page article informing the world that pharmaceutical "manufacturing techniques lag far behind those of potato-chip and laundry-soap makers."[9] In that same article it correlated the rise in recalls with quality problems and noted that despite fines in excess of US$500 million for manufacturing failures, acceptable levels of quality were not being achieved. As Dr. Janet Woodcock (FDA's Acting Deputy Commissioner for Operations) said, "production techniques were outmoded. Just refining procedures and documentation wasn't going to change that." Since then, the FDA, the International Conference on Harmonization (ICH) and the industry have been extremely active, working together to shape the new quality requirements and standards. Compliance now requires a quality systems approach starting with "quality by design" in development and ending with scientific process control in manufacturing.

So today, products are more complex; cash is scarcer; and quality requirements require more fundamental understanding. Pharma companies will need to take action on each of these issues in a comprehensive manner. The biggest challenge, however, will be to respond to these seemingly competing drivers of change simultaneously (see Figure 1).

Figure 1. Pharma must find a way of meeting the product, regulatory and efficiency requirements simultaneously.



Source: IBM Business Consulting Services, 2005.

Quality performance appears to be improving

From an examination of some key statistics, it would appear that the FDA's effort is paying off. Inspections are down from 4,392 in 1999 to 2,965 in 2003,[10] recalls are down from 471 in 2000 to 266 in 2004 and warning letters are down from 58 in 2002 to 30 in 2004.[11] However if we look behind these statistics, a different picture emerges. There are fewer inspections as a consequence of the FDA's risk-based approach and systems-based inspections. Warning letters are down since the quality systems approach works to issue a single encompassing letter in place of multiple product- or operation-specific warnings. Finally, while the absolute number of recalls is down, the ratio of development to manufacturing issues has doubled from 1:4 to 1:2, indicating the true source of poor quality performance (see Table 1).

Table 1. Manufacturing defects account for almost three-quarters of all drug recalls.

Year	Total	Manufacturing	% of total	Development	% of total	Regulatory/ misbranding	% of total
2000	471	375	79.6	61	13.0	35	7.4
2001	271	187	69.0	58	21.4	26	9.6
2002	431	328	76.1	74	17.2	29	6.7
2003	290	221	76.2	44	15.2	25	8.6
2004	266	139	52.3	70	26.3	57	21.4
All	**1729**	**1250**	**72.3**	**307**	**17.8**	**172**	**9.9**

Source: U.S. Food and Drug Administration Enforcement Reports, 2000 - 2004.

So while there have been improvements in quality, these have been achieved through increased efforts in "testing to document quality."[12] This approach to quality carries a significant cost for superficial improvement, is not sustainable and is simply not feasible for the new, complex products in the pipeline.

FDA benchmarks outside the industry

When ex-FDA commissioner Mark McClellan sought a benchmark for future pharmaceutical manufacturing performance, he looked outside the industry, and challenged Pharma.

"You need to improve…Other high-tech industries have achieved enormous productivity gains in manufacturing in the last 25 years. We should expect nothing less from the Pharmaceutical industry."[13]

Considering some standard manufacturing benchmarks, it is clear that Pharma performance has room for improvement (see Table 2).

Table 2. Metrics to compare manufacturing capabilities.

Key performance indicators	Pharmaceutical industry now	A winning pharmaceutical plant	A world-class manufacturing plant
Stock turn	3 to 5	14	50
OTIF	60% to 80%	94.4%	99.6%
RFT	85% to 95%	96.0%	99.4%
Cpk	1 to 2	2.5	3.2
OEE	30%	74%	92%
Cycle time (hours)	720	48	8

Stock turn is a measure of how fast a business turns over stock.
OTIF is on time in full, a measure of the capability of the process to produce product when required.
RFT (right first time) is a measure of process capability and relates the variability in product to the specification limits.
Cpk is a measure of process capability.
OEE is overall equipment effectiveness, the percentage of time for which process equipment is adding value.
Source: Benson, R. S. and D. J. MacCabe. "From Good Manufacturing Practice to Good Manufacturing Performance." Pharmaceutical Engineering. *July/August 2004. vol. 24, no. 4: 26-34.*

Achieving McClellan's standard of precision – a 0.0001 percent rate of defects for semiconductor manufacturing – requires both a compelling reason to act (US semiconductor manufacturers were going out of business) and a migration away from dependence on testing and corrective actions to "quality by design." The current good manufacturing practices (GMPs) focus on examination and documentation of variability in the manufacturing processes, and so actually reinforce the "quality by inspection" approach. Semiconductor performance levels were achieved by heeding the 1950 advice of W.E. Deming, the father of modern quality, as summarized by Joiner and Gaudard:[14]

"Depending on inspection is like treating a symptom while the disease is killing you. The need for inspection results from excessive variability in the process. The disease is variability. Ceasing dependence on inspection means you must understand your processes so well that you can predict the quality of their output from upstream activities and measurements. To accomplish this you must have a thorough understanding of the sources of variation in your processes and then work toward reducing the variation. Ceasing dependence on inspection forces you to reduce variability."

Consequently, the FDA's vision for pharmaceutical manufacturing in the 21st century[15] builds on Deming's fundamentals of quality and may be articulated in five simple statements:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on a mechanistic understanding of how formulation and process factors impact product performance
- Continuous "realtime" assurance of quality
- Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation and process capability
- Risk-based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance, and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.

In other words, pharmaceutical development and manufacturing in the future will be synonymous with "quality by design," scientific manufacturing and risk-based regulatory oversight.

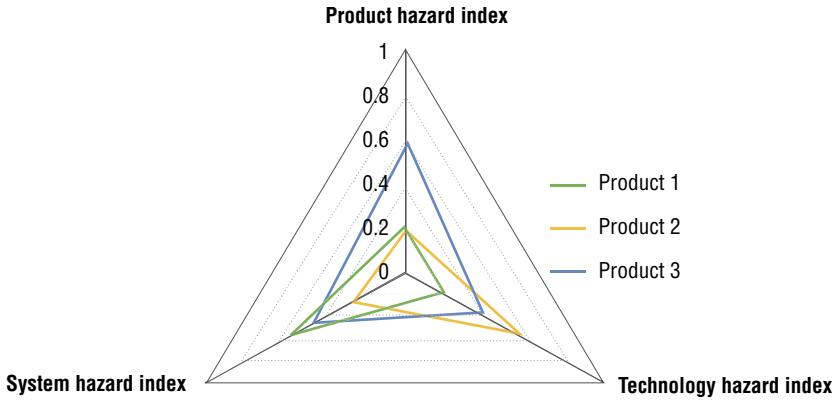
Doing nothing is not an option

Achieving the FDA's vision will likely require significant investment from Pharma. Some companies may believe that the current initiative will die out, and that no change will occur until the Code of Federal Regulations Part 210 and Part 211 (CFR Part 210 and Part 211) are modified. This might prove to be a serious error in judgment, as the FDA wishes to accelerate the rate of change through the publication of extensive guidelines, and facilitate the adoption of change through the creation of "safe harbors" for companies that embrace the changes.[16]

The risk dimension

Drug manufacturers that attempt to make modern, complex products with old quality approaches and assets are likely to expose their businesses to unacceptable levels of risk as "quality by inspection" becomes impossible. The source of that risk resides in a company's products, pharmaceutical technologies and GMP systems (see Figure 2).

Figure 2. Examples of risk profiles for three products.



Source: IBM Business Consulting Services, 2005.

Through quantitative analysis of a set of root causes that indicate the current state of manufacturing, IBM has calculated the probability of noncompliance for the industry and the financial risk that noncompliance poses. Between US$40-60 billion of future revenue may be at risk for the top 30 pharma companies alone.

Reducing this risk will be expensive. Pharma has quality systems and physical assets that were designed to meet 25-year-old GMP requirements that rely on "quality by inspection." Current investment projections, as derived from the annual reports of the industry leaders, foresee setting aside about 11 percent of sales for capital expenditure (CAPEX), amounting to US$34 billion a year. Given the degree of change required, this level of investment will not be enough. The cost of setting up a basic facility for manufacturing prescription drugs (including construction, utilities and equipment) can be as low as US$4,000 per square meter. But the cost of setting up a first-rate plant that can be used for manufacturing biologics is closer to US$12,000 per square meter[17] – three times as much. IBM research suggests that if the industry leaders are to modernize their facilities, they will need to budget an additional 20 percent of CAPEX or US$7 billion every year for the next five years,[18] divided between US$3 billion on IT and US$4 billion on physical assets.

