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# The Financial Returns on Investments in Process Analytical Technology and Lean Manufacturing: Benchmarks and Case Study

**Robert P. Cogdill · Thomas P. Knight · Carl A. Anderson · James K. Drennen III**

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**Abstract** The combined deployment of process analytical technology (PAT) and Lean manufacturing offers extraordinary financial opportunities for pharmaceutical manufacturers at every scale. While many articles have been published describing the economic and quality opportunities presented by improved pharmaceutical manufacturing performance, greater understanding of the financial benefits of PAT and Lean at the individual company level is needed to support accurate valuation of corporate investments in manufacturing performance upgrades. This paper describes research using industrial benchmarks and published data for publicly-traded companies to demonstrate the value potential posed by combined deployment of PAT and Lean in pharmaceutical manufacturing operations. A method of estimating the financial return on investments in PAT and Lean is described by considering their impact on the profitability of a hypothetical mid-sized generic pharmaceutical manufacturer. The results of the case study show that based on benchmark data for the generic drug manufacturers, it is possible to return savings of up to 6% of revenues by improving process capability and supply chain management through strategic deployment of PAT and Lean manufacturing.

**Keywords** PAT · Lean manufacturing · Process capability · Supply chain management · Pharmaceutical manufacturing

**Abbreviations**

| | |
|---|---|
| C/T | Process cycle time |
| cGMP | Current good manufacturing practice |
| CoQ | Cost of quality |
| *Cpk* | Process capability index |
| EBITDA | Earnings before interest, taxes, depreciation, and amortization |
| FG | Finished goods (inventories) |
| KPI | Key performance indicator |
| NVA | Non-value-added |
| OTC | Over-the-counter |
| QbD | Quality by design |
| PAT | Process analytical technology |
| RAROI | Risk-adjusted return on investment |
| %RFT | % Right-first-time |
| RM | Raw materials (inventories) |
| RTR | Real-time-release |
| SKU | Stock-keeping-unit |
| TQM | Total quality management |
| VAR | Value-added ratio |
| WACC | Weighted-average cost of capital |
| WIP | Work-in-progress (inventories) |

R. P. Cogdill (✉)
Duquesne University Center for Pharmaceutical Technology,
410A Mellon Hall, 600 Forbes Ave.,
Pittsburgh, PA 15282, USA
e-mail: cogdillr@duq.edu
URL: www.dcpt.duq.edu

T. P. Knight
Invistics Corporation, 5445 Triangle Pkwy.,
Suite 300, Norcross, GA 30092, USA
URL: www.invistics.com

C. A. Anderson
Strategic Process Control Technologies, LLC,
306 Winter Run Lane, Mars, PA 16046, USA
URL: www.spctechllc.com

J. K. Drennen III
Mylan School of Pharmacy, Duquesne University,
600 Forbes Ave., Pittsburgh, PA 15282, USA
URL: www.pharmacy.duq.edu

## Introduction

The combined deployment of process analytical technology (PAT) and Lean manufacturing offers extraordinary financial opportunities for pharmaceutical manufacturers at every scale. In the few years since the kickoff of FDA's twenty-first century cGMP and PAT initiatives [1, 2], many articles have been published describing the economic and quality opportunities presented by improved pharmaceutical manufacturing performance. In general, though, financial opportunities have been described in terms of aggregate impact on the industry [3–6] or, more recently, benefits to public health and the overall economy [7]. While such projections are interesting and worthwhile, greater understanding of the financial benefits of PAT and Lean at the individual company level is needed to support accurate valuation of corporate investments in manufacturing performance upgrades.

This paper describes research using industrial benchmarks and published data for publicly-traded companies to demonstrate the value potential posed by combined deployment of PAT and Lean in pharmaceutical manufacturing operations. A method of estimating the financial return on investments in PAT and Lean is described by considering their impact on the profitability of a hypothetical mid-sized generic pharmaceutical manufacturer. The remaining portions of this paper describe PAT and Lean manufacturing, how they work synergistically to unlock value from operations, and current benchmarks for operating performance in the pharmaceutical industry. Most details regarding the implementation of systems for PAT and Lean are not discussed since they are often quite subjective, and are beyond the scope of this work. While some of the financial and operational assumptions used for this work are specific to the presented case study, the estimation techniques presented are generally applicable.

## PAT and Efficient Quality Management

The main goal of PAT has often been summarized as simply being to "achieve greater process understanding" and thereby mitigate risks to product quality. Perhaps to the detriment of the rate of implementation, the potential for financial returns on investment in PAT has been treated as a secondary issue. This should not be unexpected, though, since the FDA has been clear that improving quality assurance and streamlining oversight activities has been their goal in promoting PAT and reforming cGMPs. While increasing process understanding is a laudable goal, it doesn't necessarily induce much action on the part of manufacturers if it is unclear as to whether the integration of process analytics into their operations will yield positive or negative returns.

Despite all of this, however, there is ample evidence that process analytics can be implemented with an expressed goal of improving efficiency and profitability so long as the new technology's impact on process quality assurance is positive (as detailed in advance, e.g. by a project comparability protocol). Furthermore, as noted in the Agency's PAT guidance document [2]:

> *...(PAT) is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance.*

The guidance continues with:

> *...(efficient pharmaceutical manufacturing) is a critical part of an effective U.S. health care system. The health of our citizens depends on the availability of safe, effective, and affordable medicines.*

Thus, process efficiency is an important consideration for patients and employees as well as shareholders; the potential for economic impact should be afforded ample consideration when considering the merit of investments in PAT. According to the PAT guidance, gains in quality, safety and/or efficiency are likely to come from:

- *Reducing production cycle times (C/T) by using on-, in-, and/or at-line measurements and controls*
- *Preventing rejects, scrap, and re-processing*
- *Real-Time-Release (RTR)*
- *Increasing automation to improve operator safety and reduce human errors*
- *Improving energy and material (resource) use and increasing capacity*

While the list is accurate, it is neither exhaustive nor instructive; the Agency has necessarily left it to companies to determine for themselves the financial value potential of PAT projects.

Process analytics do not inherently add value to an operation. Rather, PAT methods and tools enhance management strategies such as Lean manufacturing and Quality management which are designed to maximize yield and efficiency, thereby allowing companies to retain a greater share of the economic value added by operations. Hence, the investment value of PAT depends upon the degree to which it is integrated with corporate quality and Lean initiatives.

