



Kristie Dolan, Merck Sigma leader for Global Human Health; Michael Thien, head of Global Pharmaceutical Commercialization; and Laurel LaBauve, vice president of Merck Sigma and deployment leader



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# Rx for Success

Merck's reorganization speeds drugs to market

BY ELAINE SCHMIDT

**I**n the intensely competitive pharmaceuticals industry that is straining to contain costs while continually developing new drugs, being the first to bring a new vaccine or medicine to market is a grand slam. Merck & Co. Inc., the third largest U.S. drugmaker, is now applying Six Sigma tools across the business as part of a restructuring plan to revitalize drug development and accelerate the process of going from test tube to pharmacy.

“Dramatically improving how quickly we bring a drug to market can have a huge impact on the stability of the company,” said Laurel LaBauve, who joined Merck in 2006 as vice president of Merck Sigma and is the program's deployment leader.

The approval last fall by the U.S. Food and Drug Administration (FDA) of Merck's new HIV drug Isentress (generic name raltegravir) is a prime example of how well the Merck Sigma program is working. Michael Thien, head of Global Pharmaceutical Commercialization, said Merck Sigma shaved nine months off the four to five years normally required to bring a drug to market after it enters the clinical trials.

The financial benefits of getting a nine-month jump on an annual sales potential of \$1.5 billion are obvious, but Thien said it is impossible to put a dollar amount on a drug's acceleration. The most important metric, he said, is speeding up the process of delivering drugs to the patients that need them, while maintaining the highest standards of quality and safety. That is “what's really important,” Thien said. “It's what keeps our people working night and day.”

PHOTOS BY MERCK VISUAL COMMUNICATIONS





LaBauve joined Merck in 2006. Her long experience with Six Sigma began at AlliedSignal, one of the early adopters of the methodology.

## Company Profile

- Company name:** Merck & Co. Inc.
- Headquarters:** Whitehouse Station, N.J., USA
- Founded:** 1891
- Number of employees:** About 60,000
- Global reach:** Does business in 140 countries
- 2007 revenue:** \$24.2 billion
- 2006-2007 increase in revenue:** 7%
- Primary business offering:** Pharmaceuticals
- Website:** merck.com

## Planning to Win

Merck initially deployed Six Sigma in manufacturing in 2000. Then in early 2007, rebranding and expansion took it across the entire corporation under the leadership of new CEO Richard Clark.

The Six Sigma expansion was part of a corporate “Plan to Win,” a five-year strategy created by Clark to transform Merck, LaBauve explained, “so that we are focused on customer value drivers and a whole new operating model, which is focused on a new approach to how we discover, develop, manage and commercialize new medicines.”

The Plan to Win is all about “One Merck,” LaBauve said, which translates to the whole company working together to conquer diseases and get the right drugs to patients. That means involving medical community customers early on – physicians, patients and payors – to find out what they want and what they will pay for, and involving each Merck division along the way – from scientists to marketers – so they’re all acting in concert, without any slowdown, as the drugs move from one phase to another.

“If you look at Merck Sigma today instead of two years ago,” she said, “you’ll see a global breadth in its application from product development, commercialization, marketing, sales, human resources and finance.” The program includes Six Sigma, Lean, change management and enterprise process management.

“We’re not blindly applying Six Sigma,” LaBauve explained. “We’re applying it where it makes sense. We’re not trying to impact the way we discover new drugs. But where we have processes – for example, in the R&D [research and development] space – we know we can make those processes more effective so it can make us a much stronger competitor.”

LaBauve said that Clark, who was head of Merck’s manufacturing division before becoming the chief executive officer, had a vision of “building Six Sigma into Merck’s DNA,” as a foundation for becoming a “lean and flexible company.”

Clark was under pressure to resurrect the company. He was named CEO in May 2005, amid Congressional hearings and thousands of liability suits related to the \$2.5 billion-a-year arthritis drug Vioxx, which Merck had withdrawn from the market in 2004 after it was linked to heart attacks and strokes. (See “New CEO Takes Charge,” page 27) The venerable company’s public image and stock value had suffered a crushing blow, its drug pipeline had slowed, and ahead loomed the patent expiration for its blockbuster cholesterol medicine, Zocor.

“We knew we needed to do a major transformation so we would be successful in the future,” LaBauve said.

## Merck Sigma and Isentress

Now, two years into the transformation, Merck has regained its footing. The number of compounds in the

pipeline has almost tripled since 2002 and eight new products have been launched in the last two years. Merck is reaping the rewards of its expanded Six Sigma efforts with one of those products, Isentress. Although some of the company's other recent FDA approvals, including the type 2 diabetes drug Januvia, have been helped by cycle time improvement, LaBauve said Isentress is the "first true soup-to-nuts example of a drug benefiting from Merck Sigma."