The operational cost dimension

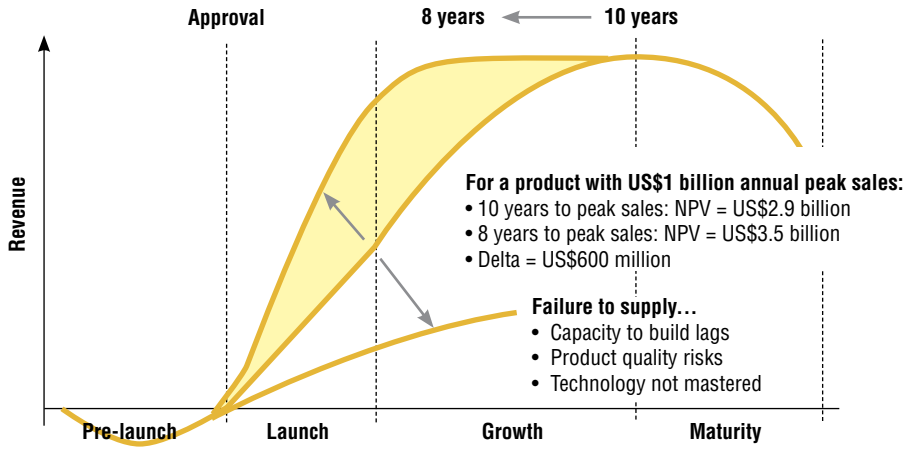
That said, the financial advantages of meeting the FDA's development and manufacturing requirements could also be considerable. Many numbers have been published regarding manufacturing costs, the highest being US$90 billion.[19] A generally accepted figure for cost of goods sold (COGS) is 20 percent of sales. In

2003, the top 30 companies collectively generated pharmaceutical sales of US$311.2 billion.[20] Using these numbers puts the cost of manufacturing closer to US$62 billion for the top 30 companies. As most manufacturing executives know, Pharma has six sigma products on the market but only three sigma processes.[21] IBM believes that most pharma companies are operating with a process capability closer to 2.5 sigma. By investing in "quality by design" to achieve 4.5 sigma, companies may be able to reduce COGS by up to 16 percent. This would release close to US$10 billion in annual savings for the top 30 companies.

The time to peak sales dimension

When supply is a rate-limiting factor such as for Roche's FUZEON[22] or Johnson & Johnson's CYPHER,[23] process understanding can help to accelerate the time new products take to reach their sales peak, and thus increase the overall amount of revenue generated over their lifecycle. IBM analysis[24] suggests that improving new product and process development to produce robust manufacturing processes prior to the launch of new products could help to reduce the period from launch to peak sales by as much as two years. That, in turn, would unlock an enormous amount of additional value. As Figure 3 shows, a drug with peak annual sales of US$1 billion could generate an extra US$600 million over its lifetime.

Figure 3. Process understanding can accelerate time to peak sales by as much as two years.



Source: IBM Business Consulting Services, 2005

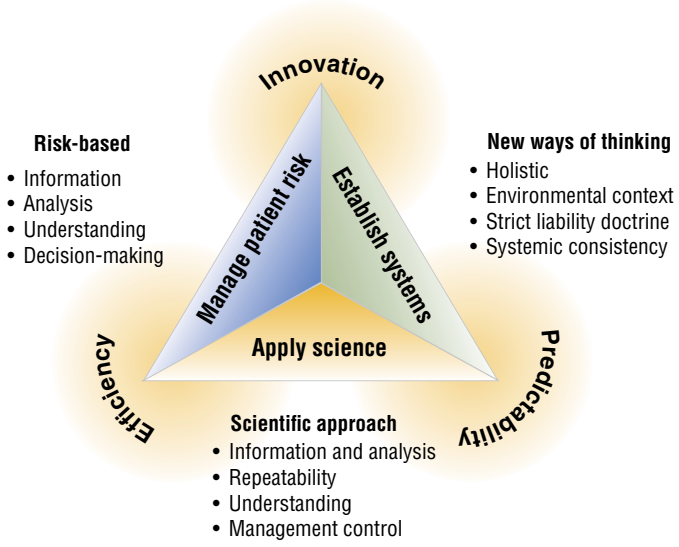
The supply chain responsiveness dimension

Making changes to facilities, equipment or processes for manufacturing can take up to two years – not to implement the physical changes, but to get prior approval from regulatory authorities. The European Federation of Pharmaceutical Industries and Associations (EFPIA) presented the European Union (EU) regulators with countless examples of quality and productivity improvements which were not realized because of the administrative burden of applying for prior approval, and the logistical burden of running multiple processes or analytical methods while waiting for authorization from all countries.[25] ICH Q10 – Quality Systems for Continuous Improvement – may provide the framework to move toward a more flexible and responsive supply chain. The FDA has concluded that modern quality systems, when coupled with manufacturing processes and product knowledge, can handle many types of changes to facilities, equipment and processes without the need for regulatory submission.[26] This is a key element in the FDA's promise of reduced regulatory burden.[27]

Pharma understands the implications of the FDA's vision

If Pharma meets the FDA's challenge to improve the predictability of its drug development and manufacturing processes, it will also gain operational efficiencies and the freedom to innovate (see Figure 4).[28] To do so, it will have to create a risk-based framework for identifying, developing and manufacturing drugs, and acquire the scientific and technological knowledge that is essential to consistently deliver quality attributes that are critical to patients.

Figure 4. The FDA's challenge is three-fold: to improve innovation, efficiency and predictability in drug development and manufacturing.



Source: IBM Business Consulting Services and FDA, 2004.

This framework will require a major shift in the industry's thinking – not only in manufacturing, but in many other areas of the value chain, as shown in Figure 5.

Figure 5. Pharma will have to make changes throughout the value chain, if it is to meet the FDA's challenge.

	Research and development	Supply chain	Sales and marketing	Information technology	Human resources
Manage patient risk	• Better understanding and improved efficacy • Clinical trial data mining	• Multifaceted supply risk • Track and trace from API to bedside	• Safety and efficacy expectations • Patient feedback to R&D	• Access, organize and analyze information from multiple internal and external sources	• Risk management professionals • Multiskilled sales and marketing teams
Apply science	• Time to understand • Scientific evidence to support manufacturing capability	• Scientific manufacturing • Predictable quality • Dynamic, innovative engineering	• Price pressures • Outcome Economics • Mathematical models to determine payments	• Realtime data acquisition • Multivariate statistical analysis capabilities • Terabyte storage	• Skill shortages • Pharmaceutical Engineers • Chemical Engineers • Applied Statisticians • Quality Managers
Establish systems	• Systemized GMP in development cGMPs in Phase I INDs • Continuous improvement in development	• Management accountability • Systemic failure impacts entire portfolio	• Price pressures • Increased control on sample management and tracking	• Consistency despite complexity • Common solutions within and across GMP systems	• Skill shortages • Production technicians and engineers • Job Enrichment

Source: IBM Business Consulting Services, 2005.

It is clear that, at the moment, two distinct groups exist within the top 20 pharma companies: those who wholeheartedly embrace the challenging change and are moving forward, and others who are adopting a "wait and see" strategy, believing that the FDA will never follow through with this. IBM believes the latter to be an extremely high-risk attitude that companies may come to regret.

Defining the end states

Those companies that do embark on the journey from "quality by inspection" to "quality by design" will need to identify where they are today against a set of capabilities required for a quality systems approach and scientific manufacturing. Identifying where there are deficits, and the magnitude of those gaps, provides a good indication of the extent of the transformation and remediation required to achieve the FDA's vision of manufacturing in the 21st century (see Appendix for a description of the required shift from current practices to target end state).