### Quality Management and the Total Cost of Quality

Within the context of this work, quality management refers to practices used to systematically identify and suppress operational and design factors which contribute to product quality variation. Based on the description provided by the FDA guidance, the objectives of PAT systems are closely

analogous with popular quality management systems, such as Six Sigma [8] and Total Quality Management (TQM) [9]. Investments in quality management systems generate financial returns by lowering the total cost of quality (CoQ). The "P-A-F" CoQ model, established by Armand Feigenbaum in 1956, groups quality costs according to elements of Prevention, Appraisal, and Failure (internal and external), each of which is described in the following paragraphs [10–12].

Failure costs are the price of operating imperfect processes. Internal failure costs are incurred as defective units (i.e. batches of product) are identified prior to release for distribution, resulting in expenditures for investigation, documentation, rework (and re-inspection), or write-off and disposal. The financial burden of internal failure costs for an operation are a direct function of the ability of the process to maintain product quality within specified limits, as characterized by process capability indices such as the *Cpk*:

$$\mathrm{Cpk} = \min\left[\frac{\mathrm{USL}-\mu}{3\sigma}, \frac{\mu-\mathrm{LSL}}{3\sigma}\right] \quad (1)$$

where, $\mu$ and $\sigma$ are the mean and standard deviation, and USL and LSL are the upper and lower specification limits, respectively, for a product quality measurement. The process capability index, Cpk, is directly related to the so-called "process sigma" such that a $6\sigma$ process corresponds to a Cpk of exactly 2.00, or 2.0 defective parts per billion (PPB), assuming $\sim N(0,\sigma)$ quality variance distribution (an alternative calculation for process sigma estimates 3.4 defective parts per million for a $6\sigma$ process; see "Appendix" for discussion on the calculation of process sigma) [8].

External failure costs are incurred as defective units are identified following shipment to distributors or consumers, resulting in expenditures for complaint investigations, product recall, and penalties. External failures can be the result of finite process capability, as well as product design (e.g. degradation or lack of performance). Many CoQ models include intangible and opportunity costs related to (internal and external) failures; such costs might include erosion of brand image, loss of confidence by supply chain partners, or, perhaps, increased regulatory scrutiny. Pharmaceutical manufacturers are required by law to provide assurance that products released for distribution meet strict quality criteria; thus, the expected value of external failure costs should be zero. Since the actual capabilities of production and inspection systems are finite, however, external failure costs should be built into operating CoQ and risk models.

All other quality costs are attributable to either prevention or appraisal activities. Appraisal costs are operating expenses associated with determining the degree of conformance to quality requirements, including inspection of raw materials (RM), work-in-process (WIP), and finished goods (FG), as well as the cost of maintaining inspection systems (calibration, maintenance, depreciation, labor, etc.), whether conducted by the quality unit, production, or an external laboratory [10]. The labor costs associated with quality control and assurance (QC/QA) can account for more than two thirds of operating labor, or approximately 10% of revenues of pharmaceutical manufacturers. The significant financial burden imposed by such extensive quality units is the result of operating for many years with quality systems which were geared more toward "quality by inspection."

Prevention costs, which are incurred in keeping failure and appraisal costs to a minimum [10], can be more difficult to evaluate since many standard protocols, such as process and product design, new product review, and supplier evaluations have built-in aspects of defect prevention. There are many defect prevention investments, though, for which costs can be more directly appraised, such as quality training, quality risk assessment, and process controls. Investments in defect prevention, such as quality by design (QbD), continuous improvement, and PAT-enabled controls, which are emphasized by FDA's twenty-first century cGMPs, reduce total CoQ by increasing process capability, which both reduces failure costs and enables reduced spending on inspection activities.

## Lean Manufacturing

Lean manufacturing describes a management philosophy and associated practices concerned with improving profitability by systematic identification and suppression of activities which contribute to waste. Wasteful activities (or *muda*) which must be minimized include overproduction, waiting, transportation, inappropriate processing, unnecessary inventory, unnecessary motion, and production of defective units; all of which have the effect of increasing the proportion of non-value-added (NVA) activities and, therefore, process cycle time. Processes which have a high percentage of NVA activities will by definition have relatively high C/T, and will correspondingly have a low rate of inventory turnover. Inventory turnover scales directly with the inverse of C/T, and is estimated by calculating the ratio of cost of goods sold (COGS) to the average value of inventories over the same time period. Total inventory turnover rate, along with the rates of RM, WIP, and FG turnover, and process value-added ratio (VAR) [13], are key performance indicators (KPI) of supply chain and working capital management effectiveness.

Low inventory turnover can also be an indicator of hidden problems in production; operations plagued by frequent batch failures, for example, utilize overproduction to maintain a "safety stock" of WIP or FG inventories to

avoid downtime or reduced customer service (e.g. delayed shipment of orders). As process capability degrades, variance in C/T increases, or if there are many products which must share the same production flow path, it is commonplace for some managers to build even greater WIP queues to maintain high capacity utilization rates [14]. While RM, WIP, and FG queues ensure that "no people or machines sit idle," they also ensure that plenty of people are busy transporting, documenting, and monitoring the inventories. Moreover, the value of inventories can consume a significant portion of financial working capital, rendering it unavailable to be deployed for potentially more valuable investments.

Investments in Lean manufacturing systems generate financial returns by reducing average inventory levels, thereby reducing both carrying costs, and working capital [15]. Perhaps as a consequence of FDA's definition of PAT, which is necessarily focused on quality management, Lean manufacturing has not typically been considered as an integral component of PAT implementations. This is unfortunate, however, since the deployment of PAT is critical to achieving the maximum benefit of Lean manufacturing initiatives. Specific PAT projects enable Lean operation by enabling real-time-release (RTR), by reducing the C/T of operations, and by improving the predictability (i.e. reducing the variability of) C/T.

In addition to overhead and working capital savings related to inventory management, the value of improved customer service is often overlooked as a driver for implementing Lean manufacturing in the pharmaceutical industry. While branded drug manufacturers are less threatened by the availability of alternative suppliers for their products, manufacturers of generic and over-the-counter (OTC) drug products have significant motivation to maintain low order lead-times as a way of differentiating their products (and avoiding late-delivery penalties) in a make-to-order marketplace. Alternatively, considering make-to-stock scenarios, such as an inventory buildup in advance of a new product launch or period of market exclusivity, Lean manufacturing can be an important factor in assuring that a sufficient, timely supply of product is available (during the challenges of initial operation of a new process).

