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Digital Manufacturing at Amgen

On a Friday afternoon in January 2020, Myra Coufal, principal scientist at biotechnology (biotech) company Amgen Inc. (Amgen), ended a call with her colleague, principal engineer Chris Garvin, and sighed. In the coming weeks, Coufal and Garvin would need to make some tough decisions. Amgen, which developed and manufactured therapeutics for a range of conditions and diseases, had since 2015 tasked Coufal and Garvin's team with infusing digital technologies into some of its manufacturing processes. Since then, their team—called Digital Integration and Predictive Technologies (DIPT)—had made considerable progress. But the road had been bumpy, with enthusiasm for digital manufacturing bubbling up in some pockets of the company and resistance lingering in others.

The team's flagship technology was a platform called real-time multivariate statistical process monitoring (RT-MSPM). It analyzed data generated by sensors on the equipment that Amgen used to manufacture its products. RT-MSPM collected thousands of data points, such as temperatures, yields, and pH levels. If the data fell outside acceptable parameters (determined according to historical performance data), RT-MSPM triggered a multivariate alarm (which was an early alarm for detecting weak signals before any other process alarms were triggered) on the manufacturing floor, prompting staff to investigate and resolve the issue.

By catching problems early in the manufacturing process that might ultimately prevent the loss of a batch, RT-MSPM could save Amgen as much as $1 million to $2 million dollars per lot of product. Building on the RT-MSPM momentum, the DIPT team had recently started experimenting with predictive models. Instead of signaling staff to investigate an issue and then take appropriate action, these models, grounded in machine learning (ML), leveraged historical data to identify and resolve problems on their own by directly sending an appropriate command to equipment control systems.

On their call, Garvin had informed Coufal of two new opportunities. The first was a request to work with a team based in Puerto Rico to build an RT-MSPM model for a fairly new commercial product called the mAbX. Like those that preceded it, this new model would detect and alert staff of mAbX manufacturing anomalies. The DIPT team had extensive experience building such models, but they were concerned about the limited production data available for mAbX on which the RT-MSPM model would be based. In addition, while Coufal and Garvin had built strong relationships with several teams in Puerto Rico, they had never previously worked with the mAbX team. Without sustained buy-in from the manufacturing team, it was unlikely that the model would be adopted.

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The second opportunity was a request from a team in Rhode Island to build a predictive ML model that would automate one step of the manufacturing process for a top-selling product. This team had ample data and a long history manufacturing the product with very few failures. Coufal and Garvin had also worked with the Rhode Island team in the past. But given the importance of the product, they knew that any such innovative predictive model would need to be built with an abundance of caution.

Coufal and Garvin now needed to evaluate the potential impact and risk of each opportunity and decide which request to prioritize.

Industry Overview

The biotech industry included companies that utilized living organisms and advanced scientific techniques to make food, medicine, and other products that humans needed.[1] In 2019, companies in this highly competitive industry generated revenues of $113.4 billion.[2] Major players included AbbVie (which owned 23.5% of the market), Genentech Inc. (20.3%), Gilead (18.8%), Amgen (15.7%), and Bayer AG (7.9%).[3] These companies invested heavily in research and development (R&D), devoting about 20% of revenues to this area in 2019.[4] Biopharmaceutical (biopharma) companies, or those that produced health products from biological matter, were the fastest-growing segment of the biotech industry, outpacing other segments like crop science. Due largely to the growth of biopharma, analysts expected biotech industry revenues to increase by 2.9%, annualized, from 2020 to 2025.[5]

Most biopharma companies developed *biologics*—therapeutics derived from living cells—as opposed to the more traditional *small molecule products*, or drugs made from chemical compounds. To produce small molecule drugs, pharmaceutical companies synthesized known chemical compounds. These compounds were relatively small (often no larger than 100 atoms) and stable.[6] Biologics, by contrast, were much larger (up to 50,000 atoms) and, given the natural variation present in living cells, were subject to a more complex and fragile manufacturing process.[7]