While some of the top 20 pharma companies have recognized the need to attain the FDA's vision of manufacturing in the 21st century, the journey there poses many problems. Many of today's products cannot meet the new requirements, and depending on their lifecycle stage, it may make more sense to delist the product rather than invest to redevelop the formulation process or analytical specifications. Likewise, certain pharmaceutical technologies may be too old or too novel to deliver zero defects, and while scientific manufacturing demands a higher skilled workforce, some locations may just not have the appropriate labor pool available.

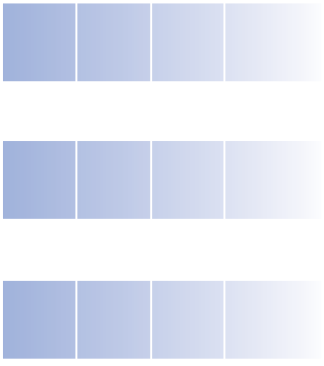
To configure the production capabilities required for this new era of manufacturing, decisions need to be made on products, technologies and sites. Given the richness of portfolios, the breadth of technologies and the number of sites that a given pharmaceutical company possesses, the potential permutations and combinations that need to be investigated is staggering.

Whether for traditional white tablets or for the new complex products coming down the pipeline, building a new facility from scratch may be more effective than force-fitting new technologies and ways of working into existing sites.

Attaining the vision presents a challenging journey

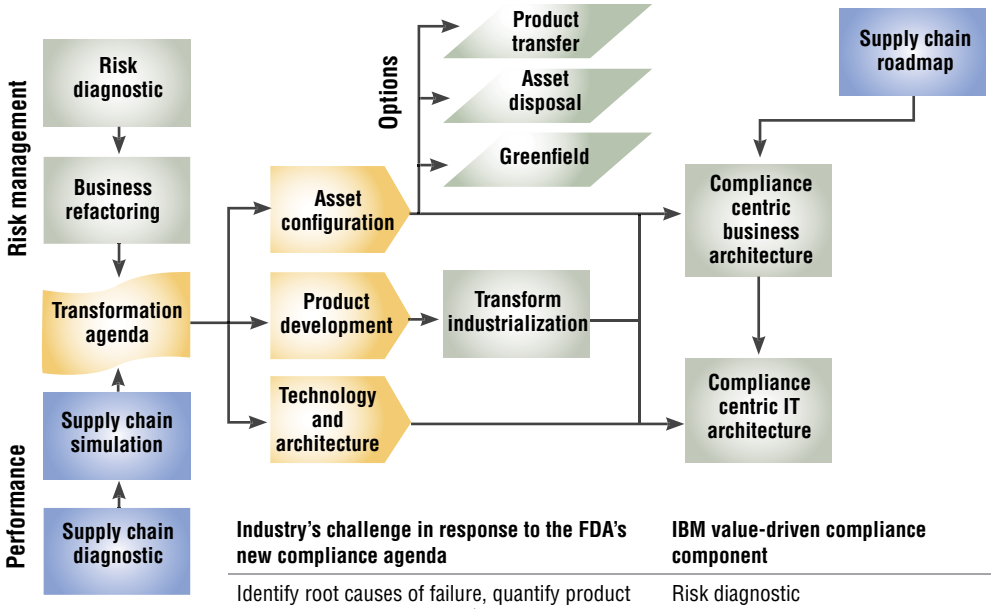
Pharma companies across the globe have helped articulate the future vision of manufacturing. They know they need to make that vision real, but addressing the multiple dimensions of change is highly complex with many subtle interdependencies: the nature of the problem (multiple variations of product, technology and site mixes); the clarity of direction; the timing of actions; and the magnitude of investments. The key decisions to be made revolve around:

- Which products should be retained, delisted or redeveloped?
- Which technologies should be phased out, acquired or monitored for impact on quality?
- Which facilities are fit for purpose?
- What is the right sequence of investments, where should investment be focused, and over what time frame should the investments be deployed?



IBM has invested considerable time and effort to understand the challenges, and has created a framework (see Figure 6) that includes an analytical route mapping model to enable effective trade offs in decision making and fact-based quantitative risk management. The IBM value-driven compliance approach allows pharmaceutical companies to benefit from best practices developed from other industries; mathematical models developed jointly with IBM Research; manufacturing and process control concepts and approaches from in-house semiconductor fabrication; and real-life experience from client consulting projects over the last ten years.

Figure 6. IBM value-driven compliance approach.



Industry's challenge in response to the FDA's new compliance agenda	IBM value-driven compliance component
Identify root causes of failure, quantify product quality risk and translate to $s	Risk diagnostic
Prioritize, schedule and cost justify the best set of actions to reduce and manage the risk profile	Business refactoring
Build quality into products and processes using science, systems and technology to reduce risk	Transforming industrialization
Drive a cultural revolution to embed quality into everyday operations and reduce compliance costs	Compliance-centric business architecture
Provide the visionary architecture to enable value-driven compliance, and demonstrate feasibility	Compliance-centric IT architecture

Source: IBM Business Consulting Services, 2005

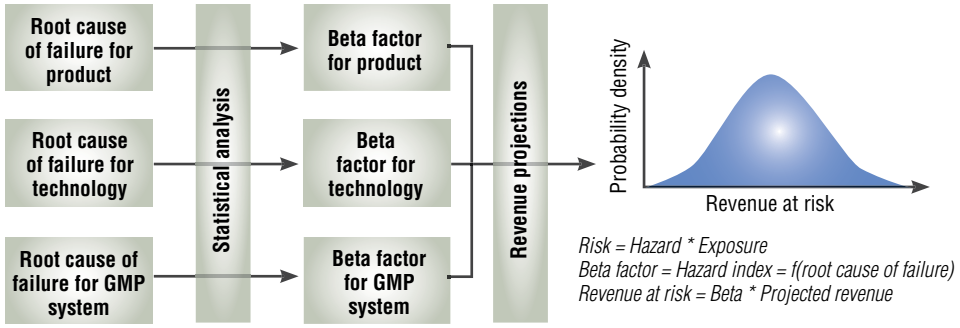
Risk diagnostic – Identifying and quantifying quality and compliance risk

Risk management in the pharmaceutical industry is performed at various levels of maturity. Within manufacturing, a traffic light approach (red, amber and green) is most often used. With the FDA's emphasis on risk, techniques such as Failure Mode and Effect Analysis (FMEA) and Hazard and Operability Studies (HAZOPS) are finding their way into operations. While both of these techniques have merits, they tend to remain heuristic in nature and subjective in outcome. If Pharma is to take a robust approach to risk management, then lessons may be learned from the financial community.

Every stock has an associated beta factor which is a measure of its volatility relative to the market norm and which reflects the individual level of risk it carries. The same concept can be applied to drug manufacturing. By identifying root causes of quality and compliance failures and calculating the probability of these failures occurring, beta factors can be derived for any product, pharmaceutical technology or GMP system.

By analyzing batch records, deviation reports, out-of-specification (OOS) reports, nonconformance reports and customer complaints, the root cause of failures can be identified and attributed to inherent characteristics of products, pharmaceutical technologies and GMP systems. Using advanced statistical analysis techniques, it is then possible to assign a probability to each root cause and derive the cumulative "beta" factor for any given source (see Figure 7). By adding revenue projections to the equation, it is possible to derive a probability density distribution that represents a company's revenue at risk over a particular time horizon.

Figure 7. Calculating the beta factors for products, technologies and GMP systems produces an overall measure of the risk inherent in the product portfolio.



Source: IBM Business Consulting Services, 2005

A maze of multiple choices

A multinational pharmaceutical company might typically have a European manufacturing business that spans 20 product families, 4 technology platforms (solids, liquids, creams and parenterals) and 5 sites. There are potentially 400 (20x4x5) combinations with 400 different beta factors.

A number of remediation actions are possible:

Product – 4 options: delist, transfer to another site, transfer to another technology, send back to development
Technology – 3 options: transfer to different technology, transfer to new technology, remediate technology
Site – 2 options: remediate, close

To assess the impact of each remediation action would require study of 80x12x10 permutations – 9600 for each planning period across the transformation time horizon. A 3-year plan would typically include 9 planning periods (8 quarters and one 12-month cycle) and so require analysis of 86,440 options.