## Pharmaceutical Manufacturing Benchmarks

### Cost of Quality

Unfortunately, even though CoQ is a well-accepted concept in operations management, few companies have implemented rigorous CoQ systems; as a result, management tends to drastically underestimate the total magnitude of quality costs paid by their organizations [11]. Consequently, no specific benchmark data for CoQ in the pharmaceutical industry was found. There are, however, many different published estimates of process capability for the pharmaceutical industry. Some recent estimates of percent right-first-time (%RFT), or yield, range from 85–95% [4, 16], 90–95% [6], 2–3$\sigma$ (96–99% RFT) [5]. A recent industrial benchmarking study conducted by Macher and Nickerson (with the cooperation of the FDA) estimated the average process yield for a sample of pharmaceutical manufacturers to be approximately 96% [17], which corresponds to Cpk of ~0.7, or ~2.0$\sigma$. Despite the lack of published quantitative data for the relative magnitude of individual cost components of internal failure for the pharmaceutical industry, it should be apparent that internal failure costs are greater than simply the 4% of production which must be either reworked or scrapped.

### Lean Manufacturing

Estimates from the Macher and Nickerson report indicated average WIP C/T of approximately 27 days, which implies approximately 13.5 WIP inventory turns per year [17]. Despite the fact that the observed variance of reported C/T data was quite extreme (the standard deviation of C/T was greater than 28 days), the published estimates are corroborated by WIP turn rates calculated from the industrial financial data shown in Table 1 and Fig. 1.

Since the total time to complete the most common unit operations required for solid dosage manufacturing is far less than 27 days, it is apparent that pharmaceutical production operations are plagued by quite high levels of NVA activities, or, alternatively, operate at very low VAR [13]. Turnover rates for the companies reporting inventory data are shown in Fig. 2.

It is sometimes opined that pharmaceutical manufacturers are limited in their ability to increase inventory turnover due to the need to maintain large safety stocks of FG inventories. The fact that non-pharmaceutical manufacturers held substantially greater FG safety stocks as a proportion of total inventories tends to contradict this theory.

The total inventory turnover rates for mid-sized and generic manufacturers are roughly similar to the turnover rates shown for larger companies on an absolute basis (Fig. 2). After adjusting for the relationship between inventory turnover and gross margins, however, it can be seen that generic drug manufacturers are unique in having particularly low rates of inventory turnover (Fig. 3). A 2006 report by Supply Chain & Logistics Canada indicates that, surprisingly, pharmaceutical supply chain management performance has actually degraded relative to other manufacturing industries in recent years. While North American

**Table 1** Tabular comparison of market cap, breakdown of revenues, components of inventories, and inventory turnover rates for major branded, mid-sized and generic, and non-pharmaceutical process-based manufacturers

| | Major branded pharma | | | | Mid-sized/generic pharma | | | | Non-pharma manufacturers | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Median ($Bil.) | High ($Bil.) | Low ($Bil.) | Sample (*n*) | Median ($Bil.) | High ($Bil.) | Low ($Bil.) | Sample (*n*) | Median ($Bil.) | High ($Bil.) | Low ($Bil.) | Sample (*n*) |
| Market Cap. | 120 | 190 | 67 | 10 | 5 | 37 | 0.95 | 9 | 30 | 200 | 0.50 | 14 |
| Components of revenue | Median (%) | High (%) | Low (%) | Sample (*n*) | Median (%) | High (%) | Low (%) | Sample (*n*) | Median (%) | High (%) | Low (%) | Sample (*n*) |
| COGS | 26 | 44 | 16 | 10 | 51 | 71 | 22 | 9 | 52 | 85 | 26 | 14 |
| R & D | 15 | 21 | 10 | | 8 | 14 | 4 | | <1 | 8 | 0 | |
| SG & A | 32 | 37 | 27 | | 21 | 35 | 15 | | 30 | 63 | 3 | |
| Operating margin | 27 | 34 | 9 | | 8 | 29 | −23 | | 13 | 19 | −6 | |
| Components of inventory | Median (%) | High (%) | Low (%) | Sample (*n*) | Median (%) | High (%) | Low (%) | Sample (*n*) | Median (%) | High (%) | Low (%) | Sample (*n*) |
| Raw materials (RM) | 21 | 31 | 8 | 7 | 35 | 63 | 22 | 9 | 22 | 47 | <1 | 8 |
| Work-in-process (WIP) | 35 | 68 | 24 | | 15 | 33 | 1 | | 9 | 25 | 4 | |
| Finished goods (FG) | 41 | 54 | 27 | | 49 | 64 | 36 | | 65 | 84 | 38 | |
| Inventory turn rates | Median (turns) | High (turns) | Low (turns) | Sample (*n*) | Median (turns) | High (turns) | Low (turns) | Sample (*n*) | Median (turns) | High (turns) | Low (turns) | Sample (*n*) |
| Raw materials (RM) | 13 | 19 | 6 | 7 | 8 | 12 | 2 | 9 | 23 | 4153 | 11 | 8 |
| Work-in-process (WIP) | 7 | 14 | 2 | | 15 | 8 | 5 | | 36 | 218 | 15 | |
| Finished goods (FG) | 6 | 8 | 5 | | 4 | 7 | 2 | | 8 | 30 | 3 | |

All data were gathered from 2006 annual reports from publiclytraded companies. Non-pharmaceutical companies were chosen randomly from manufacturing industries having similar processes to pharmaceutical manufacturers (chemical manufacturing), and from food manufacturers who are expected to face similar requirements for cGMP production and inventory controls.

manufacturers in all industries have increased their aggregate supply chain efficiency by 20% since 1992, inventory turnover has actually decreased by 36% for pharmaceutical manufacturers in the same survey [18].

### The Cost of Inventory Management

The annual cost of poor C/T performance can be estimated by considering the carrying costs associated with maintaining excess RM, WIP, and FG inventories. Inventory carrying costs include two major components—weighted-average cost of capital (WACC), and overhead.

WACC is a company-specific measure of the cost of allocating capital to internal investments which includes components related to financing costs (e.g.—interest rate on debt), as well as opportunity costs incurred by consuming working capital to finance inventories (e.g.—the expected return on equity from alternative internal investments). Despite the fact that the cost of debt financing and risk premiums are near all-time lows, WACC for the pharmaceutical industry is still quite high due to the opportunity costs of capital allocation. Estimates based on January 2007 data indicate WACC for drug companies of 11.97% [19].

Overhead costs associated with inventory carry include items such as expiration loss, cost of facilities, insurance, paperwork, transportation and physical handling, spillage/damage, and theft/pilferage. While published data for inventory overhead costs for the pharmaceutical industry were not found, a survey on inventory carrying cost estimates suggests the combination of WACC and overhead is likely to be greater than 25% [20]. The Supply Chain & Logistics Canada report indicates, however, that 20% is the generally-accepted standard inventory carrying cost rate assumed by pharmaceutical industry management professionals [18]. Hence, based on the more-conservative estimate of inventory carrying costs, companies can expect to return 20¢ in ongoing cost savings for every dollar's worth of inventory reduction. In addition to carrying-cost savings, however, every dollar of inventory reduction yields an equivalent one-time cash return of working capital which can be applied toward debt reduction or more profitable alternative investments in growing the company (e.g. R & D).