The FDA granted accelerated approval to Isentress in October 2007 for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. "Isentress is a brand-new, first-in-its-class HIV drug," LaBauve said. "Controlling HIV is all about combinations of therapies," she explained. "When one of the drugs in a therapy is failing, you can add Isentress as a new combination and drop

**"It's not about cutting corners – it's about discipline, focus and finding alternatives we haven't found before to reduce cycle time."**

–Michael Thien

the drugs to which you've developed a resistance."

Thien added, "These are patients who have run out of options in their fight against AIDS, which of course is terminal. This represents a new, effective option."

Thien's group, Global Pharmaceutical Commercialization, is responsible for a drug's chemical formulation and analytical development from Phase II of the clinical trials through the end of the international launch. It is also responsible for making clinical supplies and initial commercial launch supplies. To tell the Isentress story, Thien described some of the elements of the drug development process.

"We may have a molecule that we think will become a new drug. Someone has to figure out the process of how that drug will be made and formulated. We have to create a process from laboratory to manufacturing and while we're doing that, we have to make the actual drug for clinical trials since we can't just order it from a pharmacy." The clinical trials have to be set up, which means approving protocols and enrolling all the people who will participate.

### Manufacturing

Design of experiments (DOE) is just one of the Six Sigma tools used in deciding what chemistry and what type of formulation will be used for the drug and then selecting the final shape, size and color, Thien said. *Manufacturing* typically refers to chemical processing, formulation and packaging – both primary packaging (the bottle or blister pack) and secondary packaging (the box, carton, etc.). The chemical process for Isentress was put into a Lean Six Sigma production environment before

launch, which Thien said resulted in a "substantial leaning of the process."

Design for Six Sigma (DFSS) tools were used to identify ways to speed up manufacturing. "The DFSS tools allow the team leaders to better manage variability as we go through the process," Thien said. "FMEA [failure mode and effects analysis] and other risk assessment tools can provide a disciplined approach. Too often teams think they know the risks, but a disciplined and formal approach really pushes quantitative thinking about those sources of variation. It's not about cutting corners – it's about discipline, focus and finding alternatives we haven't found before to reduce cycle time."

Manufacturing for Isentress was also accelerated by a new system Merck had created to execute late-stage process development and launch in the same facilities,

with the same equipment. The system encompasses new business processes, organization, team structure and governance, all designed using elements of DFSS and other Six Sigma tools, said Thien, who co-led the creation of the system. It interacts with the early development group in the Merck Research Laboratories and ultimately transfers the product to the supply area for long-term production.

Full-scale manufacturing can start a year or more before a new drug application is filed with the FDA because the agency has specific manufacturing requirements that must be included in the application. One of the final items to be approved by the FDA is the exact wording of the product labeling, Thien said. "Once word-

## Six Sigma Snapshot

**Deployed:** First launched in manufacturing in 2000; Merck Sigma launched company wide January 2007

### Number of Belts:

Green Belts: 1,100

Black Belts and Master Black Belts: 500

Executive Belts: 450

**Projects:** 700 active

**Six Sigma goals:** Build Merck Sigma skills into the DNA of Merck employees to deliver breakthrough business results





Thien, LaBauve and Dolan look over some of the promotional materials for Isentress, which were submitted for FDA review early because of Merck Sigma streamlining efforts. Merck tailors communications toward patients, payors and physicians.

ing is approved, the manufacturing organization is skilled at quickly moving labeling copy through the printing process and providing labels and circulars to the packaging floor so that drug can be made available to patients in the shortest time possible.”

### Clinical Trials

In 2005, when the Plan to Win was initiated and Isentress was in development, Thien said DMAIC tools were used to determine why the cycle time of Merck’s clinical trial process was longer than that of the rest of the industry.

“We actually went out and looked at how we enrolled people for our clinical trials and found that the process was not really robust,” LaBauve said.

“We were batch processing patient information,” Thien explained. One big cycle time delay lay in the fact that data entry for the trial didn’t begin until the last patient in the study was identified and that patient’s information was in hand. “We switched to a flow process, which means we don’t wait for a whole bunch of data to be sitting there before we begin entering it,” he said. It was also determined that switching from manual entry to electronic capture would save additional time throughout the course of the trials.