Business refactoring – Risk mitigation

Once a company has calculated the beta factors and derived their potential impact on future revenues, it must decide what to do to reduce the root causes of failure and reduce the potential impact on revenue. The action taken by management will be influenced by many factors including the company's attitude toward risk, the type of products in its pipeline, budgetary constraints, the scope of remedial action required, and the order and sequence in which actions should be performed.

Though experience and intuition are important, they are not enough to determine the optimal course of action when so many permutations and combinations are possible (see sidebar: A maze of multiple choices). This is where an analytical means of processing the options is essential – and one such tool is the strategic sequencing model developed by IBM Business Consulting Services in conjunction with mathematicians at IBM Research. The model builds on the work of Dr. Ignacio Grossman, professor of chemical engineering at Carnegie Mellon University and an expert in the development of discrete-continuous optimization methods for solving problems in process systems engineering.[29]

At the heart of the model is a mathematical engine that uses a mixed integer linear program to calculate a company's revenue at risk, based on the computed beta factors for its products, technologies and GMP systems, and its projected product revenue streams. The engine then determines the optimal course of action, taking into account the capital cost of every option for mitigating risk, the reduction that option can be expected to have on the company's revenue at risk, and the company's goals and constraints. The end result is a route map that shows the company how best to reconfigure its manufacturing capabilities – what to do, when, in what order, and with what investment.[30] This process is known as business refactoring.

The model has been verified in a real-life pharma environment[31] with a comprehensive study covering 18 months of data on 3,500 batches from 13 product families manufactured at 3 separate sites. The root causes of all incidents of nonconformance were identified, quantified and classified in more than 90 different

categories. The information was then used to calculate the beta factors for all 13 product families and 7 technology platforms. The output was used to simulate 5 future scenarios, including the sequence of actions required to reach the desired end state. One scenario was then chosen for further analysis.

Business refactoring provides the input for a company's transformation agenda that can help it achieve the FDA's vision for pharmaceutical manufacturing for the 21st century. It also provides the business case for change, together with the sequence and timing of remediation actions, and the investments required over the transformation time horizon. Although each company's agenda will be different, there are a number of common change initiatives that all companies will need to address. These are described in the following sections.

Transforming industrialization

Cross-functional data sharing to demonstrate science of design

The FDA's vision requires significant collaboration across different scientific disciplines (development, quality and manufacturing) and functions (chemistry manufacturing controls (CMC) review and current good manufacturing practice (cGMP) investigations) responsible for pharmaceutical quality. This collaboration is required to develop mechanistic understanding of factors that impact product quality and performance, and to include this scientific data to demonstrate science of design[32] in the CMC section when the draft ICH Q8: Pharmaceutical Development guideline[33] becomes final. The key enablers of this collaboration are data, information and knowledge management.

Product lifecycle management (PLM) is a concept for managing product data throughout its lifecycle from early development to retirement. PLM is the electronic backbone that facilitates the flow of data on products and processes between development and manufacturing (see Figure 8). It provides an integrated framework for regulatory compliance, strategic sourcing, product specification and data management, manufacturing and corrective actions, and control of product safety and quality. The two-way data flow is important, passing data back from manufacturing to development to inform the design of new products and processes, particularly as these products and processes become increasingly complex.

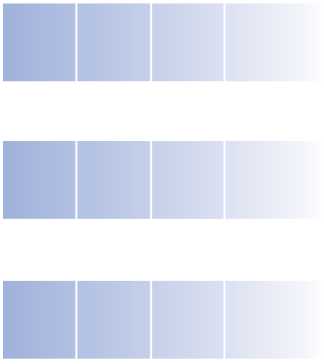
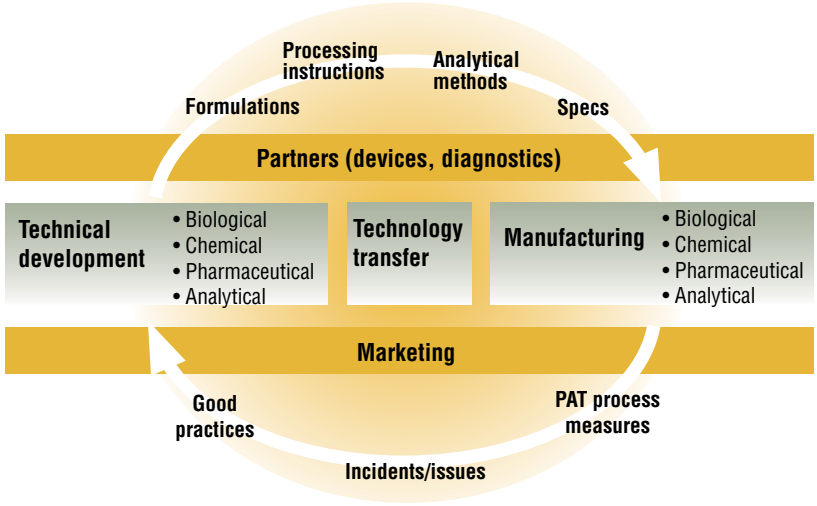


Figure 8. Product lifecycle management is the electronic backbone enabling the flow of product and process data to and from manufacturing.



Source: IBM Business Consulting Services, 2005.

ExxonMobil uses PAT to direct and track processing and blending[34]

The oil giant ExxonMobil has developed sophisticated process analytical technologies to increase the value it extracts from its crude oil feedstocks. These technologies enable the company to direct and track the path of the hydrocarbons as they pass through its refineries; analyze their molecular characteristics in realtime; and feed the data into a predictive model that can then be used to optimize its manufacturing operations.

"Molecule management," as the technique is called, has greatly improved ExxonMobil's ability to decide which hydrocarbons to blend into which end products, and thus to improve its return on investment. It has helped the oil major to increase margins in its lubricants business by US$1.2 billion over a period of three years – through a combination of greater manufacturing reliability, higher product values and lower raw materials costs.

"Quality by design"

Experience from industries outside of Pharma indicates that preferred technology platforms are a starting point for "quality by design." The criteria for choosing platforms and dosage forms in development need to be extended to cover not only the physical and chemical characteristics of the raw materials and marketing considerations, but also the ability to manufacture on an industrial scale. Using preferred technology platforms helps reduce the cost of goods, reduce variability, increase the richness of the platform's design space and improve a company's understanding of its formulation processes.

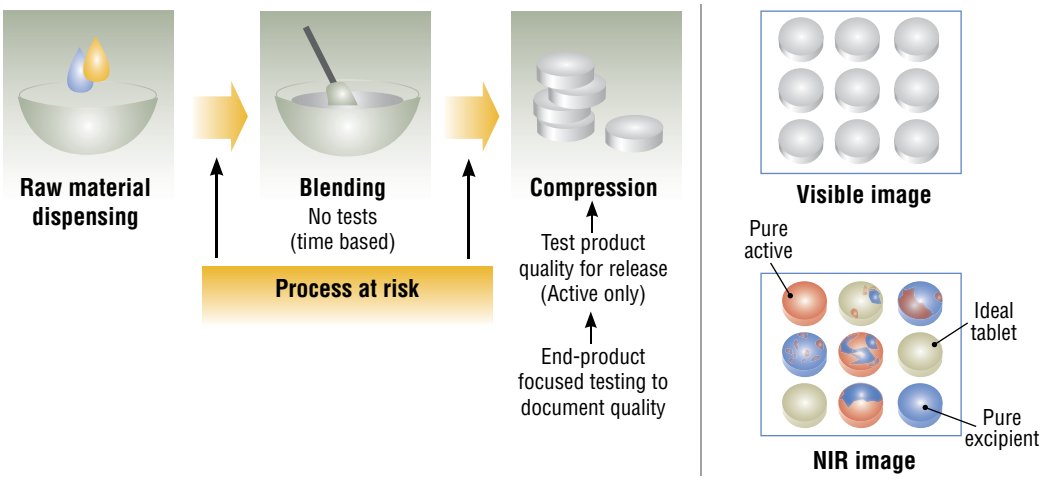
Process analytical technologies (PAT) play a key role in enabling "quality by design" and scientific manufacturing. PAT is both a framework and a system, the aim of which is to understand and control the manufacturing process. Analytical technologies include integrated chemical, physical, microbiological, mathematical and risk analysis methods. PAT has been applied in non-pharma industries for many years, yielding cost savings and manufacturing efficiencies (see sidebar: ExxonMobil uses PAT to direct and track processing and blending).

