

## DOCUMENTATION

# Genentech Error Proofs Its Batch Records

by **Robert Bottome and Richard Chua**

In Food and Drug Administration (FDA) regulated manufacturing environments, such as those in the life sciences, biotech and pharmaceutical industries, complete and accurate documentation of processes and the completion of process steps are critical.

Documentation, however, is prone to a variety of human errors: slips, lapses, mistakes and violations (see Table 1 for a few characteristic examples). Even though these are common problems across these industries and the majority of document errors do not impact product quality, FDA regula-

### In 50 Words Or Less

- **Genentech, a biotechnology firm regulated by the Food and Drug Administration, chartered an error proofing project.**
- **The goal was to reduce the rate of errors by 50% and maintain the new rate for three months or more.**
- **Six Sigma and lean tools led to sustainable breakthrough improvements.**

**TABLE 1**

**Document Errors Caught During Batch Record Review**

Type of error	Description
Attention lapse	<ul style="list-style-type: none"><li>• Forgot to record storage location, time and transfer after moving product from cold room.</li><li>• Forgot to make required entry on one of three equipment use logs tied to transfer lines and tanks.</li><li>• Forgot to enter information just entered on ticket on a use log.</li></ul>
Slip	<ul style="list-style-type: none"><li>• Transposed lot number.</li><li>• Forgot to initial and date a page as reviewed for completeness.</li></ul>
Rule based mistake	<ul style="list-style-type: none"><li>• Incorrectly excluded entry as not applicable.</li></ul>

tions mean they have to be controlled.

A decision by Genentech’s senior management to error proof such documentation resulted in the achievement of sustainable breakthrough improvements through the focused deployment of Six Sigma and lean project teams.

**Launch**

The error proofing project was chartered in September 2003 by the good manufacturing practices core team at Genentech. The objective of the project was to reduce the inspection risk associated with document errors and lost tickets. This objective was expressed as the following dual goal:

- **Goal one**—Reduce the rate of document errors recorded in the discrepancy management system by 50% relative to the first and second quarter 2003 baseline by September

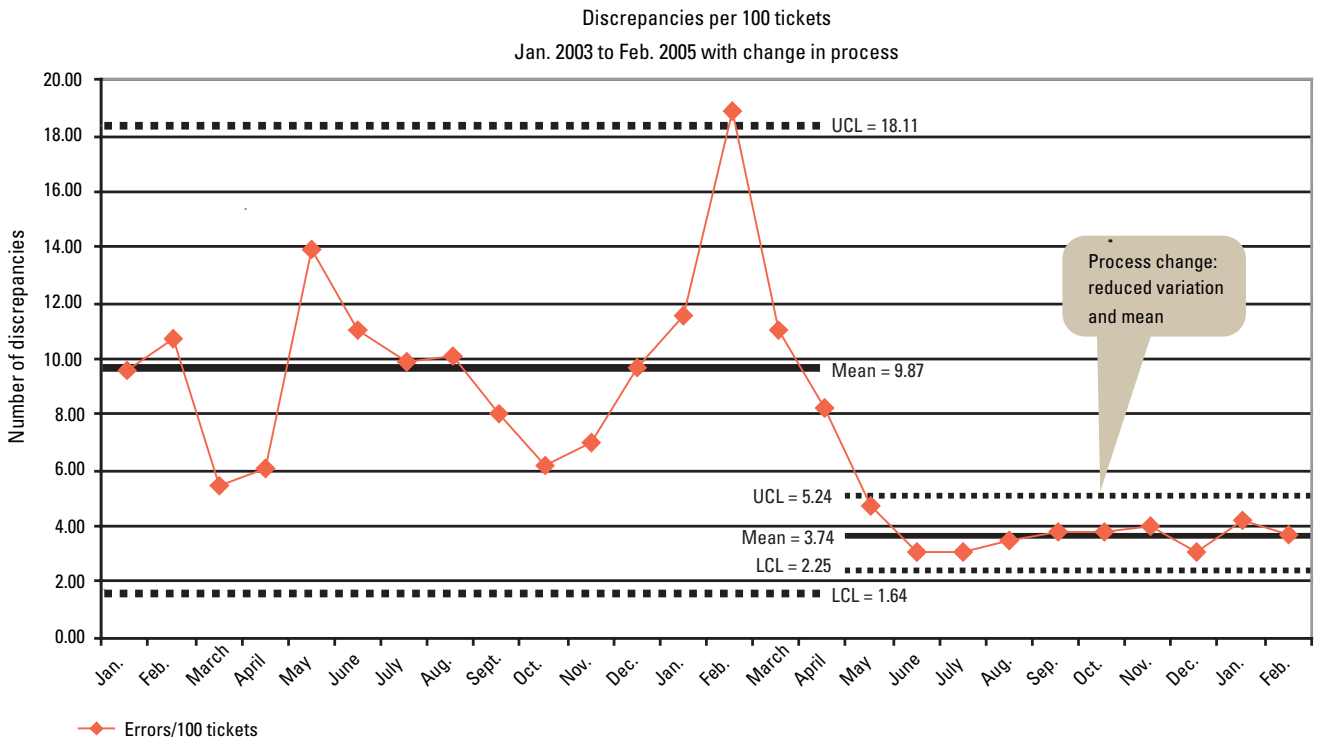
2004. Maintain the document error rate within this new zone of control: less than five document errors per 100 tickets (main batch record documents) for three months or more.