Five months was cut from the clinical trials’ cycle time, Thien said. “We now have moved from fourth quartile in cycle time to first, in part due to the many [Merck] Sigma cycle time efforts, as well as having a lean and efficient mindset.”

### Promotional Materials

Kristie Dolan, who leads Merck Sigma for Global Human Health, the sales and marketing division of the company, said the acceleration of Isentress was also aided by a project that applied Six Sigma tools to the creation of promotional materials. “We mapped out every single step, from the idea stage, to the finished product with promotional materials in the hands of physicians,” she explained. The project team determined which steps added value and which did not.

“It’s a matter of asking what in the process would a patient or physician be willing to pay for,” Dolan said. “If something had to go through 17 approvals for some internal reason, well that’s something the customer would not be willing to pay for.

“Due to the streamlined promotional development process, Merck was able to submit Isentress promotional materials prior to the FDA deadlines,” she said.

### Supplanting Skepticism

The Isentress acceleration is what LaBauve called an early win in a three-level process of getting Merck Sigma into the DNA of the entire corporation by 2010.

“Level One is building a foundation, an infrastructure and training Belts. It’s about getting those early wins to convince people that it works,” she said.

“At the beginning there was a certain amount of eye-rolling in sales and marketing,” LaBauve recalled. “They

said it worked well in manufacturing, but it's not going to work here." In part, the skepticism has been overcome through the use of topical examples in training, so that sales and marketing people are given sales and marketing examples. Plus the success of the promotional materials project helped prove the worth of the tools.

LaBauve emphasized how important it is that employees across the company view the Merck Sigma tools as essential additions to their existing skill sets. That includes the engineers.

"We are infusing DFSS tools in engineering in order to

tools could be applied outside the manufacturing area.

Thien said he found out how when he was involved with creating the new system for integrating development and launch. "We flailed for the first two weeks until we took a look at the Merck Systems Design Model from the Merck Sigma toolbox, and then we made a lot of progress. Then as we got into detailed design and were asking how do we start a business process from scratch, someone brought to my attention the tools in the Six Sigma toolbox." DFSS "enabled the solution," he said.

Dolan, who is a certified Master Black Belt, added that

## "At the beginning there was a certain amount of eye-rolling in sales and marketing!"

—Laurel LaBauve

address needs in the design process and production in a more focused way," Thien said. "(The skeptics) have to see that these tools don't supplant science and engineering, but enhance it. Ideas still have to be generated to provide solutions, but Six Sigma helps us focus our thinking in a disciplined way."

Thien, who has a doctorate of science in chemical and biochemical engineering, pointed out that he himself was once "a card-carrying member" of the early resisters.

"I'd been in research and development with Merck, in product and process development, for 18 years and I have a great respect for the 'science and engineering first' principle." He did not initially understand how Six Sigma

Merck Sigma tools have enabled sales and marketing people to identify savings that are applicable throughout the company, across the globe.

"We have reduced redundancy," she said, which had resulted from a lack of communication and not knowing what other groups were doing. "Where there's a similarity of studies between two regions, those regions communicate now."

Dolan pointed to the fact that communication identified a wide variability in the number of days sales representatives spent in training before talking to physicians. A DMAIC project team, which included sales and marketing people from eight Merck markets, developed a core sales

## New CEO Takes Charge

Richard Clark was a 32-year Merck veteran when he was picked in May of 2005 to lead the company out of its morass of troubles. The decision-making process that made Clark CEO was headed by Larry Bossidy, the former chief of AlliedSignal and Honeywell, who was a member of the Merck board of directors.

After eliciting input from Merck employees, executives and investors, the new CEO galvanized the company with his "Plan to Win," which upended the traditional approach to drug development, more closely aligning the scientific and commercial sides. The five-year strategy emphasizes the waste-eliminating aspects of Lean, and hallmarks of Six Sigma such as reducing variation, listening to customers, cross-functional communication and continuous improvement.

According to Merck Sigma leader Laurel LaBauve, the Plan to Win consists of five principal focus areas:

- 1. Priority disease areas** – Atherosclerosis and cardiovascular; diabetes and obesity; respiratory, bone, arthritis and analgesia; oncology; neuroscience and ophthalmology; vaccines; infectious disease therapies
- 2. Redefining product research and development** – Leverage technologies to facilitate drug discovery and development while increasing pipeline productivity
- 3. A new commercial model** – Partner with customers to improve patient outcomes
- 4. Emerging markets** – Leverage local capabilities in manufacturing, R&D and services to meet healthcare needs in these regions
- 5. Flexible cost structure** – Achieve operational efficiencies through standardized and scaleable global processes

training curriculum that can be tailored to the needs of the various regions and businesses.