Within Pharma, there have been a number of successful PAT-based comparability protocol submissions, ranging from single-unit operation application at GlaxoSmithKline[35] to a more all-encompassing application covering both drug substance and drug product at sanofi-aventis.[36] The lessons learned to date highlight the benefit of a regulatory dialog focused on science and technology and not inspection, a questioning of the future roles of quality assurance and quality control, and a rethinking of traditional approaches to quality systems and validation.

Scientific manufacturing

PAT and scientific manufacturing are required to improve the assurance of product quality. The following illustrative case demonstrates why.[37] With tablet production, pharmaceutical companies test a relatively small number of tablets in every batch – typically 30 out of 1,000,000. This does not provide any information about the processes they are using, nor does it necessarily identify common problems. Figure 9 shows the results of a case designed to demonstrate the inability of visual inspection to assure the quality of a critical attribute such as blend uniformity.

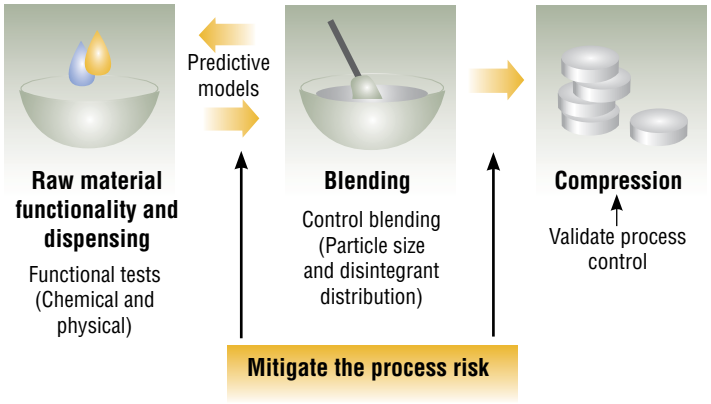
Figure 9. The current method of testing tablets focuses on the end product, but often fails to spot problems like uneven distribution of the active ingredient.



Source: Watts, D. Christopher. "Process Analytical Technology: What's in a Name?" U.S. Food and Drug Administration Science Seminar Series for the Office of Commissioner. April 9, 2004.

Appropriate in-line measuring and monitoring generates a much better understanding of the processes. Going one step further, continuous control prevents tablets from falling outside the manufacturing specifications (see Figure 10).

Figure 10. Focusing on the process that is used to make tablets eliminates major variances in the quality of the product.



Source: Watts, D. Christopher. "Process Analytical Technology: What's in a Name?" U.S. Food and Drug Administration Science Seminar Series for the Office of Commissioner. April 9, 2004.

Manufacturing to nano-measures

The IBM semiconductor factory in East Fishkill, New York, is one of the world's most highly automated 300mm fabs. A sophisticated manufacturing execution control system manages every step in the chip-making process in this "touchless" environment. Development is colocated with manufacturing and linked through common automation systems. The control system collects realtime data on every process and adjusts relevant process control parameters automatically. This approach has delivered numerous benefits:

- The elimination of product transfer and scale-up from development to manufacturing has significantly reduced time-to-market.
- Before a machine knows it has developed a problem, the fault detection system inhibits the machine from further processing, provides data to suggest the source of the problem, and notifies maintenance. A significant percentage of error recovery procedures can be executed automatically.
- Process automation enables the attainment of nine sigma processing in specific sectors.

Scientific manufacturing starts with the creation and transfer of robust processes from development into manufacturing. This lays the foundation for achieving six sigma performance in full-scale production. Development will have to identify critical control points for quality, and manufacturing will have to understand, monitor and take appropriate action when those points are exceeded. Ideally, manufacturing will adopt adaptive process control strategies and technologies, borrowing from experience in other sectors such as the semiconductor industry, where "touchless manufacturing" prevails (see sidebar: Manufacturing to nano-measures).

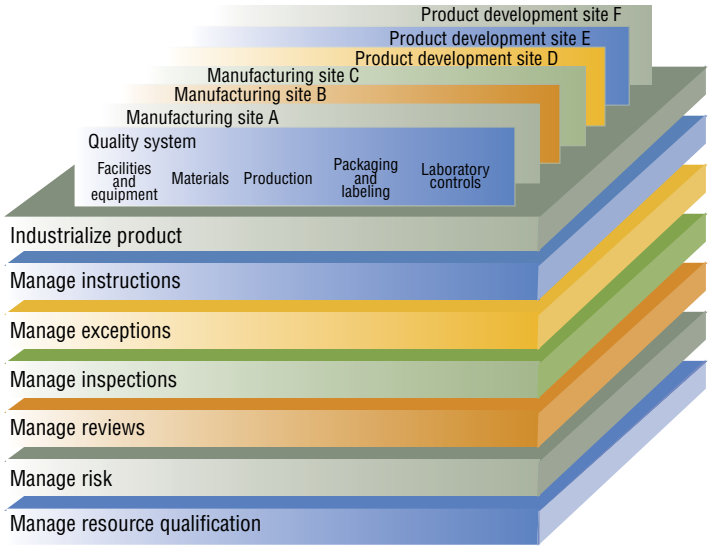
Compliance-centric business architecture

Building a "quality by design" culture

Any pharmaceutical company wanting to achieve the FDA's vision for manufacturing will need to create a compliance-centric business architecture that embeds quality into all of its manufacturing processes and products. This provides a blueprint for organizational design and process excellence.

The business architecture is the framework that aligns a company's development and manufacturing operations with its six GMP systems,[38] manages its activities via a set of standardized quality and compliance macro processes, and controls those processes through business process management (BPM) and supporting BPM technologies (see Figure 11).

Figure 11. The GMP systems within a framework of processes that manage product quality and regulatory compliance.



Source: IBM Business Consulting Services, 2005.

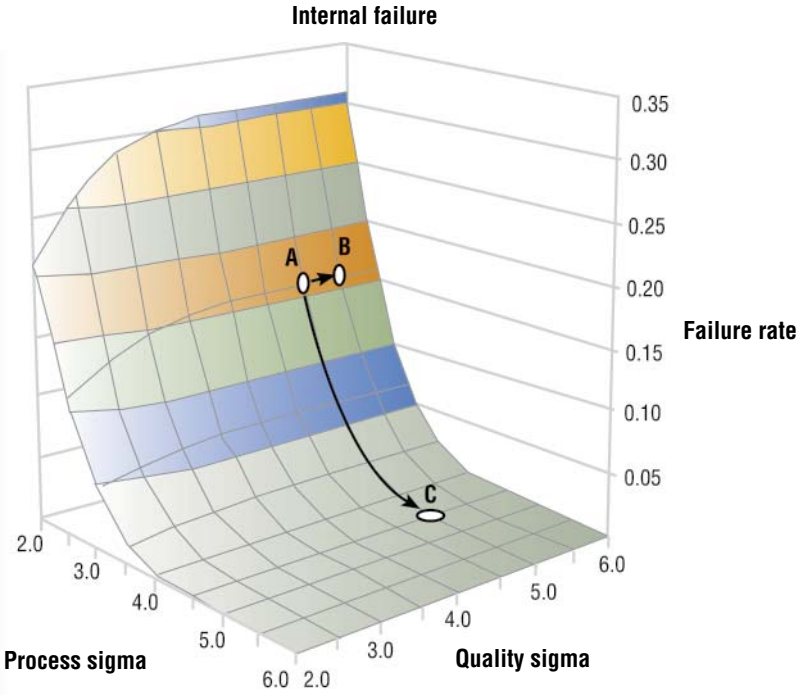
The critical factor in moving toward a systems-based approach is the definition, ownership and execution of a quality plan for each GMP system. This helps ensure that each GMP system has clearly defined its objectives, quality and regulatory requirements, resources, training needs, performance standards, controls, and targets for continuous improvement, irrespective of which department owns the GMP system.