- **Goal two**—Reduce the overall volume of master ticket errors by 50% relative to the first and second quarter 2003 baseline.

Six error proofing teams were chartered in October 2003 to investigate the drivers for this pattern of error and variability. Consultants working with the teams asked them to use one or more of the following industry standard methodologies:

- DMAIC (define, measure, analyze, improve and control), which is intended to analyze and diagnose the root causes of the problem, develop and implement remedies and hold the gains—as Joseph Juran would put it—to achieve breakthrough results that are sustainable.

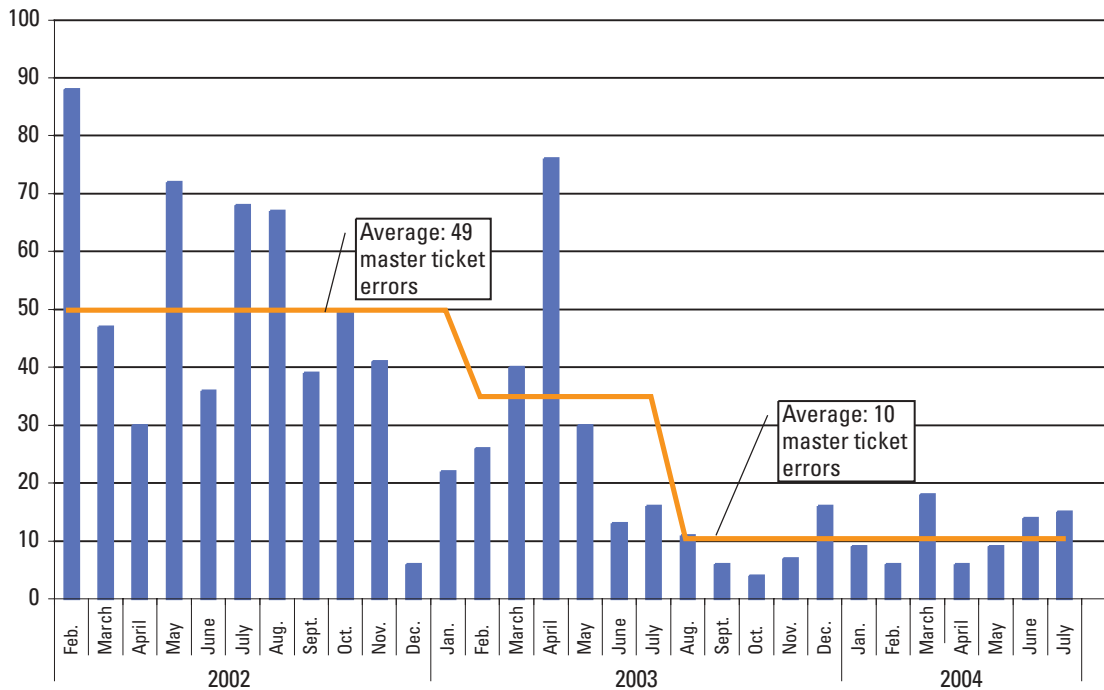
**FIGURE 1** Document Error Rate



Event codes e1.1, e1.2 and e1.3 per 100 tickets stamped complete in production operations management system per month, January 2003 through November 2004.

UCL = upper control limit. LCL = lower control limit.