“It’s more efficient and we’re able to deliver it at a lower cost than before,” she said. “It gets reps into the field more quickly, which drives the revenue of the business.”

**Training Centralized**

Merck Sigma training is a fundamental part of Level One. A centralized corporate group, the Center of Expertise, designs and leads training in Six Sigma, Lean and change management around the globe in the languages required, and also provides project governance. “It’s critical that we’re seen as supportive in each region,” said LaBauve. “We make sure that we mentor everyone as they go through training.” Mentoring standards are set by the center.

Early in the program, people could “self select” for

training but when that proved unsuccessful, new procedures were put in place. “Merck Sigma leaders work with their line leadership to identify key projects for their area,” LaBauve explained. “Once the project is selected, they pick the appropriate person to lead the project and get Belt certified.” This resulted in a jump in certifications from 26 percent, when people self selected, to 59 percent in 2007, she said.

Merck has its own certification program governed by the Center of Expertise. To get certified, Black Belt candidates must complete two projects, Green Belts, one. In addition, a certification board quizzes candidates orally on body of knowledge. The goal is to have 1 percent of employees Black Belt certified and 5 percent Green Belt certified by 2010. “We are looking for our best and brightest to become Master Black Belts,” LaBauve said.

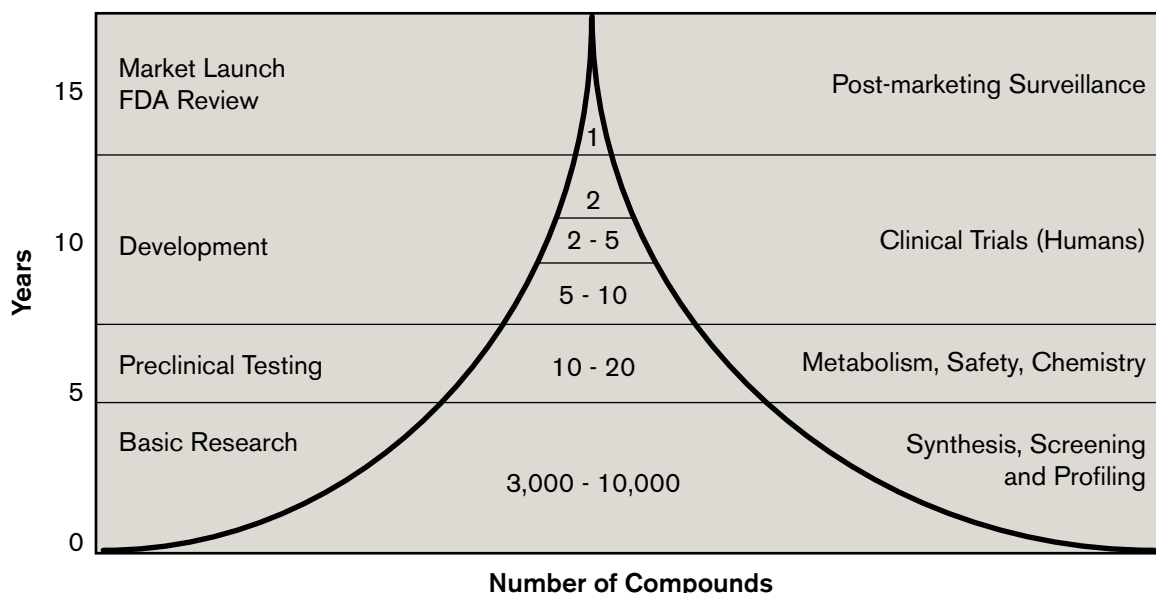
## Discovery and Development of a Successful Drug

The development of a drug is a lengthy process that begins with basic research on compounds – thousands of them. The probability of success of a particular compound is extremely low in discovery but increases as it progresses to each subsequent development stage.

Preclinical testing of a drug is done on laboratory animals; the clinical trials on humans are conducted in three phases, beginning with healthy volunteers in Phase I. If a com-

pound makes it through the trials and is approved by the FDA, the drug is ready for launch.

But the FDA does not enter the picture just at the end. It reviews progress on the drug at several points during development. The final review comes when the pharmaceutical company files a new drug application asking approval to market the drug in the United States. The agency scrutinizes everything about the drug, from the



Source: Based on PhRMA analysis, updated for data per Tufts Center for the Study of Drug Development database. Graphic courtesy of Merck & Co. Inc.