## Case Study

### Description of Operations

Consider the situation for a mid-sized company which manufactures small-market branded, generic, and OTC solid oral pharmaceutical dosage forms having a market capitalization of ~$1 billion; which is roughly the size of

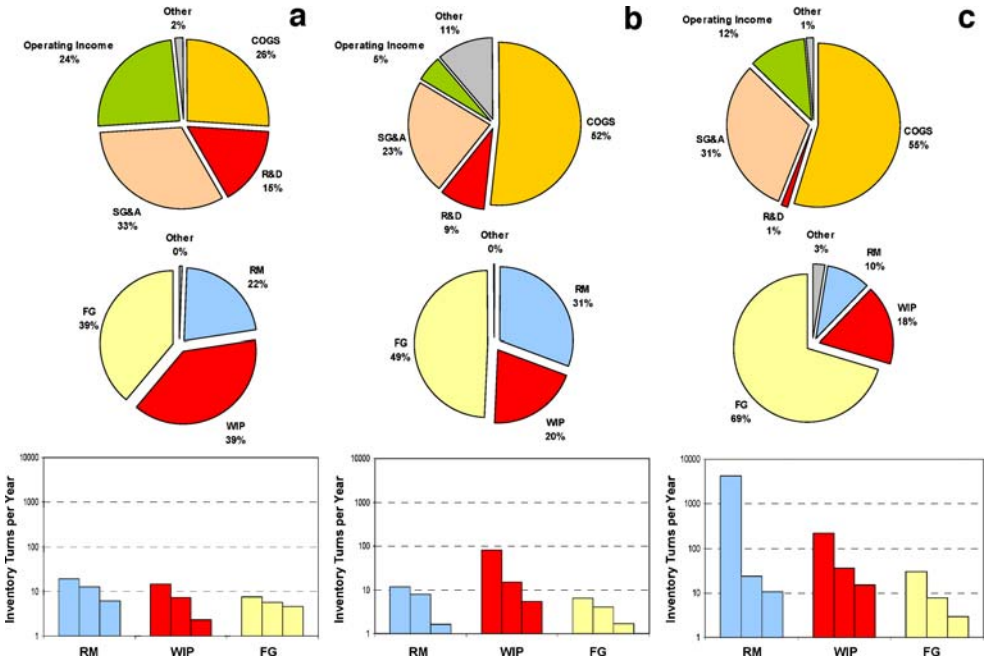


**Fig. 1** Graphical comparison of (*top to bottom*) the breakdown of revenues, components of inventories, and inventory turnover rates for major, branded (**a**), mid-sized and generic (**b**), and non-pharmaceutical process-based manufacturers. The *vertical bars* in the lower graphs correspond to maximum, median, and minimum turnover rates

the smallest public drug company surveyed for this research. While the company utilizes only a single technology platform based on high-shear wet granulation, dozens of SKUs are scheduled through the flow path to generate approximately $450 million in annual sales. The average C/T map for the company is shown in figure (Fig. 4). Only 24% of the average WIP cycle is related to value-added activities, and only 3.7% of the total C/T is related to value added (VAR=0.037). It is important to distinguish between value-added and "required" activities; while multiple QC activities are required for this operation, they add nearly 20 days of NVA to the average C/T. The company reports inventory cycle times for RM, WIP, and FG of 46, 25, and 91 calendar days, which translates to inventory turnover rates of approximately 8, 14.6, and 4 per year, with an overall inventory turn rate of 2.25 per year. In line with its peers, the company maintains process capability of ~0.7, or ~2.0$\sigma$. Since there is no formal CoQ accounting system in place, however, the total expenditure on maintaining quality for each unit of

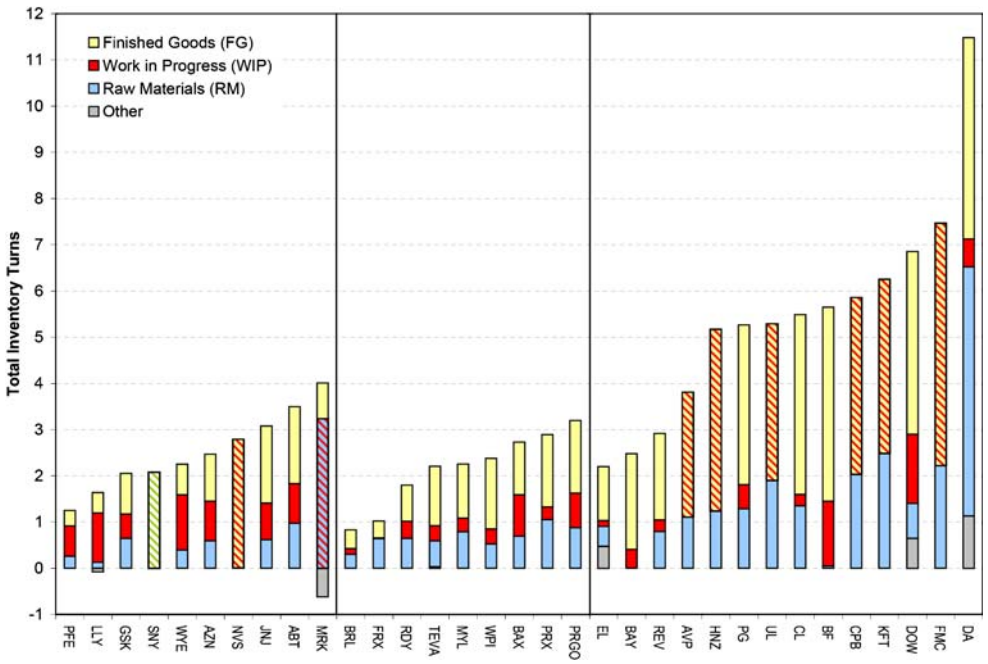


**Fig. 2** Graphical comparison of total inventory turnover for major branded, generic and mid-sized, and non-pharmaceutical process-based manufacturers. The *heights of the segments within each bar* correspospond to the portion of total inventories for each company accounted for by raw materials, work-in-progress, and finished goods. *Cross-hatched bars* indicate companies reporting incomplete inventory data; *negative inventories* correspond to accounting adjustments