**FIGURE 2** Master Ticket Errors Per Month



- DMADV (define, measure, analyze, design and verify), which is intended to guide a team in the development and deployment of a new system or process that will prove capable of reliably meeting the prioritized needs of customers—internal and external, as appropriate.
- Lean/value stream mapping (VSM): a lean manufacturing technique designed to achieve error free operations through cycle time compression and simplification. This approach is characterized by a team’s decomposing a process through VSM, followed by quick analyses and brainstorming and rapid implementation of improvements.

The wave one teams were chartered so their implementations would begin in March 2004 and deliver measurable document error rate reductions by June 2004.

The six projects were:

1. Timely feedback using DMAIC.
2. Change to volume and timing using DMAIC.

3. VSM in growth hormone and recovery operations using lean/VSM.
4. Document rule clarification using DMAIC.
5. Document development using DMADV.
6. Document complexity using DMADV.

### Breakthrough Results And New Control Zone

As illustrated in Figure 1, the teams achieved the first goal in May of 2004, and document errors have been held within the new zone of control ever since.

The teams achieved the second goal almost immediately, and the incidence of master ticket errors has not returned to first and second quarter 2003 levels since the project began (see Figure 2).

Heightened awareness, improved visibility and control over the document development process were recently formalized into an improved management system through the efforts of the document development team.

**Key Findings**

The key findings and their associated implementations include the following:

- More timely feedback.
- Better timing of changes.
- Reduced change volume.
- Different ink color.
- Centralized equipment log location and other rapid improvements.
- Reduction of documentation rule confusion.
- Central coordination for document changes and other actions to decrease word processing errors.
- Less complex documents.
- Improvements to other factors.

**More timely feedback.** Based on interviews across all shifts, the project team concluded the timing and utility of feedback provided varied across production teams. In particular, the project team found a mechanism for timely feedback was present only in certain instances.

The team set out to correlate the presence or absence of timely feedback to document error rates. Table 2 shows the correlation.

Teams with timely feedback performed 50% better than those with incomplete or delayed feedback (see Figure 3).

As predicted by the team, the document error rate took its first significant shift toward a new zone of control in April 2004, immediately after the timely feedback mechanisms were introduced.

**Better timing of changes.** The change volume and timing project team—working on a DMAIC project—set out to investigate the relationship between document effective and release dates with regard to errors per document.

By correlating the interval between release and effective dates to the document errors recorded per execution of the ticket, the team was able to show

**TABLE 2** Chi-Square Test Showing Correlation Between Timely Feedback and Document Error Rates

Expected counts are printed below observed counts.

Chi-square contributions are printed below expected counts.

< One week

	Feedback S	0 Feedback S	Total
1	25 20.20 1.138	19 23.80 0.967	44
2	20 24.80 0.928	34 29.20 0.788	54
Total	45	53	98

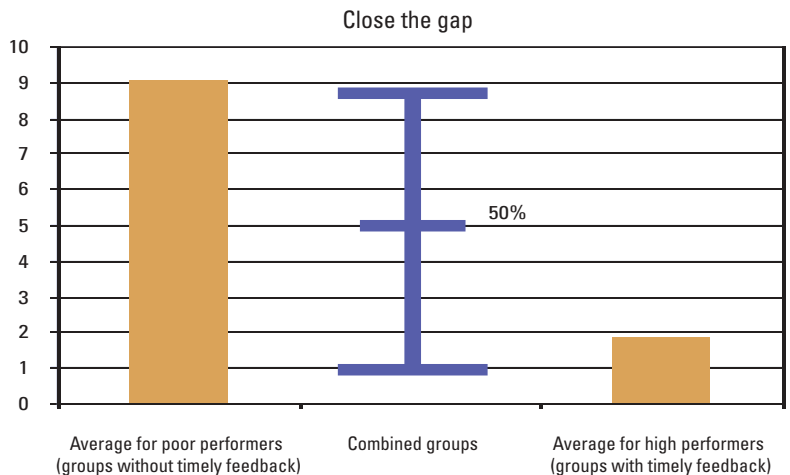
Chi-square = 3.820; delayed feedback = 1; P-value = 0.051.

There is a statistical relationship of dependence between the lack of feedback and the groups identified as high and low performers (on document errors).

Feedback S = timely feedback provided (< one week).

0 Feedback S = no timely feedback or feedback provided.

**FIGURE 3** Master Ticket Errors Per Month



the documents made effective within three days of their release dates carried a disproportionate number of error discrepancies (see Figure 4).