To take a biologic to market, companies invested substantial time and money—on average, nine years and $1 billion—with many promising pipeline drugs failing along the way.[8] Biopharma companies could either manufacture their biologics themselves or outsource to specialized third-party companies called contract manufacturing organizations (CMOs). A biopharma company might use a CMO to produce niche products, for which the per-unit adjustment costs were quite high, but rely on its own manufacturing facilities for other types of products. Biologics were a growing market; analysts projected that from 2018 to 2026, product sales would grow at a compound annual growth rate of 9.5%.[9] By late 2019, some 350 biologics were commercially available in the U.S.[10]

Companies seeking regulatory approval for biologics in the U.S. faced a stringent review process by the Food and Drug Administration (FDA).[a] Companies that developed new biologics could seek intellectual property rights via patents at the U.S. Patent and Trademark Office, as well as market exclusivity terms awarded by the FDA.[11] In the U.S., biopharma companies were entitled to 12 years of regulatory exclusivity for biologics, which differed slightly from the guidelines for other types of therapeutics.[12] For example, the exclusivity period for orphan drugs and new chemical entities was seven and five years, respectively.[13]

[a] For a summary of the pathways to approval from the FDA, see: https://bit.ly/3t7zreW. For a review of the approval pathways in Europe, which were established by the European Medicines Agency, see: https://bit.ly/3lIGsxO.

Digital Transformation in Biotech

Throughout the 2010s, digital transformation, defined as the application of digital technologies to enhance the operational ability and scale of enterprises, gained traction across industries.[14] During this decade, the amount, speed, and types of data generated in the world vastly increased.[15] Concurrently, the computing power required to process large datasets improved, and the options for storing such data expanded. Methods for analyzing data also evolved. While established methods like linear and multivariate regression offered a statistical approach for explaining the relationship among variables, emerging data science methods like ML presented new opportunities for deeper analysis.

ML was based on algorithmic models that independently "learned" from data over time without explicit instruction from a programmer.[16] Companies across industries had used ML to diagnose medical conditions, recognize and translate spoken words, and predict loan defaults, among many other applications.[17] While ML was capable of generating deeply sophisticated insights, it was not perfect. Like all statistical modeling, it was subject to false positives and false negatives.[b] In addition, because ML models were so complex, it was often impossible to isolate the specific inputs that generated a model's outputs, leading some to call them an opaque "black box."[18]

In biotech, companies could apply analytics to their business models in several ways; for example, to refine marketing and sales efforts, to optimize quality and compliance processes, and to improve manufacturing approaches.[19] But many biotech companies had been hesitant to adopt new digital technologies. A 2018 Deloitte survey found that most (75%) of these companies were either just beginning, or were in the middle stages, of investing in digital capabilities; very few companies were "digitally mature."[20] Caution in this industry, opined one observer, was "largely due to regulatory constraints, intellectual property issues, and a generally conservative culture."[21] Regulatory filings often included exhaustive detail about how products would be developed, making it impossible to introduce deviations or automated steps without going back to the regulatory body. Any black box technology that could not be easily explained would likely face difficulty gaining FDA approval.

Amgen

Founded in 1980, Amgen was a biotech company headquartered in Thousand Oaks, California. Its 23,000 employees worked to develop a range of human therapeutics for the treatment of certain cancers, cardiovascular disease, and inflammation, among other conditions. Major products included Enbrel®, which treated rheumatoid arthritis and plaque psoriasis; Neulasta®, which was used to prevent hospitalization among certain chemotherapy patients; and Prolia®, which addressed bone health.[22] Amgen held dozens of patents associated with its products in the U.S. and Europe.[23] While the company produced both small molecule products and biologics, the latter accounted for the majority of its products.