Defining and implementing a set of standardized processes to manage quality and compliance across operations improves the consistency and quality of execution, standardizes training needs and helps ensure the delivery of sustainable quality and compliance.[39] Once these processes are harmonized and the information content is standardized, BPM and other technologies can play a role in enforcing process conformance, assessing process performance and delivering process excellence.

The major cultural change in manufacturing will be to shift the focus from "quality by inspection" to "quality by design." Most pharmaceutical companies currently rely on resource-intensive quality control systems (functioning at five sigma or more) to prevent defective products from leaving their factories. When defective products turn up outside of the company's walls, the typical reaction is to increase the controls. While this incremental investment in quality systems increases the likelihood that internal failures will be detected, it has little impact on external failure rates and actually increases costs.

Conversely, investing in "quality by design" can result in robust production processes, reduce both internal and external failure rates, and lower costs by cutting the volume of rework and rejects and reducing quality control activities. IBM analysis shows that improving the performance of a production process (process sigma) from 2.5 to 4.5 sigma yields a 1,000-fold greater decrease in defect rates than improving the performance of the quality control system (quality sigma) from 5 to 5.5 sigma (see Figure 12 and sidebar: Delivering higher-quality products).

Figure 12. Improving the performance of a production process yields much greater returns than improving the quality control system.



Source: IBM Business Consulting Services, 2005.

Delivering higher-quality products – the interplay between process and quality system capabilities[40]

Poor quality comprises internal failures and external failures. The process sigma is derived from internal failure rates (scrap, rework, waste) and provides a measure of process robustness and understanding. The quality sigma is derived from the ability of the quality system to prevent any of the internal failures created by the production process from escaping to the external environment, and in so doing to create no "false negatives."

A – Most companies are here with process sigma of 2.5 and quality sigma of 5.0, i.e. (2.5, 5.0).

B – Many companies will invest to improve "quality by inspection" without changing production processes to get here, i.e.(2.5, 5.5). This will actually increase the internal failure rate.

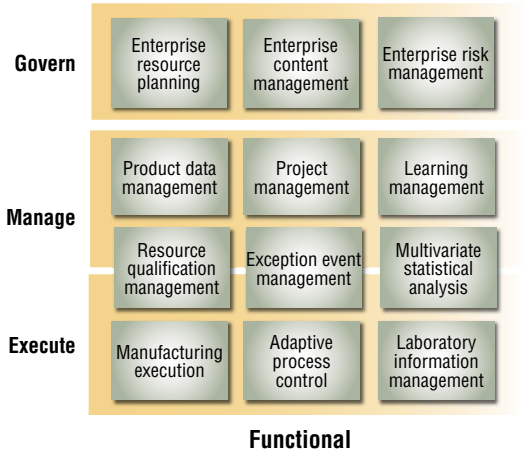
C – If a company were to invest to bring process sigma levels to 4.5 or greater to reach (4.5, 5.0), the impact on failure rate reduction would be over 1000 times greater than that obtained by improving the quality system alone.

Compliance-centric IT architecture

Lastly, every pharmaceutical company will need to move toward a compliance-centric IT architecture (CCITA). This provides a topology of system functionality to support integrated quality, manufacturing and compliance processes, and a service-oriented technical design that leverages existing IT solutions and provides services to the quality and compliance macro processes.

The functional architecture identifies the system functionalities required to support "quality by design" and scientific manufacturing (see Figure 13). Focusing on functional components (e.g., multivariate statistical analysis) instead of specific applications helps ensure that the architecture genuinely meets the needs of the business rather than reflecting the assumptions of the vendor.

Figure 13. The functional architecture required to support "quality by design" and scientific manufacturing.



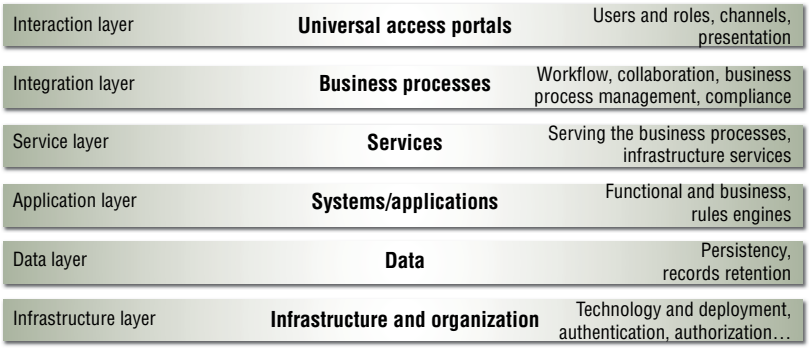
Source: IBM Business Consulting Services, 2005.

A number of these functional components – including resource planning, content management and risk management – span the entire enterprise. Others focus on the ongoing management of key components like product data, projects and learning across development and manufacturing. Yet others provide two-way links between management and execution, such as resource qualification management, exceptional event handling and multivariate statistical analysis of realtime production data. And still others cover the manufacturing execution, adaptive process control and laboratory information management required to automate manufacturing and product release using process control strategies. Together, these functional services facilitate scientific manufacturing using realtime feed-forward and feedback control loops and offline statistical analysis across manufactured lots.

With an increased emphasis on the importance of data for quality and compliance, the challenge of information lifecycle management comes to the fore. Companies need electronic archiving processes that automatically identify the point at which information is no longer being used, confirm its status and move it to a storage vault. “Right-time archiving,” as this technique is often called, requires a complete understanding of the data model that is used, including clear identification of which records are GMP-relevant and their appropriate retention requirements.

The final dimension in the CCITA is the technical architecture, which facilitates business integration and supports the functional needs of the organization (see Figure 14). It has multiple layers, each of which can be implemented and modified without affecting the others.

Figure 14. The technical architecture must be designed as a series of layers.



Source: IBM Business Consulting Services, 2005.

The technical architecture must be designed according to certain guiding principles (see Figure 15). These include open standards, common specifications and a service-oriented structure – essentially, a structure that operates as a collection of services that communicate with each other, either to pass data or to coordinate two or more activities.

Figure 15. The technical architecture must be designed according to a set of guiding principles.

Enterprise systems management
- Common systems management infrastructure and tools
- Improved operations processes
- Operations support integration with applications
- Server consolidation program

Event-driven, message-based integration
- Assured-delivery messaging infrastructure for business event distribution
- Asynchronous application integration
- Common infrastructure for data distribution and transformation

Common front end architecture
- Common infrastructure for web enablement of applications
- Common portal platform
- B2B service enablement

Service-oriented architecture
- Functionality of applications exposed as services
- Well-defined loosely coupled interfaces between well-balanced application components
- Standard technologies (e.g. XML, SOAP, Web services) used for implementation
- Services coupled through BPM

Data and content integration architecture
- Reduce the number of different technologies used for data replication
- Coherent Operational Data Store (ODS) strategy
- Master data management and data synchronization

Common security architecture
- Common security policies implemented
- Common infrastructure for identity management (authentication, credentials)
- Common infrastructure for authorization
- Enterprise-wide security management

Source: IBM Business Consulting Services, 2005.

There are significant advantages in adopting a service-oriented architecture (SOA). It provides services to the quality and compliance macro processes, and enables users to concentrate on the high-level processes rather than on the lower-level applications. An SOA can lower the cost of connections to applications, reduce complexity of integration, deliver platform and technology independence, lower maintenance costs, reduce the impact of organizational change, and facilitate the reuse of existing IT assets. While no pharma company will move directly to an SOA, IT investment decision makers today need to keep the design principles in mind. This promotes a staged migration strategy away from today's point-to-point solutions.

Summary and implications

Pharma's current performance suggests existing quality and compliance systems are stretched to their limit. "Quality by inspection" is expensive to maintain, does not deliver sustainable performance and is just not feasible for complex drug products.

The targeted treatment solutions, which IBM first forecast in its "Pharma 2010" reports[41] in 2002, are prerequisites for the industry's future commercial success. They demand more of today's quality systems and without fundamental changes in development, manufacturing and quality, Pharma will probably be unable to produce these complex new products in an economic, compliant and defect free-manner.