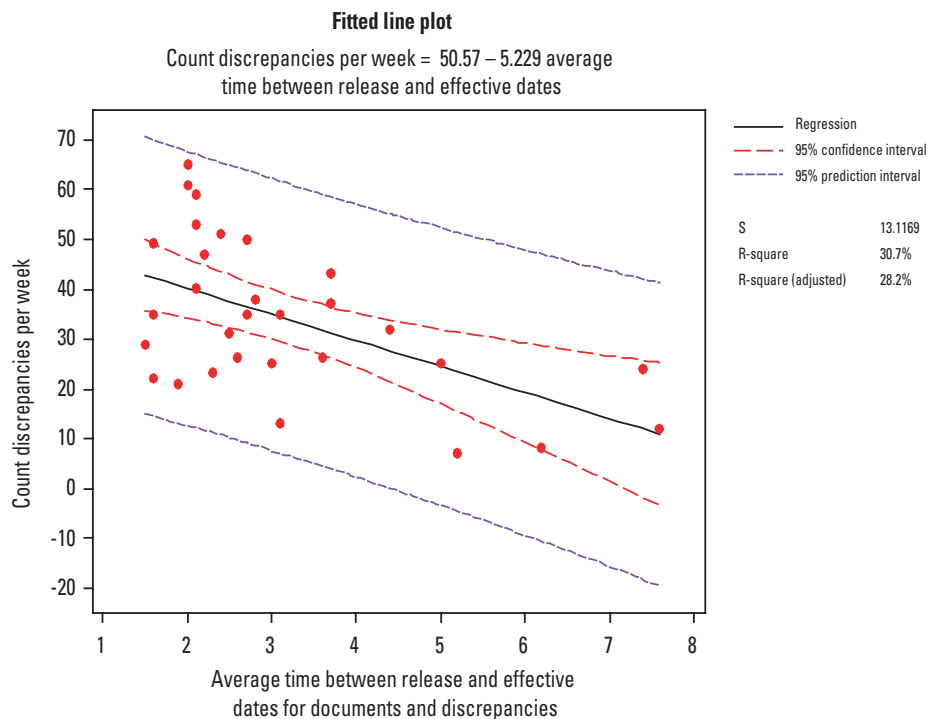
Because 45.7% of tickets had less than two days between release and effective dates, these documents represented a significant driver of document errors on the floor. As the team investigated further, they confirmed one- to three-day intervals did not permit meaningful document training to take place across shifts.

Currently, the centralized document management function created in response to recommendations from this team (and the document development and complexity teams) uses the release to effective date interval as a leading indicator of document error generation. We can expect the document error rate to remain low as long as we enforce the minimum interval.

**Reduced change volume.** Another driver of document errors confirmed by the change volume and timing team was the number of times a document gets changed in a year. More than 1,440 ticket changes were initiated by Genentech's South San Francisco (SSF) manufacturing facility—the company's main operation—in 2003. By comparing the discrepancy rates recorded for documents changed more than three times in a year to those changed less often, the team confirmed frequent revisions drove errors (see Table 3 and Figure 5, p. 30).

The team proposed enforcement of a mechanism to pull documents with more than three changes per year, coupled with a system to make revisions more visible. The team remained convinced these measures would yield further document error reduction benefits.

**FIGURE 4** Relationship of Time Between Release And Effective Dates and Discrepancies



**Different ink color.** The lean/VSM team in growth hormone recovery operations generated a list of error proofing implementation ideas during its rapid improvement phase. One of the ideas with evident universal utility grew out of an analysis of the factors that contribute to omission errors.

The team noted when entries were made in black ink on batch records, forms and logs printed in black ink, it could be hard to see where an entry that was required might be missing. The team proposed switching to blue ink in an attempt to enhance the contrast between entries made and printed text.

After the details were negotiated with SSF quality assurance and compliance, the necessary SOP changes were made to permit the use of blue ink without requiring it. A memo was circulated explaining the rationale for the change and asking managers to enforce the consistent use of blue ink.

The blue ink initiative was implemented in March 2004, just as the omission error rate dropped below five for the first time. Manufacturing online

auditor data collected in July and August 2004 suggest omissions are detected twice as often now that blue ink is in routine use (see Figure 6).

**Centralized equipment log location and other rapid improvements.** Another successfully implemented rapid improvement idea started when the growth hor-

more recovery lean/VSM team looked at the centralization of equipment use logs.