In 2019, Amgen reported total sales of $22.2 billion, of which Enbrel®, Neulasta®, and Prolia® accounted for 50% (see **Exhibit 1** for consolidated financials, **Exhibit 2** for product sales by type, and **Exhibit 3** for a stock chart).[24] Amgen primarily sold its products to wholesale distributors, who then sold to pharmacies and hospitals.[25] While the company's products were available in over 100 countries, about three-quarters of 2019 sales occurred in the U.S.[26] Like most biotech companies, Amgen invested

[b] In manufacturing terms, a false positive occurred when the model reported that a batch was healthy when in reality it might have performance issues, and false negatives occurred when the model reported that a batch might have performance issues when in reality it was healthy.

heavily in R&D, spending over $4 billion (17.6% of total revenues) in 2019.[27] The company had built a robust pipeline of new potential products that it believed held significant promise.

Amgen produced, packaged, and shipped its products from 190 properties worldwide. Operations were organized into six functions: 1) manufacturing; 2) administration; 3) R&D; 4) sales and marketing; 5) warehousing; and 6) distribution, with locations specializing in one or more of these functions (see **Exhibit 4**). Amgen was particularly proud of its internal manufacturing capabilities, which took place in several plants in California, Massachusetts, Rhode Island, Puerto Rico, Ireland, the Netherlands, and Singapore. Not all manufacturing plants engaged in the same activities. Explained Coufal: "Our plants overlap in terms of scope for both redundancy and also for a particular capability, so while Puerto Rico does everything from cell thawing to the final product, Rhode Island only does drug substance."[c]

Puerto Rico Located in Juncos, about 30 miles from San Juan, Amgen's Puerto Rico facility boasted 26 years of experience. From 2002 to 2019, the site underwent a $3.7 billion expansion, yielding a manufacturing footprint of 1.7 million square feet.[28] Nearly 2,000 staff worked there, 56% of whom held bachelor's degrees, and 18% of whom held either a master's or PhD.[29] The site manufactured 18 products, including many of Amgen's top-sellers.

Rhode Island Located in West Greenwich, roughly 20 miles from Providence, Amgen's Rhode Island site manufactured Enbrel®, as well as a number of other products. Over time, Amgen had invested $1.5 billion in this facility to add 500,000 square feet of capacity.[30] In 2020, the company added a next-generation, 120,000-square foot plant at the Rhode Island site, which Amgen described as "the first of its kind in the United States and its most innovative to-date."[31]

Across Amgen's sites, specialized, cross-functional teams managed the manufacturing process. These teams comprised: manufacturing; engineering; information systems/automation; supply chain/procurement; process development (which designed the manufacturing process); and quality assurance/control (which ensured compliance with regulatory requirements). The backgrounds and skill levels of employees varied widely. Many staff working on the manufacturing floor had bachelor's degrees and earned hourly wages, whereas most of the salaried scientists and biologists in more specialized roles held advanced degrees in their fields. There was significant diversity within manufacturing staff, too. "Some of them are chemical engineers by training with a lot of interest in the technical aspects of the job," said Garvin. "Others have been doing this for 25 years and have little appetite for straying from the traditional standard operating procedures."

Amgen also used third party CMOs for additional manufacturing capacity, when needed. It was generally costlier to produce a batch via a CMO versus internally.

The Biologics Manufacturing Process

Most Amgen biologics were built atop a specific protein. Thus, to manufacture its products, Amgen cultured and grew batches of living cells that produced the desired protein. From start to finish, producing one batch took about two months and involved a series of sequential steps, detailed below.