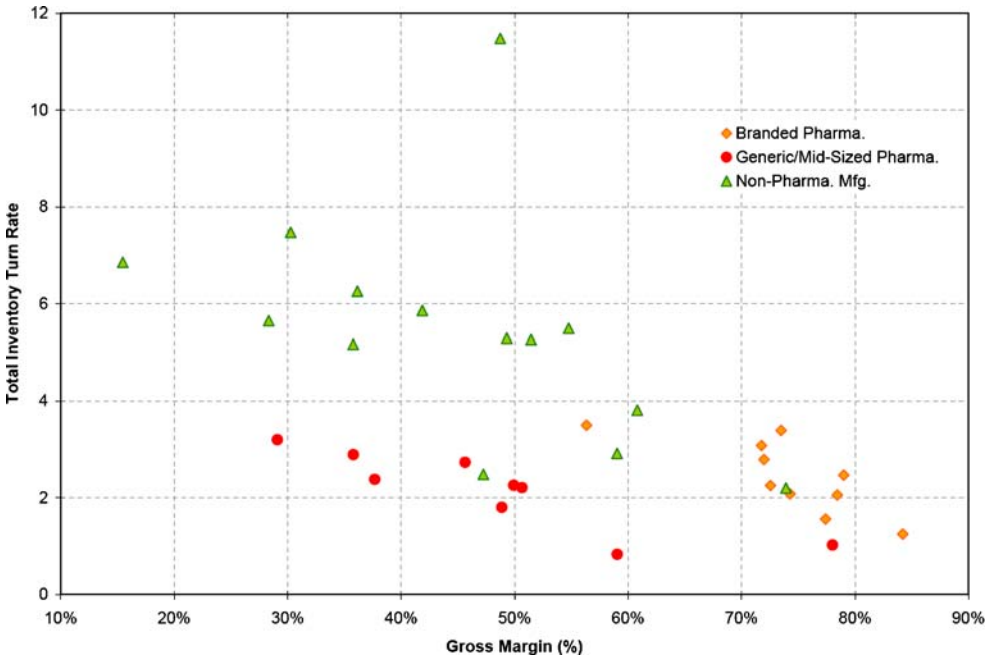


**Fig. 3** Cluster diagram illustrating the statistical correspondence between total inventory turn rate and gross margins

production is unknown. Based on the reported breakdown of revenue components shown in Fig. 5, the company maintains a 10% operating margin, and is valued at approximately 22× EBITDA (earnings before interest, taxes, depreciation, and amortization).

## Project Strategy

Facing an increasingly competitive marketplace and relentless pressure on margins from its biggest customers, the management team decides to undertake a manufacturing performance campaign focused on reducing CoQ and overhead expenses related to low supply chain velocity. In order to maximize the impact of their initiative, the company incorporates selected PATs into their plans which will allow them to achieve real-time-release (RTR) of finished products while simultaneously improving the efficiency of their quality operations. The company's initiative included three main elements: planning and assessment, IT infrastructure, and process analytics.

## Planning and Assessment

Within the context of this example, strategic operational planning and assessment encompasses all non-technology, project management aspects of the initiative. The project

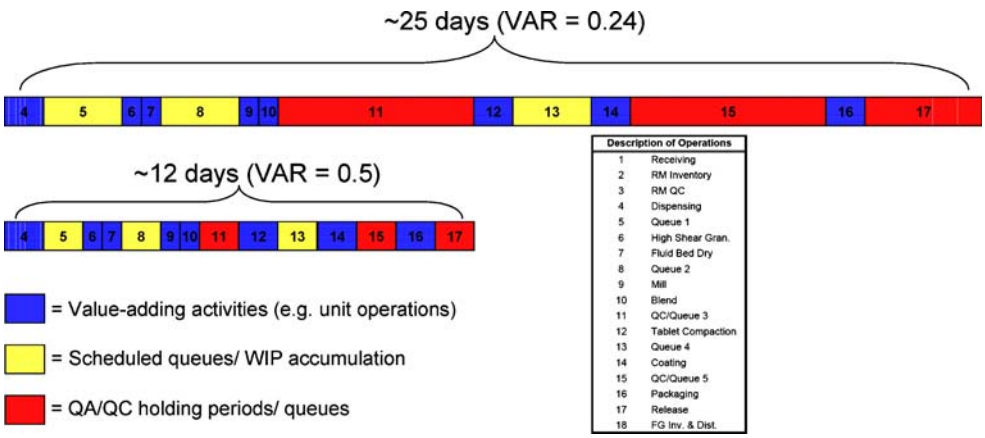


**Fig. 4** Graphical illustration of the transformation of C/T before and after deployment of PAT and lean flow path management (FPM). The *length of each segment* corresponds to the relative portion of total C/T consumed by the operation or activity (as denoted by the cross-referenced number in the inset table). Implementing PAT and FPM enable compression or elimination of non-value-added (NVA) activities, thereby increasing the value-added ratio (VAR), or the portion of total C/T devoted to value-added processes

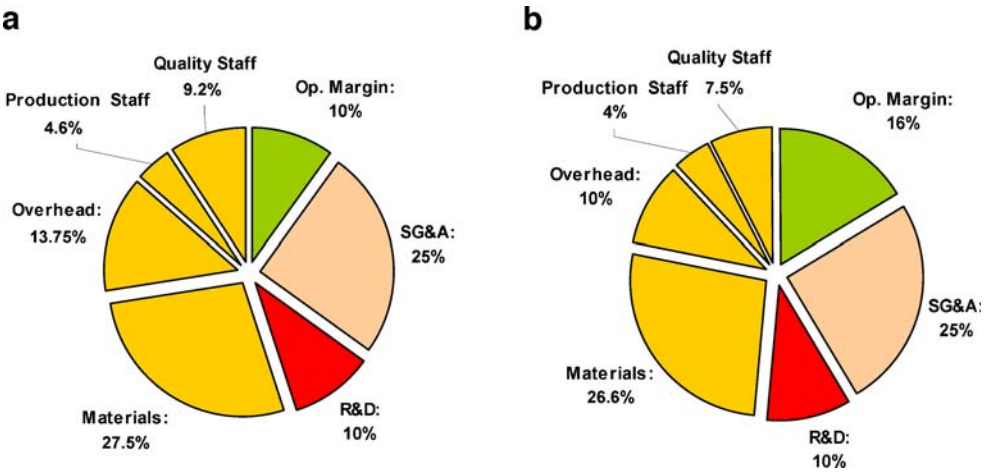


**Fig. 5** Graphical illustration of the approximate breakdown of revenues before (**a**) and after (**b**) deployment of PAT and flow path management (FPM) for a hypothetical pharmaceutical manufacturing company. The pre-PAT data (**a**) are based on average data for generic and mid-sized pharmaceutical companies; **b** reflects the expected impact of operational performance enhancements enabled by PAT

begins with organization of an internal team to champion the initiative, establishment of preliminary goals, and initiation of communication between the project team, company management, and the FDA. Assessments are ongoing throughout the performance initiative, and are used to prioritize individual projects to improve efficiency, reform NVA activities, and mitigate risks to quality. Project design and management should follow a logical structure, such as the DMAIC (Define, Measure, Analyze, Improve, Control) cycle [9]; it is important that the plan incorporates sufficient flexibility to address the needs specific to the company. Besides prioritizing investment activities, the planning and assessment functions within the initiative can have a dramatic impact on performance by facilitating redesign of operating procedures (e.g. cleaning and changeover protocols).