Pharma's manufacturing capabilities were built to meet 25-year-old GMP requirements and are unlikely to be capable of supporting 21st century product, quality and operational requirements. Significant investment in sites, pharmaceutical technology platforms, people, processes and IT is required. Failure to do so can expose a company to significant quality and compliance risk, threaten millions of dollars of future revenues, damage reputation in the market and erode shareholder value.

IBM believes that companies that embrace the new manufacturing paradigm can decrease internal failures from 16 percent to less than 1 percent, reduce COGS from 20 percent to 17 percent, and achieve process performance levels of 4.5 sigma. For the top 30 pharma companies alone, savings of around US$10 billion a year are achievable. Achieving production effectiveness rapidly can speed time to peak sales by up to two years, generating incremental revenue of US$600 million for a drug with peak sales of US$1 billion per year. Companies that can demonstrate scientific process understanding will benefit from reduced regulatory burden allowing them to build supply chains that are responsive to changing market and product needs.

Pharma companies must now engage. They must take a critical look at where they are today in terms of the quality and compliance performance of their products, technologies and GMP systems. They must quantify their risk, and identify their pathway through a multitude of subtly interrelated decisions. The path will depend on their product pipeline, supply chain strategy, investment ambition and appetite for risk. They will then need to commit to the resulting multiyear transformation agenda.

Companies that quantify their quality and compliance risks, and then plan the strategic actions to mitigate those risks, while building a foundation for "quality by design" and scientific manufacturing, will likely be rewarded with business certainty, operational efficiencies, reduced regulatory burdens and the freedom for real process and product innovation. Those companies that choose to remain in the old paradigm may not be around to see the next revision of the GMPs.

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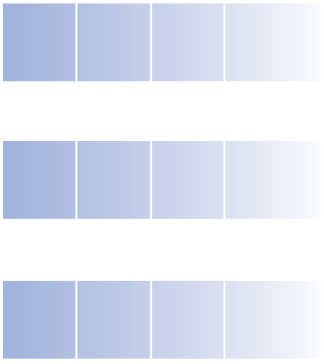


Appendix

Organization and culture

- Quality and compliance ownership is embedded in all domains of operations
- Alignment of roles and responsibilities within operations to the six GMP systems
- Root cause analysis and preventive actions encouraged and rewarded

Current state	End state
Quality owned by QA and the QC unit	Quality ownership is devolved throughout the organization via the definition of roles, responsibilities and metrics
QA expertise trapped in functional silos and focused on independent audit and control	Personnel from line operators to plant manager acquire the skills to understand quality and the application of science in development and manufacturing
QC focused on deviation reporting and escalation of problems	The quality unit focuses on root cause analysis, critical control point observation and continued process improvement
Limited interaction within the organization and externally to the regulators	The quality unit contributes to cross-functional plant driven continuous improvement
Manufacturing is measured and rewarded based on cost-centric operational metrics	Manufacturing is measured, remunerated and rewarded based on quality Key Performance Indicators and objectives
Dynamics of relationship with regulators shaped by fear and mistrust	Collaboration with regulators from early development phase; Relationship based on trust with patient safety the common goal
Quality measured by macro indicators such as number of recalls, number of inspections passed	Quality is measured through cascaded Key Performance Indicators

End-to-end process understanding

- Specific process parameters and control limits linked to patient Critical-To-Quality attributes (CTQs)
- Realtime quality intervention – "Autonomation"
- Full parametric release wherever scientifically possible
- Continuous manufacturing
- Elimination of process and system validation

Current state	End state
Univariate process understanding	Multivariate process understanding
Focus on retrospective destructive testing	Focus on realtime feedback loops using Process Analytical Technologies (PAT) to correct and modify process parameters
Manufacturing processes are variable, unstable and fragile	Manufacturing processes are demonstrated to be reliable, stable and robust
Acceptance of, and planning for, poor quality, e.g., retest	Critical control parameters enable multivariate scientific verification of process performance
Three batch validation runs	Validation runs replaced through demonstrated scientific process and product knowledge
Document-centric computer system validation	Science-based process understanding applied to non-pharma processes

Process integration

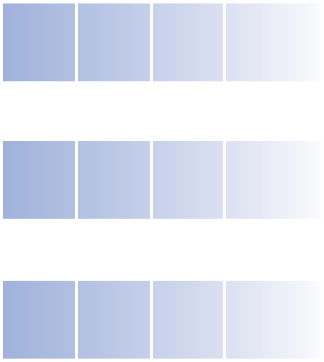
- Business process components are shared across nonclinical development and manufacturing – e.g., Standard Operating Procedures (SOPs), development reviews, bills of materials, material specifications, manufacturing instructions, analytical methods and specifications

Current state	End state
Paper handover and manual conversion of manufacturing procedures and specifications from development to operations (composition to bill of material, formulation process to process instruction)	Collaboration between development and manufacturing in the definition of specifications and methods
Handover of completed development report	Ongoing manufacturing review of development reports throughout dossier assembly
SOPs developed by each and every department	Common SOPs used in development and manufacturing
Material specifications are defined in development without consideration of impact in manufacturing	Material specifications are defined within manufacturing ranges
Formulations are defined without consideration of impact in manufacturing	Formulations are defined with consideration for manufacturability
Analytical methods and specifications are defined without consideration of impact in manufacturing	Analytical methods and specifications consider realistic manufacturing constraints such as resources, equipment and costs
Design and development activities based on experimental knowledge, intuition and rough guidelines. Design documents in descriptive "recipe" format (e.g., executed batch records, SOPs)	Science of design demonstrated in the Chemistry Manufacturing Controls (CMC) section in line with ICH Q8 Guideline for Pharmaceutical Development

Technology integration

- Dedicated technology components are linked together in an open architecture
- Business processes have access to data that is accurate, timely, relevant and complete
- Business process management (BPM) provides automated process control and performance metrics
- Single cross-domain compliance-centric applications

Current state	End state
Isolated point solutions	Virtually connected open architecture of solution components – laboratory information management systems, manufacturing execution systems, enterprise resource planning systems
Redundant data	Single master data source
Manual data reentry	Manual data entry by exception
Information trapped in unstructured data	Data is interchangeable across structured and unstructured sources – e.g., extensible markup language (XML)
Historical data embedded in legacy system	Systems are freed up by intelligent background archiving of data
Custom interfaces	Enterprise application integration technologies replace point-to-point interfaces
Ad-hoc hybrid information retrieval processes	Automated information retrieval processes based on time and frequency of access needs
Data incompatibility	Atypical data forms are not a constraint
Difficult to connect with external partners	External collaboration is technically enabled



Science-based decision making

- Realtime data is sourced directly from the appropriate process and technology components
- Analytics are used to support scientific, fact-based quality, compliance and risk management decision applications

Current state	End state
Decision making is intuitive	Quantitative and qualitative data used to support decision making
Poor quality data supports decision making	High confidence in data quality and integrity. Scientific robust decision making
Data is redundant, incomplete, inconsistent, unreliable and trapped in system silos	Data sourced from across the value chain increases quality of decision making
Data access inhibits systematic, multivariate analysis	Data pushed to systematic, multivariate analysis engines
Decision making is constrained by data collection speed	Realtime, data-driven decision making
Decision making based on retrospective data analysis	Decision making based on balance of retrospective analysis and predictive modeling

Value-driven compliance

- Sustainable inspection readiness across the value chain
- 4.5 sigma for business processes directly impacting quality and compliance
- Cost of quality < 10% of controllable costs

Current state	End state
Specially assigned team prepares for inspection	Inspection is handled by day-to-day, operational staff
Peaks and troughs of inspection readiness	Continuous, consistent and sustainable level of inspection readiness
Paper-based inspection	Electronic reading rooms and virtual inspection capability
4 sigma level perceived – 2 sigma actual	4 sigma level tending to 5
Cost of quality unknown	Cost of quality measured and tracked
Costs of poor quality steadily increasing	Cost of quality down 20 - 25% to <10% and decreasing
Compliance effectiveness unmeasured	Metrics defined and objectives set to achieve greater compliance/quality effectiveness

References

1 Bruttin, F., and D. Dean. Best Practice Performance in Pharmaceutical Production. Pharmaceutical Manufacturing International. Boardroom Issues, pp. 13-16, vol. 1997.