The company sourced its raw materials (i.e., the nutrients for Amgen's proprietary cell lines) from third parties. Once at Amgen, the nutrients were mixed into a broth to provide the cells with an optimal growth environment in flasks, which encouraged them to start dividing and replicating. Once they outgrew the flasks, they were placed in bags (which, to date, maxed out at 2,000 liters),[32] and then in a

[c] Drug substance was the early, unprocessed version of the drug before Amgen developed it into its finished, marketed form. (Refer to **Exhibit 5**.)

stainless steel tank called a bioreactor.[33] As the cells inside the initial bioreactor grew, they were transferred to bioreactors of increasing volume. The largest bioreactors involved in this process could hold as much as 20,000 liters.[34] "We make the bioreactors as hospitable as possible," said Garvin. He continued:

> It's a like a spa package—it's the perfect temperature, an all-you-can-eat buffet, lots of oxygen, with a whirlpool to boot. We feed nutrients into the reactor as needed and control the important variables that ensure the desired growth behavior. At some point in the process, we change the conditions in the bioreactor slightly to encourage the cells to open and release their contents (including our desired product) into the broth. We need to time this perfectly to get as much product as possible while minimizing cell death and the presence of undesirable byproducts.

After the bioreactors completed their work, Amgen used a large centrifuge to separate the desired protein from the excess unnecessary material (e.g., cell debris and other cellular products). Manufacturing staff then purified the product, which Amgen sent in temperature-controlled containers to one of its facilities to be formulated into vials or syringes in dose-specific volumes, then packaged and shipped for use around the world. (**Exhibit 5** depicts this process.)

Regardless of the product being made, most biopharma manufacturing processes generally followed the steps detailed above, but the specifics could vary quite a bit. If the product was intended for a larger end market, for example, it could be continuously manufactured throughout the year, whereas the equipment used to manufacture products intended for smaller markets needed to be thoroughly cleaned, sterilized, and reset for the next manufacturing cycle. Even when manufacturing many batches of a single product, the company needed to thoroughly clean and sterilize the equipment between batches. "In between products, we call the process 'changeover,'" said Garvin, "and it includes not just cleaning but sometimes also swapping in different equipment or replacing components within the equipment."

The biologics manufacturing process was delicate. Only in a strictly controlled environment could the cells flourish and produce the specific protein required for each Amgen product. The process was also vulnerable to contamination by organisms such as viruses and bacteria, which could irreparably harm the cells.[35] "Contamination happens if there's a system integrity breach or if the contaminant is present in a raw material that gets added to the bioreactor," said Garvin. "This will quickly result in a scrapped batch." Another issue that could render a batch unusable was equipment failure; for example, a valve in the bioreactor might not open fully, leading to lower gas flow, which could negatively affect the batch. The later in the process that Amgen detected these issues, the costlier they became, given the additional materials and time that went into the manufacturing process at each sequential step.

Determining when to move the cells from one bioreactor to the next was also a delicate process. To check that the cells had grown enough to warrant the transfer, Amgen had to take a sample from the bioreactor. This process cost Amgen time and introduced contamination risk.

Discarding a batch cost Amgen $1 million to $2 million, on average; these costs were typical across the industry. While the company did not publicly disclose its batch failure rate, biopharma companies reportedly lost a batch once every nine months on average, due most often to contamination, material or equipment failure, or operator error.[36] (See **Exhibit 6**.) Given the costs, companies put in place strict process controls to reduce the chance of failure. At Amgen, a number of standard operating procedures (SOPs) governed the manufacturing process and ensured compliance with regulatory filings and adherence to process design requirements.

To monitor the health of a given batch, Amgen's bioreactors were outfitted with sensors that tracked several important pieces of information, including pH levels, dissolved oxygen, temperature, pressure, agitation speed, gas flows (nitrogen, air, carbon dioxide), bioreactor weight, as well as information on the various control loops (e.g., agitator motor output; air flow valve opening). "But even with all of the things we measure," said Garvin, "there are many more things happening inside a cell that we cannot measure directly, like cell metabolism and productivity."

At Amgen, the manufacturing process generated as many as 800 million new data points each day.[37] The wealth of data had led the company to apply evolving digital technologies, such as RT-MSPM, to improve their manufacturing processes. (For additional reading on the topic, see endnote [38]).