## Process Analytics

With regard to analytical instrumentation, many solid dosage manufacturing operations will benefit from three major types of installations. In many cases the first PAT installation should be focused on developing more rapid, comprehensive analytical capabilities for raw materials analysis within the dispensary. Deployment of enhanced solid-state characterization tools for raw materials identification is a very low-risk way to introduce new technologies while building a critical understanding of the true variability of materials which may impact downstream processes. Additionally, the sensor data collected within the dispensary may ultimately be important as a basis for efficient calibration of downstream sensors [21].

The second phase of instrumentation involves developing control systems for critical unit operations such as granulation, blending, or coating. In some cases control models can be built using existing process data (e.g. air temperature, torque, etc.); in many cases, though, technologies such as near-infrared spectroscopy [22] and in-line particle size analyses will be necessary to develop effective process controls. While not specifically considered a production operation, significant efficiency gains may be realized by introducing new analytical devices to compress downtime operations, such as deployment of ion mobility spectroscopy (IMS) to reduce delays for cleaning verification.

The third phase of instrumentation is related to rapid quality analysis. Rapid (or real-time) quality analysis is critical to the success of continuous improvement by providing timely characterization of process capability at higher levels of statistical confidence than traditional release testing protocols. Finally, the integration of raw material characterization, unit operation control data, and finished product quality analyses will enable RTR of finished products, which, in many cases, will be the most important factor in achieving the financial benefits of PAT.

## Production and Supply-chain Management Systems

In addition to deployment of new sensor technologies, co-deployment of operations management and scheduling systems capable of capitalizing on the operational changes related to PAT (e.g. RTR) have a synergistic effect in accelerating production flow. For example, without updating process schedules, elimination of QC hold times might simply result in new WIP accumulation queues. Additionally, without deploying systems to measure the impact of operational changes on process performance (including WIP velocity and CoQ) the actual ROI from individual projects may be understated or attributed to other factors, thereby putting future investments in advanced manufacturing technologies at risk. The value of PAT projects is enhanced significantly by including

systems for Lean manufacturing, such as flow path management [14].

## Results

After assembling a project team and performing the first process risk and efficiency assessments, the team agreed to work toward three stretch goals: increase average Cpk from 0.7 to 1.0, double the rates of RM, WIP, and FG inventory turnover, and reduce labor components of CoQ by 15%. Additionally, the team agreed to implement technological or procedural changes to address the highest-priority risks to quality identified during operational assessments.

### Process Capability Enhancement

For many solid dosage manufacturing operations, increasing Cpk to 1.0, or process sigma to 4.3, is a stretch goal well within feasibility. The financial benefit of process capability enhancement was calculated by reducing each component of COGS by 3.3%, which corresponds to the portion of production recovered by reducing the rate of batch failure. Based on the distribution of revenue components shown in Fig. 5, process capability enhancement reduces COGS by ~$8.2 million annually. The estimated savings do not include components related to savings on disposal fees, opportunity costs of failure, or potential for increased sales due to recovered production volume, all of which would compound the savings due to improved quality performance.

### Flow Path Management

Acceleration of the process and inventory is achieved by three factors: elimination or minimization of inspection hold times, reduction of NVA activities, and optimization of production scheduling. For this case study the improvement goals included doubling the rate of inventory turnover, which merely brings performance up to the median rate of turnover observed for the non-pharma companies surveyed, which is still well below the level of "world class" supply chain efficiency. By achieving RM, WIP, and FG turn rates of 16, 30, and 7.6, respectively, and assuming 20% inventory carrying costs (ref KPI survey), more than $13 million annual overhead savings would be realized. Additionally, the 50% reduction in total inventories carried would free up more than $66 million in cash from working capital.

### Reduced Cost of Quality

The opportunity to significantly reduce CoQ beyond the direct effects of improving Cpk is a major financial benefit of implementing PAT, yet is often not identified as a strategic goal. This is not to suggest that traditional QC/QA functions must be completely displaced by PAT sensors or process models. Rather, the implementation of real-time analytical methods enables parallel operation of important QC activities to be maintained out of the C/T critical path, thereby facilitating more efficient scheduling of off-line quality operations. It is important to also consider indirect effects on CoQ related to Cpk improvement such as the reduction of laboratory and root-cause investigations which often divert laboratory resources from more productive activities, such as R & D support. Indeed, the quality unit will have an important role in establishing and maintaining PAT sensor systems. Such activities can be managed outside of the C/T critical path, however, and in many cases can be outsourced to external experts. For the fictitious company described in this case study, 15% reduction of CoQ labor related to routine inspection and failure investigations would yield more than $6 million in annual savings. Ultimately, as companies continue to gain internal expertise in deploying improved analytical and control technologies it is reasonable to expect that significantly greater reductions in CoQ will be realized.

## Discussion

### Discounted Value of Savings

Ignoring implementation costs, and assuming gains are first realized in the third year of the initiative, the 10-year discounted (WACC ~12%) value of the savings described in the preceding paragraphs is more than $175 million (including $66 million in working capital savings). The operational transformations responsible for the savings described in Figs. 4 and 5 are the expected direct results of three main factors:

- Process capability was improved by deployment of PAT-enabled process controls and by implementing an effective continuous improvement system
- Process and supply chain velocity increased following elimination of QC/QA hold times, the achievement of RTR, and by optimizing inventory levels through deployment of a real-time flow path management system.
- Implementation of PAT for real-time quality analysis enabled reductions in labor and resources required for operation of the quality unit.