Using a survey tool and spaghetti maps, the team tested the hypothesis that having equipment use logs scattered throughout the work area increased technician wear and tear and, incidentally, the risk of document errors.

After centralizing the logs in one location, 95% of the survey respondents agreed the system was much easier to use (less travel, less time, less difficulty). Document error rates in the area continued to drop after the logs were centralized.

Rapid improvement efforts to identify single points of contact, provide walkie talkies and structure communications for clarity, directness and simplicity have all contributed to a reduction in the impact of uncontrolled communications with employees on the floor.

**Documentation rule confusion.** Interviews with operators who executed tickets confirmed a high degree of confusion around the rules for cross outs, ruling out sections as not applicable, entering time correctly and other fine points of batch record creation. This confusion was identified as a potentially significant driver of documentation errors.

Many of the errors that resulted from confusion were crossed out and then corrected during online review without generating a discrepancy. However, such cross outs could still raise questions during an FDA audit because they reflect the operator's struggle to create the batch record correctly the first time.

The team systematically catalogued the points of confusion (sub-Y's) and then completed a cause and effect analysis for each to identify the drivers—f (X's). Examples of these validated sources of confusion (proven X's) include:

- Documents use ambiguous language (for example, "approximately"), which causes confusion about document rules, leading to document errors.
- Some documents include information about alert limits only; others include information about alert limits and action limits. This inconsistency causes

**TABLE 3** Kruskal-Wallis Test

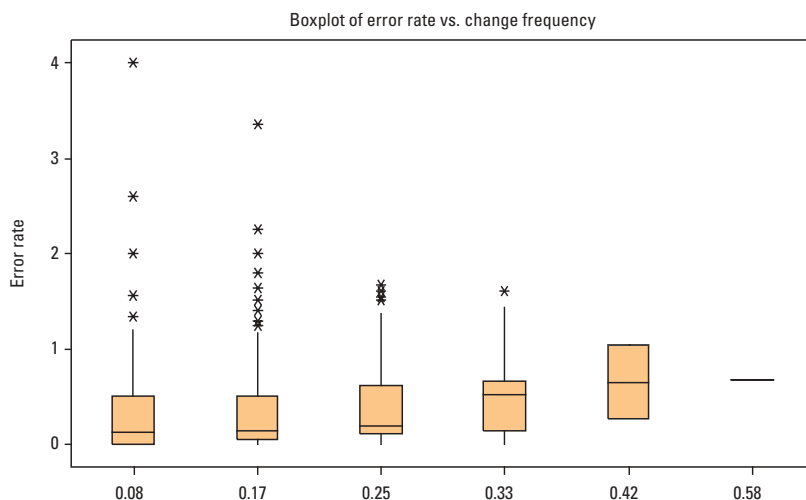
Change frequency	N	Median	Average rank	Z
0.08	215	0.1268	188.4	-3.06
0.17	127	0.1429	208.0	0.29
0.25	45	0.1875	243.8	2.30
0.33	20	0.5227	269.0	2.46
0.42	2	0.6483	317.0	1.33
0.58	1	0.6800	344.0	1.17
Overall	410		205.5	

H = 18.09 Degrees of freedom = 5 P = 0.003  
 H = 18.28 Degrees of freedom = 5 P = 0.003 (adjusted for ties)

H is the Kruskal-Wallis statistic.  
 P is the p-value of the statistical test.  
 Test shows significant differences in median document errors across different document change frequencies.

Note: For more information on the Kruskal-Wallis Test, go to [www.ticalc.org/archives/files/fileinfo/98/9837.html](http://www.ticalc.org/archives/files/fileinfo/98/9837.html).

**FIGURE 5** Change Frequency and Error Correlation



**TABLE 4** Correlation Results, Complexity Score and Error Rate

	Combined		Fermentation		Recovery	
	p	R	p	R	p	R
Complexity score	0.000	0.673	0.000	0.859	0.018	0.338
Total data entries	0.000	0.632	0.000	0.829	0.093	0.242
Total pages	0.000	0.618	0.000	0.925	0.006	0.385
SOP/standard record (SR) references	0.000	0.617	0.000	0.748	0.001	0.457
Operator steps	0.000	0.611	0.000	0.868	0.010	0.366
Form numbers to refer	0.000	0.600	0.000	0.773	0.018	0.336
Total SOPs/SRs	0.000	0.584	0.000	0.699	0.005	0.399
Other G-code	0.000	0.575	0.000	0.713	0.007	0.380
Verifier steps	0.000	0.491	0.000	0.877	0.016	0.343
Labeling steps	0.000	0.442	0.000	0.838	0.021	0.328
Calculations	0.000	0.395	0.019	0.466	0.134	0.217
Attachments	0.032	0.249	0.000	0.738	0.210	0.182
Verifier/operator	0.470	-0.085	0.748	-0.068	0.832	0.031

confusion about document rules, which leads to document errors.