Digital Transformation at Amgen

RT-MSPM had grown out of digitization and digitalization work that had been ongoing at Amgen for more than a decade. In 2009, Cenk Ündey, at the time a principal engineer based in Rhode Island, led a small team that had helped the company transition from a paper-based to an electronic documentation system in the early 2000s. Next, he worked to streamline Amgen's process monitoring systems. He was interested in seeing what else his team could achieve using data and digitalization.

At the time, there was very little ability to monitor the manufacturing process in real-time or to anticipate issues that might affect production batches. "So we developed a proof of concept to address this," said Ündey. "Instead of monitoring one variable at a time on the manufacturing floor, looking at every single chart, we decided to monitor many variables simultaneously. That was the genesis of the RT-MSPM program." Ündey's team partnered with Umetrics (which later became known as Sartorius Data Analytics), a Swedish company, to begin building a global platform that used multivariate statistics to analyze manufacturing data in real-time. When Amgen was ready to pilot its first RT-MSPM model, Ündey trained 250 manufacturing staff working five different shifts at the Rhode Island site. "I remember waking up at midnight, 2:00 a.m., to go and lecture staff at the end of their shift, show them the tool, and answer questions. They became so fluent in the platform that they could use the technology without having all of the statistical knowledge."

Each RT-MSPM model began by analyzing historical data from the production process in question. Amgen then built the RT-MSPM model using a multivariate technique called principal component analysis, which identified and analyzed a small number of summary variables that offered insights into the larger dataset. Explained Ündey: "With principal component analysis, instead of looking at 40 different variables, you can tell what's going on overall just by monitoring two statistics in real-time. I sometimes compare it to the NASDAQ. Because it is composed of so many different stocks, it gives you an idea of how the segment is doing overall." RT-MSPM models initially took about 200 person-hours to build; by 2020, Amgen had reduced the time required to build models by nearly 95%.

Once constructed, Amgen worked with the information systems team to load the RT-MSPM model onto the main server at the plant, which then fed the model raw, real-time data generated by the sensors on Amgen's equipment as the manufacturing process progressed. If the data deviated from acceptable bounds at any point (if the temperature, for example, was too high or too low), the model triggered an alarm that flashed on a large monitor on the manufacturing floor. Staff responsible for that particular process then had to make a decision of what to do about the alarm. (See **Exhibit 7**.)

A simple RT-MSPM model might alert a manufacturing team of an unexpected change in pressure within a bioreactor during production of a biologic. After investigating, the team might discover that a hose on the bioreactor had begun to leak. The team would then reconnect the hose, setting the

production process back on track. "To be clear," added Ündey, "we are talking about open-loop monitoring. That means there is no automated action. When the alarms go off, people on the manufacturing floor are the ones investigating. We have kept humans in the loop." Given the costs associated with batch failure, management in most Amgen manufacturing plants were hesitant to remove humans from the loop altogether.

After several early successes, in 2012 Amgen leadership tasked Ündey and his small team with scaling the RT-MSPM platform company-wide. Adoption, however, had been varied. "At some places," said Coufal, "there was no engagement. They just turned off the monitor. At other places, they requested additional models." Added Garvin, "In the early days, we tried a heavy-handed, top-down approach, mandating adoption. Later, we shifted our approach to working with teams who seemed to have a real interest in implementing these models."

Some teams had gone a step further, opting to build RT-MSPM models themselves. In 2017, Steve Fuller, who led a manufacturing team in Rhode Island, approached Ündey and Garvin with the idea for manufacturing staff to build RT-MSPM models. With help from Garvin, Fuller's team built a model that identified when the cells at the beginning of the manufacturing process—in flasks—had reached the minimum required level to be transferred to the next phase of the scale-up process. This eliminated both the need to take samples of the cells, which saved Amgen time, and the risk of contamination at this point in the process. "A challenge," said Fuller, "was that this is not the typical job of a manufacturing staff member on the floor, expecting them to build a multivariate model. Some people were more interested in this work than others. And simply finding the time to work on building the model within the confines of their normal shift, asking them to do something so far outside their comfort zone, was something that had never before been done in the company."