In addition to the direct effects of these factors there are many indirect savings which may add to the value of the PAT + Lean initiative. For example, some companies may be able to realize significantly greater CoQ savings by

levering PAT installations to further reduce fixed and variable costs of monitoring compliance. Furthermore, studies in other process-based industries have shown that overhead costs are more directly related to the number of transactions than production volume [23]; hence, manufacturers with more complex flow paths (e.g. generic and OTC) can expect outsized gains from improved turnover. Other potential long-term gains from PAT + Lean include more efficient process development and scale-up, technology transfer, reduced regulatory burden, and increased production flexibility.

## The Synergy of PAT and Lean

Of the $27.7 million in total estimated annual cost savings, only the $8.2 million related to Cpk enhancement would be classified as being related only to PAT. The remaining 60% of savings require aspects of both PAT and Lean manufacturing. For example, while real-time analytics and controls obviates the need for QC holds, improved scheduling is required to adjust to the faster pace of production. It is difficult to accurately quantify all of the synergistic aspects of co-deploying PAT and Lean using only a hypothetical example. There is, however, a fundamental relationship between process variability and C/T which demonstrates the strategic value of deploying process controls to manage variability. Hopp and Spearman [24] described the "corrupting influence" of variability on process C/T; they developed a mathematical relationship which describes queuing time ($CT_q$) as a function of the coefficients of arrival and process time variability, $c_a$ and $c_e$, capacity utilization, $u$, the number stations, $m$, and the mean process time of a job (i.e. unit operation), $t_e$:

$$CT_q = \left(\frac{c_a^2 + c_e^2}{2}\right)\left(\frac{u^{\sqrt{2(m+1)}-1}}{m(1-u)}\right)t_e \qquad (2)$$

Hence, as described by Eq. 2, queuing time, the amount of time which WIP must wait for equipment availability for processing, increases with the square of both arrival- and process-time variability. Furthermore, process variability tends to cascade through operations; the variability in process time for one operation becomes the arrival time variability for the next, leading to additional scheduling problems and delays. While process buffers can mitigate $c_a$, enabling higher capacity utilization, process acceleration requires true mitigation of process variance.

Indeed, failing to mitigate variation before initiating a lean manufacturing initiative will often result in counterproductive results. It is for these reasons that the projects described for this case study were planned such that process capability and quality management were addressed first through deployment of PAT, followed by active management of production to minimize inventories.

## Reality Check

Admittedly, some simplifying assumptions were made within this example which may reduce the potential value of savings in a real implementation scenario. Additionally, the magnitude of investments required in terms of capital, labor, and time related to actually implementing the changes were not discussed. It is important to realize, however, that the financial gains were generated not by bringing a "benchmark average" pharmaceutical manufacturer up to world class, but rather by bringing operational performance up to nearly the median performance of process-based manufacturers in other industries. Indeed, given the current state of manufacturing performance in the pharmaceutical industry, only relatively modest improvement in process capability and supply chain velocity are needed to realize outsized gains. Based on these relatively conservative estimates only a fraction of the estimated gains would be required to repay the cost of most any PAT system which would be implemented on such a scale. Furthermore, most branded and generic drug manufacturers are much larger and have much greater throughput than the company used for the case study, and therefore have greater potential for gains.

As noted earlier in this manuscript, the tremendous opportunity for pharmaceutical manufacturers to reap significant cost savings through deployment of PAT and Lean has been described many times before. Despite these data, the rate of investment in advanced processes and controls among pharmaceutical manufacturers still lags far behind most other process-based industries. For a company to invest significant capital in new manufacturing technologies the risk-adjusted return on investment (RAROI) must be worthwhile relative to available alternatives (e.g.—additional staff, increased warehouse space, R & D spending). Ordinarily this would imply that the risk-to-return profile of PAT investment is less favorable in these sectors.

Five years ago the real and perceived technological and regulatory risks associated with implementing process analytics for real-time monitoring and control of production processes were relatively high. The regulatory reforms that have been deployed in conjunction with FDA's PAT initiative [2, 25] have significantly reduced the regulatory risks associated with incorporating process analytics into established operations. Furthermore, the published experiences of early-adopters of PAT in the pharmaceutical industry, academia, and technology suppliers, as well as many years of collective experience in process analytical chemistry (PAC) from other industries, have ironed out

many of the technical issues involved with deploying PAT. Most of the significant technological risks associated with investments in PAT have been addressed. As the potential for significant financial rewards become more apparent, and as the regulatory and technical risks and uncertainty have faded, one would have to wonder why more management teams don't choose to invest in PAT. As cited by Vernon, Hughen and Trujillo [7]; Nelson and Winter [26] demonstrated empirically that "it is not uncommon for industries to evolve more slowly to capitalize on such inefficiencies than orthodox economic theory would predict." On the other hand, though, it may be that early attempts at PAT projects have left some companies feeling burned after experiencing many new costs with few tangible benefits stemming from insufficient planning and lack of internal experience with PAT.

## Summary

The purpose of this manuscript has been to describe in detail some of the opportunities for financial returns on investments in PAT. Investments in process analytical sensors and controls generate such returns indirectly by removing operational, technological, and regulatory roadblocks which have historically prevented management from achieving maximum process efficiency. A hypothetical case study based on publicly-available benchmarks was used to illustrate the magnitude of savings due to PAT, quality management, and Lean manufacturing which could be expected for a small manufacturer of pharmaceutical solid dosage forms. By achieving conservative levels of operational performance improvement in terms of process capability enhancement, flow path management, and reduced cost of quality, it was shown that a company having revenues of $450 million could reasonably achieve nearly $27.7 million in annual cost savings, and could return more than $66 million in cash from working capital. If it can be assumed the cost savings are not invested elsewhere in the operation, the company would increase operating margins by more than 600 basis points from 10% up to 16%, ultimately having a dramatic effect on both the magnitude of earnings and the predictability of operating costs.

## Appendix

### On the Calculation of Process Sigma

Due to its widespread success, and the proliferation of consultants it spawned, competing approaches to Six Sigma have evolved from the original process developed by Motorola, leading to considerable confusion about the true intent and spirit of Six Sigma [27]. Consequently, the true method for calculating the sigma level for a process, and its relationship with Cpk, is often misunderstood. According to Keki Bhote, who helped develop the Six Sigma process during his 42-year career at Motorola [27], the sigma level of a process corresponds directly to the sigma used in the denominator for calculation of Cpk (for a centered process) [8]. Thus, based on Eq. 1, the sigma level for a centered process will be equal to three times its Cpk score. In other words, the distance between the control limits for a process centered at zeros will be $\pm 6\sigma$.