2 "Innovation and Continuous Improvement in Pharmaceutical Manufacturing Pharmaceutical CGMPs for the 21st Century." Department of Health and Human Services, U.S. Food and Drug Administration. September 2004. http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf (accessed April 6, 2005).

3 "COMPANIES THE AMERICAS: Pulling Vioxx cuts Merck profits by 29%." *Financial Times*. October 22, 2004.

4 IBM Business Consulting Services analysis, 2005.

5 Ibid.

6 Datamonitor PLC. "Benchmarking Blockbusters: Identifying winning products and therapy areas to 2008." July 2003. Reference code: DMHC1927.

7 Hovey, Hollister. "J&J Recalling 300 Cypher Stents Sent To 145 Hospitals." *Dow Jones Newswires*. January 15, 2005.

8 U.S. Food and Drug Administration. "Final Report on Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach." September 2004. http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm (accessed April 6, 2005).

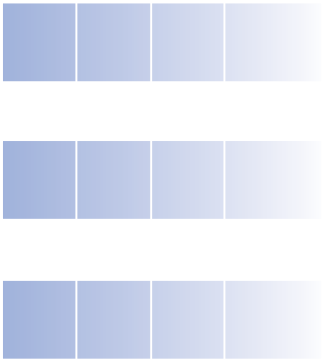
9 Abboud, Leila and Scott Hensley. "New Prescription for Drug Makers: Update the Plants." *The Wall Street Journal*. September 3, 2003.

10 "FDA Drug GMP Warning Letters." *The Goldsheet*, vol. 38, no. 4, April 2004. http://www.thegoldsheet.com/FDC/Monthly/Gold/TOC.htm (accessed April 7, 2005).

11 Ibid.; "FDA's Drug GMP Warning Letter Usage." *The Goldsheet*, vol. 39, no. 3, March 2005. http://www.thegoldsheet.com/FDC/Monthly/Gold/TOC.htm (accessed April 7, 2005).

12 Hussain, Ajaz. "FDA ACPS Process Analytical Technology (PAT) Subcommittee Meeting #3 Opening Remarks." October 23, 2002. http://www.fda.gov/ohrms/dockets/ac/02/slides/3901S1_01_Hussain_files/frame.htm (accessed April 6, 2005).

13 Abboud, Leila and Scott Hensley. "New Prescription for Drug Makers: Update the Plants." *The Wall Street Journal*. September 3, 2003.



[14] Joiner, Brian L., Marie A. Gaudard. "Variation, Management and W. Edwards Deming." *Quality Progress*, December 1990, pp. 29-37. http://deming.eng.clemson.edu/pub/den/files/varman.txt (accessed May 17, 2005).

[15] "Innovation and Continuous Improvement in Pharmaceutical Manufacturing Pharmaceutical CGMPs for the 21st Century." Department of Health and Human Services, U.S. Food and Drug Administration. September 2004. http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf (accessed April 6, 2005).

[16] Hussain, Ajaz. "On the Road to 'Process Understanding.'" Arden House 2004, London. http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4052B1_09_Hussain-Arden-UK-Presentation.ppt (accessed April 6, 2005).

[17] Personal interview with pharmaceutical company fabricator, December 2004.

[18] IBM Business Consulting Services analysis, 2005.

[19] Scherzer, R. "Quality by Design: A Challenge to the Pharma Industry." CAMP, U.S. Food and Drug Administration Science Board. April 2002. http://www.fda.gov/cder/OPS/Scherzer-Camp/index.htm (accessed April 6, 2005).

[20] Barry, Daniel. ed. Scrip's 2004 Pharmaceutical Company League Tables. PJB Publications. 2004.

[21] "FDA will seek Consultant Help in Implementing Quality Initiative." *The Goldsheet,* vol. 36, no. 9, September 2002.

[22] Roche. "Fuzeon's groundbreaking efficacy confirmed in latest edition of NEJM." http://www.roche-hiv.com/Newsandfeatures/newsdet.cfm?hnid=272 (accessed April 18, 2005).

[23] Kerberand, Ross and Jeffrey Krasner. "Johnson & Johnson missing out on stent sales." *The Boston Globe*. August 19, 2004. Stored in electronic archive at http://www.boston.com/news/globe/ (accessed December 3, 2004).

[24] Fraser, Heather E. and Walter Van Dyck. "Transforming Industrialization: A new paradigm for development." March 2005. http://www-1.ibm.com/services/us/index.wss/xs/imc/a1010452?cntxtId=a1000060 (accessed April 18, 2005).

[25] Ramsbotham, Joyce. "The 'Q10' Quality Systems Initiative aimed at harmonizing Quality Systems Stimulating Continuous Improvement." Solvay Pharmaceuticals. Parenteral Drug Association annual conference in Rome. March 2005.

[26] Ibid.

[27] Nasr, Moheb. "Risk-Based CMC Review Paradigm." Advisory Committee for Pharmaceutical Science Manufacturing Subcommittee, July 20-21, 2004. http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4052S1_10_Nasr.ppt (accessed April 6, 2005).

[28] Bush, Laura. "From CGMPs to the Critical Path: FDA Focuses on Innovation, Quality and Continuous Improvement – Inside and Out." *Pharmaceutical Technology.* July 2004.

[29] Grossman, Ignacio. Carnegie Mellon University. http://egon.cheme.cmu.edu/ (accessed April 18, 2005).

[30] For a more detailed explanation of the model, please see E. Pratsini et al. "Risk Optimization in the Pharmaceutical Supply Chain." Proceedings of INFORMS, October 24-27, 2004, Denver, Colorado.

[31] IBM Business Consulting Services analysis, November 2004.

[32] The National Science Foundation. "Science of Design." Program Solicitation 04-552. May 19, 2004. http://www.nsf.gov/pubs/2004/nsf04552/nsf04552.htm (accessed April 6, 2005).

[33] "Q8 Pharmaceutical Development ICH Draft: Step 2." November 18, 2004. http://www.fda.gov/cder/guidance/6672.dft.htm (accessed April 6, 2005).

[34] ExxonMobil Corporation. 2004 Financial & Operating Review. http://www.hoovers.com/free/co/secdoc.xhtml?ID=&ipage=http://hoovers.10kwizard.com/xml/filing.php?repo=tenk&ipage=3340204&attach=ON (accessed April 28, 2005)

[35] "GSK announces FDA approval of their first PAT submission." *AAPS NewsMagazine*. April 2004.

[36] Radspinner, David. "Implementation of PAT: An Industry Perspective." sanofi-aventis. RPS/FDA/Meeting, London, December 14, 2004. http://www.fda.gov/cder/OPS/Radspinner.pdf (accessed April 6, 2005).

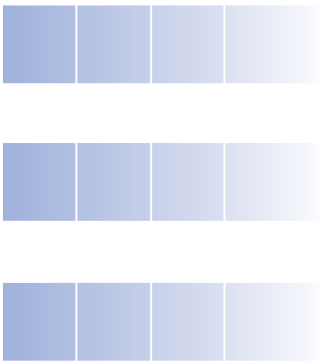
[37] Watts, D. Christopher. "Process Analytical Technology: What's in a Name?" U.S. Food and Drug Administration Science Seminar Series for the Office of Commissioner. April 9, 2004. http://www.fda.gov/cder/present/DIA2004/Watts_files/frame.htm (accessed April 6, 2005).

[38] U.S. Food and Drug Aministration. "Compliance Program Guidance Manual for FDA Staff: Drug Manufacturing Inspections Program 7356.002." http://www.fda.gov/cder/dmpq/compliance_guide.htm (accessed April 18, 2005).

[39] Dean, D., and F. Bruttin. "Risk and the Economics of Regulatory Compliance." *Parenteral Drug Association Journal of Pharmaceutical Technology*, vol. 54, no. 3, pp. 253-263, May-June 2000.

[40] Ibid.

[41] "Pharma 2010: The threshold of innovation." IBM Business Consulting Services. 2003. http://www-1.ibm.com/services/us/index.wss/xs/imc/a1001099?cntxtId=a1000060 (accessed April 18, 2005).



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