As far as Fuller knew, the model that he and his team built never saved a batch that would have otherwise failed. "But we picked up on small indications of potential issues," he said, "which we would investigate and resolve. There were a couple of examples of that." Fuller cited the support of management and Garvin as factors influencing his ability to lead his manufacturing team in building models themselves.

By 2019, Amgen had deployed more than 800 RT-MSPM models covering 1,000 operations across 14 manufacturing plants. More than 1,000 people used the platform in 2019, up by 25% from 2018.[39] Ündey noted that the support of Amgen leadership had been invaluable, estimating that the company had reaped a 10x return on its investment in RT-MSPM. Ündey and his team had earned both external and internal recognition for their efforts, winning the Providence Business News Local Innovation Award in 2010 and a global prestigious CIO100 Award for Innovation in Healthcare for Amgen in 2013. But challenges remained. "Our big statistical challenge at the moment," said Garvin, "is that we are at risk of 'alarm fatigue.' We have a lot of alarms generated by our software that are not indicative of a real problem, and people are becoming desensitized to them."

In addition, because Amgen's batch failure rates were relatively low, it had been challenging for the DIPT team to quantify return on investment (ROI). "You only benefit when something goes wrong in our facility, and not a lot of things go wrong for us. We are preventing things from happening, so any measurement of ROI is a measurement of things that didn't occur. How do you measure the value of a seatbelt? You don't know because the accident didn't happen," said Garvin.

A final challenge was concern among some manufacturing staff about the long-term implications of ML at Amgen. "Some people worry that if certain tasks are automated, they will become replaceable," said Coufal. "When this comes up, we explain that automating certain tasks frees staff to use their extensive knowledge to tackle other work or upskill in areas of interest to them." Coufal saw

a need for the DIPT team to more actively build Amgen's digital culture. "Demystifying the technology is critical," she said.

Organizing for Digital Transformation

In 2015, recognizing the growing importance of digital technologies for the company, Amgen created the Digital Integration and Predictive Technologies (DIPT) team within the Process Development organization. This formalized the work that Ündey had been doing for several years and gave the group permission to expand beyond RT-MSPM. The DIPT team was based in operations. "We are a centralized group that does ML for each Amgen operations function," explained Coufal, "from process development and manufacturing, all the way up. In addition to our centralized group, we have smaller pop-ups all over. There is a group in Puerto Rico focused on ML, for instance."

She went on to explain that ideas for new projects might come from the DIPT team or from one of the individual sites. Regardless of the origin of the idea, every project that the DIPT team undertook was in partnership with an end user like a biologist, a chemical engineer, or a plant floor manager. "Where it's worked well," said Coufal, "is when our collaborators are a smaller group and there are a couple of people we work closely with. Those people tend to be subject matter experts in their area. They know the equipment and rely on us for the modeling expertise. There is a business need that they are trying to solve for, and they're incentivized in some way to solve that problem."

To mitigate risk, before the DIPT team launched most projects, a cross-functional group of Amgen subject matter experts from process development, engineering, manufacturing, and quality control conducted a study called the failure modes and effects analysis (FMEA), which documented all the potential associated risks. "That's a useful document for us because it tells us all of the things that could go wrong," said Coufal. "It alerts us that we should make sure we have data, or simulated data, to test all of those eventualities. We are also very transparent with the end user about all the things that could go wrong so they know we're not just trying to sell them something."

Given variation across sites, it was rarely possible to replicate projects from one location to another. "Solutions are not 'plug and play,'" said Coufal, "because there is variability even in the way data are tagged and structured from site to site." There was also the question of regulatory filings. Said Coufal:

> Every product we have out in the market has been approved by the FDA and other regulatory bodies. We have a collection of documents that detail how we are doing certain processes in our plant, so if we want to tweak a process, we have to change those documents, edit them, and have the FDA approve it. We also sometimes have to operate our processes in two different ways at a single plant because Europe has approved a variation in a specific step in the manufacturing process, but the U.S. hasn't.