It is widely acknowledged that a six sigma ($6\sigma$) process will produce approximately 3.4 defects per million opportunities (DPMO). By applying simple statistical calculations to Eq. 1, however, it can easily be shown that, according to the original definition of process sigma, a $6\sigma$ process is expected to produce approximately 0.02 DPMO, or 2.0 defective parts-per-billion (PPB). The startling disparity between the figures is the result of major differences in how they are calculated, and a "fudge-factor" known as the "$1.5\sigma$ shift," or the "shift and drift" offset.

Calculation of the "shifted" sigma is achieved by evaluation of the inverse standard normal cumulative distribution, or probit, function for a ~$N(0,1)$ process at a given %RFT [28]. There is, unfortunately, no direct equation for calculation of the probit function; hence, practitioners often rely on web-based calculators, third-party software products, or manual interpolation from tables

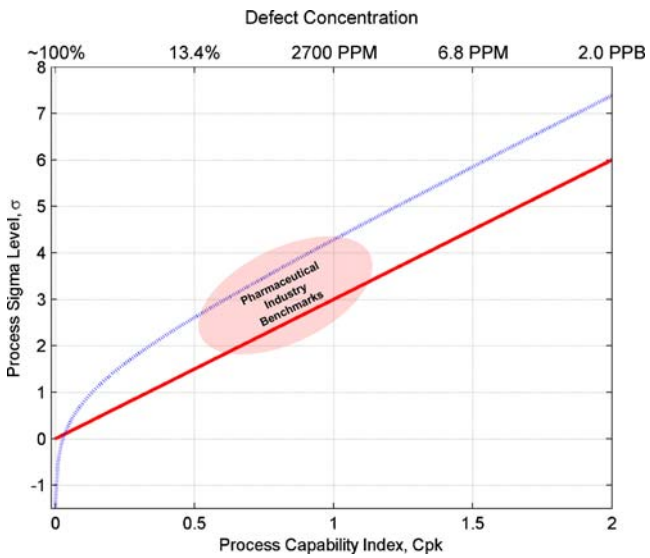


**Fig. 6** Graphical illustration of the correspondence between Cpk, defect concentration, Process Sigma, and the "shifted" process sigma. Most benchmarks indicate that pharmaceutical manufacturers operate within the shaded region near Cpk ~0.7

relating process sigma values to DPMO or %RFT to estimate the sigma level of their processes. The shifted process sigma estimate can be calculated using a modified version of an Excel® spreadsheet formula described by Pyzdek [28]: '=NORMSINV($X$)+1.5', where $X$ is %RFT.

While there are numerous arguments attempting to support the 1.5$\sigma$ drift as a correction for such things as long-term "natural drift" of processes, or as an adjustment for differences between customer perception and internal control limits, a brief review of the available Six Sigma literature did not yield a truly rigorous statistical reason for the more-complicated alternative calculation. Given the historical origins of the probit function, one might speculate that perhaps the shifted sigma is more linear as an input for regression studies of process capability. An examination of the relationship between Cpk, defect rate, process sigma, and the shifted sigma, as shown in Fig. 6 and Table 2, however, would suggest that the alternative calculation is an easy way of increasing the apparent performance of operations and the 1.5$\sigma$ shift is simply the offset required to prevent difficult-to-explain negative sigma values.

**Table 2** Quantitative relationship between Cpk, % defective units, PPM, the true Process Sigma, and the "Shifted" Sigma

| Cpk | % | PPM | Process sigma | "Shifted" sigma | Sigma error |
|---|---|---|---|---|---|
| 0.01 | 98 | 976,067 | 0.03 | −0.48 | −0.51 |
| 0.05 | 88 | 880,765 | 0.15 | 0.32 | 0.17 |
| 0.50 | 13.4 | 133,614 | 1.50 | 2.61 | 1.11 |
| 0.55 | 9.89 | 98,943 | 1.65 | 2.79 | 1.14 |
| 0.60 | 7.19 | 71,861 | 1.80 | 2.96 | 1.16 |
| 0.65 | 5.12 | 51,176 | 1.95 | 3.13 | 1.18 |
| 0.70 | 3.57 | 35,729 | 2.10 | 3.30 | 1.20 |
| 0.75 | 2.44 | 24,449 | 2.25 | 3.47 | 1.22 |
| 0.80 | 1.64 | 16,395 | 2.40 | 3.63 | 1.23 |
| 0.85 | 1.08 | 10,772 | 2.55 | 3.80 | 1.25 |
| 0.90 | 0.693 | 6,934 | 2.70 | 3.96 | 1.26 |
| 0.95 | 0.437 | 4,372 | 2.85 | 4.12 | 1.27 |
| 1.00 | 0.270 | 2,700 | 3.00 | 4.28 | 1.28 |
| 1.05 | 0.163 | 1,633 | 3.15 | 4.44 | 1.29 |
| 1.10 | 0.0967 | 967 | 3.30 | 4.60 | 1.30 |
| 1.15 | 0.0561 | 561 | 3.45 | 4.76 | 1.31 |
| 1.20 | 0.0318 | 318 | 3.60 | 4.92 | 1.32 |
| 1.25 | 0.0177 | 177 | 3.75 | 5.07 | 1.32 |
| 1.30 | 0.00962 | 96 | 3.90 | 5.23 | 1.33 |
| 1.35 | 0.00512 | 51 | 4.05 | 5.38 | 1.33 |
| 1.40 | 0.00267 | 27 | 4.20 | 5.54 | 1.34 |
| 1.45 | 0.00136 | 14 | 4.35 | 5.70 | 1.35 |
| 1.50 | 0.000680 | 6.8 | 4.50 | 5.85 | 1.35 |
| 1.5484 | 0.000340 | 3.4 | 4.645 | 6.000 | 1.35 |
| 1.55 | 0.000332 | 3.3 | 4.650 | 6.005 | 1.35 |
| 1.60 | 0.000159 | 1.6 | 4.80 | 6.16 | 1.36 |
| 1.65 | 0.0000742 | 0.7 | 4.95 | 6.31 | 1.36 |
| 1.70 | 0.0000340 | 0.34 | 5.10 | 6.47 | 1.37 |
| 1.75 | 0.0000152 | 0.15 | 5.25 | 6.62 | 1.37 |
| 1.80 | 0.0000067 | 0.067 | 5.40 | 6.77 | 1.37 |
| 1.85 | 0.0000029 | 0.029 | 5.55 | 6.93 | 1.38 |
| 1.90 | 0.0000012 | 0.012 | 5.70 | 7.08 | 1.38 |
| 1.95 | 0.0000005 | 0.005 | 5.85 | 7.23 | 1.38 |
| 2.00 | 0.0000002 | 0.002 | 6.00 | 7.39 | 1.39 |

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