The majority of the Green Belts and Black Belts are embedded within divisions. “Our desire is that if someone’s going to become a Black Belt, they do that full time,” LaBauve said. “Green Belts we see as more of a 30 percent commitment.” She explained, “Part of our deployment model has people staying in their own jobs after Black Belt training. They don’t go into the Merck Sigma organization. We want them to be a Black Belt in their current role; that’s how we see it getting into our DNA.”

DFSS training is a separate track, with a Green Belt prerequisite. Merck is using DFSS and DMADV (Define, Measure, Analyze, Design, Verify) in multiple ways, LaBauve said. The effort started primarily in Thien’s drug transition group but it has been expanding rapidly. There are now two separate DFSS tracks – one for technical and one for business processes.

design of clinical trials, to the severity of side effects, to how the drug is manufactured. (Merck markets drugs worldwide. Each country has its own regulatory approval process, but there are ongoing efforts to agree upon standards of testing, thus eliminating costly, time-consuming duplication.)

Merck Sigma Deployment Leader Laurel LaBauve said the FDA is moving toward a Quality by Design (QbD) approach that emphasizes designing quality into the manufacturing process during development, rather than testing quality in the final product. “We see parallels between QbD and DFSS and are vigorously exploring those linkages,” she said.

The FDA gives *accelerated approval* to certain drugs that promise benefit for serious and life-threatening illnesses for which no therapy exists, based on surrogate measures while forgoing assessments of clinical outcomes that would normally be required. The drug company must continue its studies after the drug is on the market to test and prove efficacy. Isentress received accelerated approval.

With the organizational restructuring and all the cycle time improvements, Merck has achieved a dramatic increase in the number of compounds moving through its pipeline. As of Feb. 15, 23 compounds were in Phase I, 17 in Phase II and seven in Phase III, with one drug under FDA review. Emend, an intravenous medicine to help reduce the nausea and vomiting associated with chemotherapy, was approved by the FDA in January.

### The Next Level

The company is now on Level Two of its three-level progression to ingrain Merck Sigma. “Level Two is aligning and integrating with the rest of the company and deploying broadly across the corporation,” LaBauve said. “It’s not just the early wins and number of Belts now, but what kind of business results, revenue increases, savings, cycle time results and customer satisfaction increases are we seeing.”

One such example is a sales and marketing project that slashed the cycle time for getting product samples to physicians 67 percent, and also eliminated back orders and reduced customer complaints 76 percent. The project team was made up of representatives from three divisions and two vendors. The sigma level improved from 0.58 to 4 sigma, and the standard deviation of deliveries was reduced 82 percent.

Drug discovery and development is costly. According to GE Healthcare, the average cost is \$200 million during the discovery stage and \$600 million for development.



Productivity and efficiencies in the Merck Research Labs have helped drive growth in the company’s pipeline.



**“It’s a matter of asking what in the process would a patient or physician be willing to pay for.”**

–Kristie Dolan

Dolan leads Merck Sigma in sales and marketing. A project team mapped out the process of creating promotional materials to determine which steps added value and which did not.

“We see success very broadly across the company,” LaBauve said. “We are developing Belts and Six Sigma capabilities in every area of the company in a specialized, focused approach. It’s been a little slower with human resources and information technologies, but we’ve created programs there as well and we’re moving forward.”

The Merck Sigma leadership team, made up of the Merck Sigma leaders of each division and function as well as key leaders from the Center of Expertise, is referred to as the Merck Sigma Network. It communicates about “the world of Merck Sigma” in various ways, including a website, a project database and an annual company-wide competition. More than 200 project teams from all over the globe were nominated for the 2007 competition. Twelve awards were given out – five to sales and marketing, four to manufacturing, two to R&D and one to corporate.

Thien said there has been an element of surprise within Merck at the results of Merck Sigma efforts. “People have been amazed that a simple concept can lead to a powerful result.”

### Progressing According to Plan

Though LaBauve said Merck still has a “long way to go,” to reach Level Three – where Merck Sigma is embedded in the company’s DNA – she is happy with the wins so far. “I don’t want to give the impression that we got it done, that it’s a *fait accompli*,” she said. “But we’re really excited about the progress of the program and the fact that it’s really making a difference.”

LaBauve added that Merck’s prescription for corporate health – shortening the time to market and cost to market for new pharmaceuticals by integrating Six Sigma into the company’s culture – is in keeping with the founding principles of the company.

In 1950, George Merck III, son of the company founder, said, “We try never to forget that medicine is for the people. It is not for the profits. The profits will follow, and if we have remembered that, they have never failed to appear.” ♦

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