Another factor to consider was the personality and culture of individual Amgen plants. "As much as we try to harmonize the way we operate," said Coufal, "there are always things that differ by plant, sometimes just based on the people who work there and their background. There's also the Amgen history at each plant, which has made it into what it is today. We know from experience that Rhode Island tends to be very open to trying new things, for example."

By January 2020, the DIPT team had implemented hundreds of projects across Amgen. The team comprised about 30 full-time staff, plus a handful of graduate students and interns. The team was scattered across the globe. While Ündey and much of the team were in Thousand Oaks, for instance, Coufal was based in Cambridge, Massachusetts, and Garvin worked from Rhode Island. Demand for

the group's expertise was high. "At the beginning," said Coufal, "we were pushing and selling projects, and now we have wait lists of projects that are coming to us." Ündey added: "We now see our value-add being championed by others within the organization. Having someone else make the case for our worth is tremendously valuable."

The makeup of the DIPT team had changed over time. "In the beginning, it was mostly chemical engineers who started dabbling in data science," said Coufal. "We have since hired data scientists who have no knowledge about our industry. It's added a nice balance to the group. There's a lot of internal cross-sharing of knowledge." Given the high demand for data scientists across industries, however, recruiting had proven challenging. Amgen knew that it might be difficult to attract top data scientists with respect to the large technology companies, like Amazon and Google. "Instead," said Coufal, "we compete on other terms, like emphasizing the ability to build products faster for the good of patients."

Testing Automation

In 2019, the DIPT team had slowly begun to test more predictive models. They had started by developing probabilistic models for predictive bioreactor maintenance. Explained Garvin:

> We've said, "Given the substantial costs of losing a batch, let's avoid the risk associated with manipulating the manufacturing process itself and focus instead on influencing what happens to the equipment before product goes in." The decisions we're trying to enable are things like when to replace a faulty sensor or rebuild an equipment part. These are things that can have significant impact on our manufacturing process but can be detected prior to product introduction. That's been a much more comfortable space for us to begin to test predictive models towards improving reliability of equipment.

While the preventive maintenance process had the potential to be fully automated, Amgen had thus far retained an element of human judgment. The model generated recommended actions to take, but also permitted the decision-maker to override them and follow a different procedure if they so choose. "What we're outputting, in addition to a set of recommendations, is a confidence measure," said Garvin, "so the model will say, 'Based on our past experience, this decision is 99% likely to be the right one.' If the end user agrees, they can feel very confident in following the steps the model provides. Now if it's 25% confidence, they might choose to ignore the recommendation."

Many Amgen managers viewed fully automating tasks as exceedingly risky. "If you think about how our plants are run," said Garvin, "the plant management is incentivized to have as high a success rate as possible. The last thing we want is to lose a batch, and we know that we already have a very high likelihood of being successful. To them, why introduce something that will change that dynamic in some way? Thus, managers are more interested in preventing failure than automating."

Nonetheless, in early 2020, the company had *just* started testing predictive models with product performance management. "Our Puerto Rico site is using a predictive model to make a decision about advancing a batch from one step in the process to the next," said Coufal. "The model saves them 12 hours per batch, which is a huge amount of time in a plant that's very capacity-constrained." To get this model up and running, the local process development team in Puerto Rico spent three to four months building it with support from the DIPT team, and then another five to six months working with the manufacturing and quality assurance/control teams to generate buy-in and embed the model into the SOP for manufacturing that product. Coufal and Garvin believed that the model's inclusion in the SOP set a nice precedent for uptake of future models across the company.