- Documentation rules keep changing, which causes confusion about document rules, leading to document errors.
- Operators are trained by different trainers and

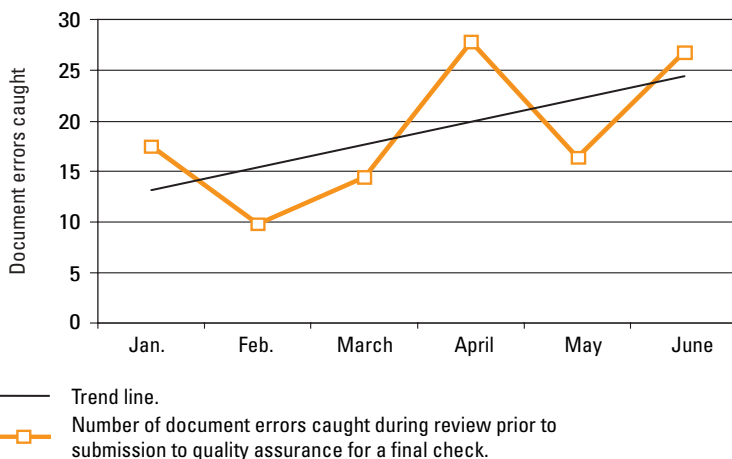
content is not consistent, which causes confusion about document rules, leading to document errors.

- Justification behind the rules (criteria for the rules) is not communicated, which causes confusion about document rules, leading to document errors.

These validated causes of confusion were converted to customer needs and used as the basis for designing a clear, central SOP for documentation and the associated training. These necessary tools were made effective and provided to operators in May 2004—just as the document error rate dropped below five per 100 tickets for the first time.

**Central coordination for document changes and other actions to decrease word processing errors.** The document development and change process team (a DMADV team) defined its problem statement around the inability of the current process to reliably produce accurate/error free documents

**FIGURE 6** Observed Increase in Document Review Efficiency



within customer defined timelines.

Data from the first and second quarters of 2003 were analyzed by the team to identify master ticket errors and map them to process steps when the error could have originated or been caught (individual errors were often mapped to multiple locations). This analysis identified the document development stage of the process—including technical writing and subject matter expert redline steps—as the most significant generator of ticket errors (see Figure 7).

A VSM of the process was created and used to show only four of the 54 steps were value adding, two were nonvalue adding and the remaining 48 were all classified as “needed but nonvalue adding.”

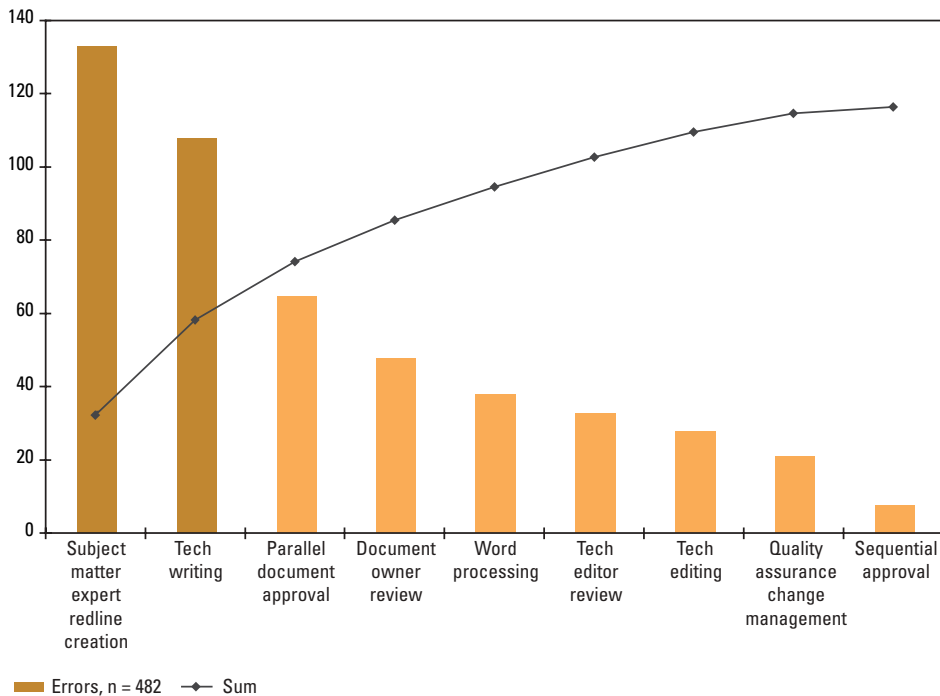
A failure mode effects analysis of the process ranked the various identified failure modes, and root causes were assigned to the most severe ones. The top 10 risk priority number scores could be assigned to three root causes: communication gaps, business process inadequacies and resource limitations.

The team designed an improved process using DMADV methodology to address the identified issues and converted three root causes to customer needs. The improved process—which features a centralized coordinator, automated step references, resource management tools and development checklists—was piloted in the fall of 2004. Compared to the baseline data, the campaign preparation effort delivered accurate documents in accordance with defined timelines.

**Less complex documents.** The problem statement devised by the document complexity team (a DMADV project) emphasized the link between document errors and instructions to manufacturing and quality assurance staff that were often overly complicated or inconsistent.

The team interviewed customers (document users) across functions and prioritized their identified needs. A Pareto chart of these findings is provided in Figure 8. The three needs identified most often were fewer pieces of paper, no conflicting instructions and fewer data entries.

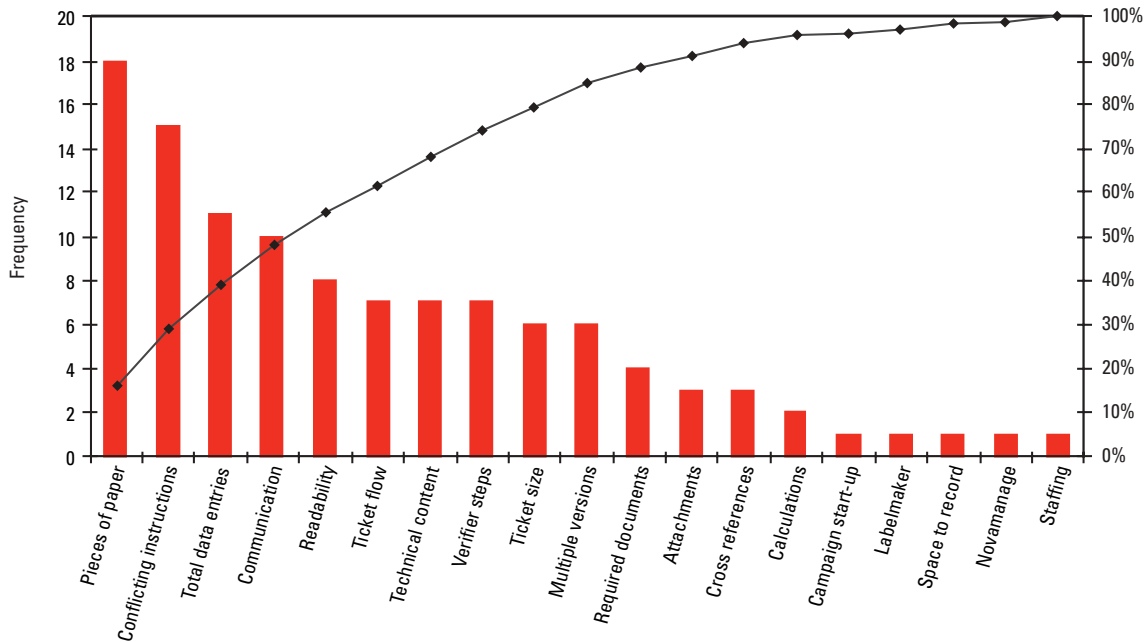
**FIGURE 7** Pareto Chart of Performance Gaps



First and second quarter 2003 data show combined origin and “miss” steps where error could have been caught.



**FIGURE 8** Pareto Chart of Customer Needs for Clear Instructions



Using these data, the team devised a system for scoring instruction complexity and applied this to a set of standard instructions. These scores were then correlated to discrepancy rates per document. As shown in Table 4 (p. 31), the error rate correlated strongly to complexity score and 11 of 12 complexity elements for the combined and fermentation only data. Recovery data correlated strongly to only nine of 12 elements.

The team used regression analyses to confirm complexity scores could predict error rates and significant complexity elements. The analyses results identified two quick fixes that were successfully implemented: preprinted labels and other attachments in a binder and a departmental controlled document to list use logs. Both fixes were implemented by June 2004.

Medium scope solutions incorporated into wave two included an effort to reduce data entries and a process to communicate when changes were made.

The long-term scope solution, of course, is a paperless manufacturing execution system, which was chartered as a standalone project in wave two.

**Improvements to other factors.** In addition to the implementations described above, the document error rate was significantly impacted by revisions to the discrepancy management SOP made effective in May 2004.

Among other things, the revisions expanded the population of errors in documents that could be verified and therefore converted to observations—not discrepancies—if caught during online review (see Figure 9, p. 34). Because the decline in document error rates preceded the SOP revision, the change can properly be viewed as a reinforcing element of the new zone of control.

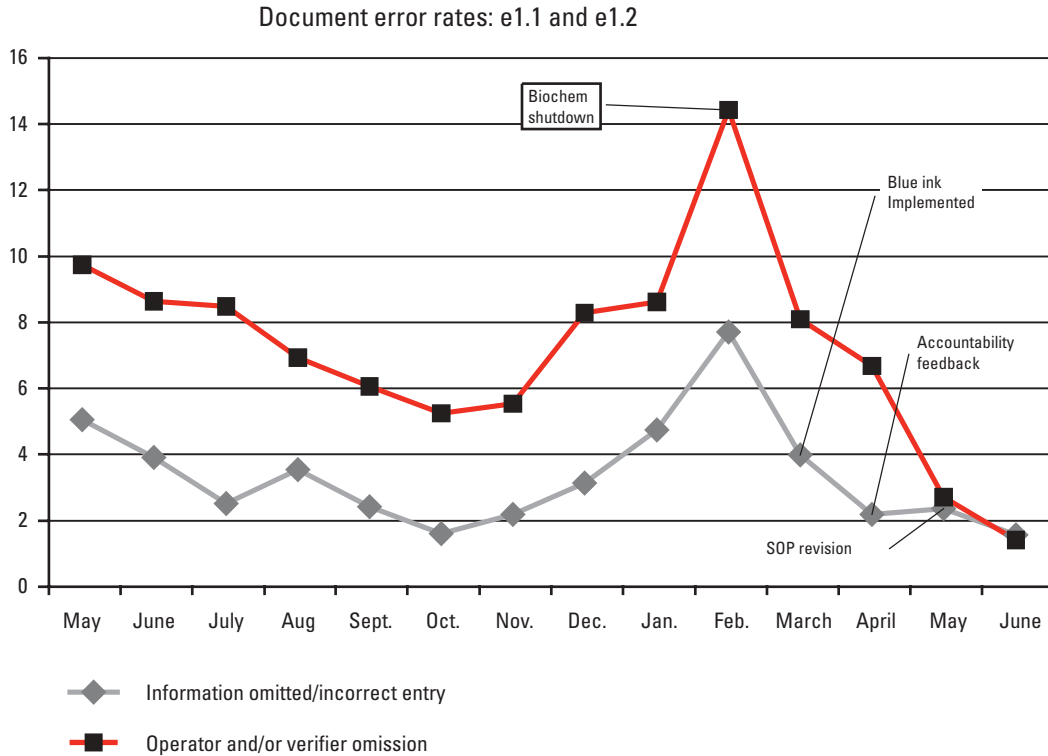
### Lessons Learned

Achieving and sustaining these breakthrough results demonstrated the power of applying project-by-project improvement using the right tools—in this case, Six Sigma and lean/VSM—coupled with the right management priority and commitment of the right resources and support.

Lessons learned include:

- Dedicated resources perform better than part-time teams because effective sponsors ensure

**FIGURE 9** Omission Rate by Type Relationship to Error Proofing Implementations



team members are not overbooked.

- Active and engaged sponsorship is key, especially during initial scope of work definition and chartering.
- Management must resist the impulse to direct teams to a solution prematurely while providing clear boundaries to the scope of the inquiry and timing of the project.
- Care should be taken to prepare for training events so logistical issues, absent sponsors and confusion about project goals do not distract participants.

In addition to these success factors, this effort taught our management one truly fundamental lesson: Put your best people on the problem, make the investment to provide them with world-class tools and support, and they will deliver lasting results.

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