January 2020

Back in their respective offices on that Friday afternoon in January 2020, Coufal and Garvin considered the potential impact and risks inherent in each of the two opportunities before them. They were deciding between: 1) building an RT-MSPM model for a fairly new product in Puerto Rico; or 2) automating one step of the manufacturing process for a well-established product in Rhode Island. Coufal and Garvin felt pressure to make the decision quickly, given capacity constraints at both sites.

Building an RT-MSPM Model for mAbX

mAbX was a fairly new commercial product with a limited production history. In late 2019, Amgen had produced 10 to 15 small batches of mAbX at its Thousand Oaks site to supply clinical trials. Amgen had production data from these short runs, but it remained unclear whether these data were fully representative of the manufacturing process at commercial scale. Since transitioning to commercial production at the Puerto Rico site, Amgen had produced roughly five additional batches.

Producing a single batch of mAbX involved a multi-step scale-up process, with each step introducing a small chance of failure. The team in Puerto Rico had asked the DIPT team to build an RT-MSPM model to detect manufacturing anomalies that would, if effective, improve the failure rate of each of the last five steps. The model might also identify other unforeseen anomalies. Coufal and Garvin had worked extensively with teams in Puerto Rico. Before moving to the Cambridge site in 2015, Coufal had been based there for over a decade. While the DIPT team had successfully partnered with several teams in Puerto Rico, they had never before worked with the mAbX team. The mAbX team appeared enthusiastic, but Coufal and Garvin knew that without sustained buy-in, the model would likely languish, unused.

Automating One Step in the Manufacturing Process for a Top-Selling Product

The second request for DIPT support came from a team in Rhode Island that manufactured one of Amgen's top-selling products. For the past five years, this team had produced 50 batches of the product per year. Rhode Island was the single-source manufacturer for the product. While the plant made other products, this was its top priority. The manufacturing process for this product was similar to that of the mAbX. Once again, the process comprised a series of steps, each of which introduced a small risk of failure. The cycle ended with a quality test, conducted by a member of the manufacturing team.

The Rhode Island team had asked for DIPT support to install an additional sensor on its already extensive array of sensors that would automate the decision around quality. Adding the new sensor would eliminate the wait for the lab results and thus slightly reduce the cycle time for each successful batch. The sensor would use an ML model to conduct the quality test, which would generate a predicted probability along with uncertainty bounds. The model, which the DIPT team would need to build, would attempt to replicate the decision that the manufacturing staff member would have made.

Like all ML models, this test would contain a tiny but non-trivial rate of false positives and false negatives. False positives gave a green light even though the batch might have had performance issues, and false negatives gave a red light even though truthfully the batch could have proceeded as planned. The plant's managers had indicated that any predictive model should minimize the probability of false positives, at the expense of false negatives. Given the importance of the product being produced, Coufal and Garvin knew that any predictive model would need to be built with an abundance of caution. They considered the impact and risks of each of these two opportunities. Where should the DIPT team devote its limited time?

Exhibit 1 Amgen Consolidated Financials, in $ Millions, except per-share data, 2015-2019

	2015	2016	2017	2018	2019
Revenues:					
Product sales	20,944	21,892	21,795	22,533	22,204
Other revenues	718	1,099	1,054	1,214	1,158
Total revenues	**21,662**	**22,991**	**22,849**	**23,747**	**23,362**
Operating expenses:					
Cost of sales	4,227	4,162	4,069	4,101	4,356
Research and Development	4,070	3,840	3,562	3,737	4,116
Selling, general and administrative	4,846	5,062	4,870	5,332	5,150
Net income	**6,939**	**7,722**	**1,979**	**8,394**	**7,842**
Diluted earnings per share	9.06	10.24	2.69	12.62	12.88
Dividends paid per share	3.16	4.00	4.60	5.28	5.80
Total assets	71,449	77,626	79,954	66,416	59,707
Total debt	31,429	34,596	35,342	33,929	29,903
Total stockholders' equity	28,083	29,875	25,241	12,500	9,673

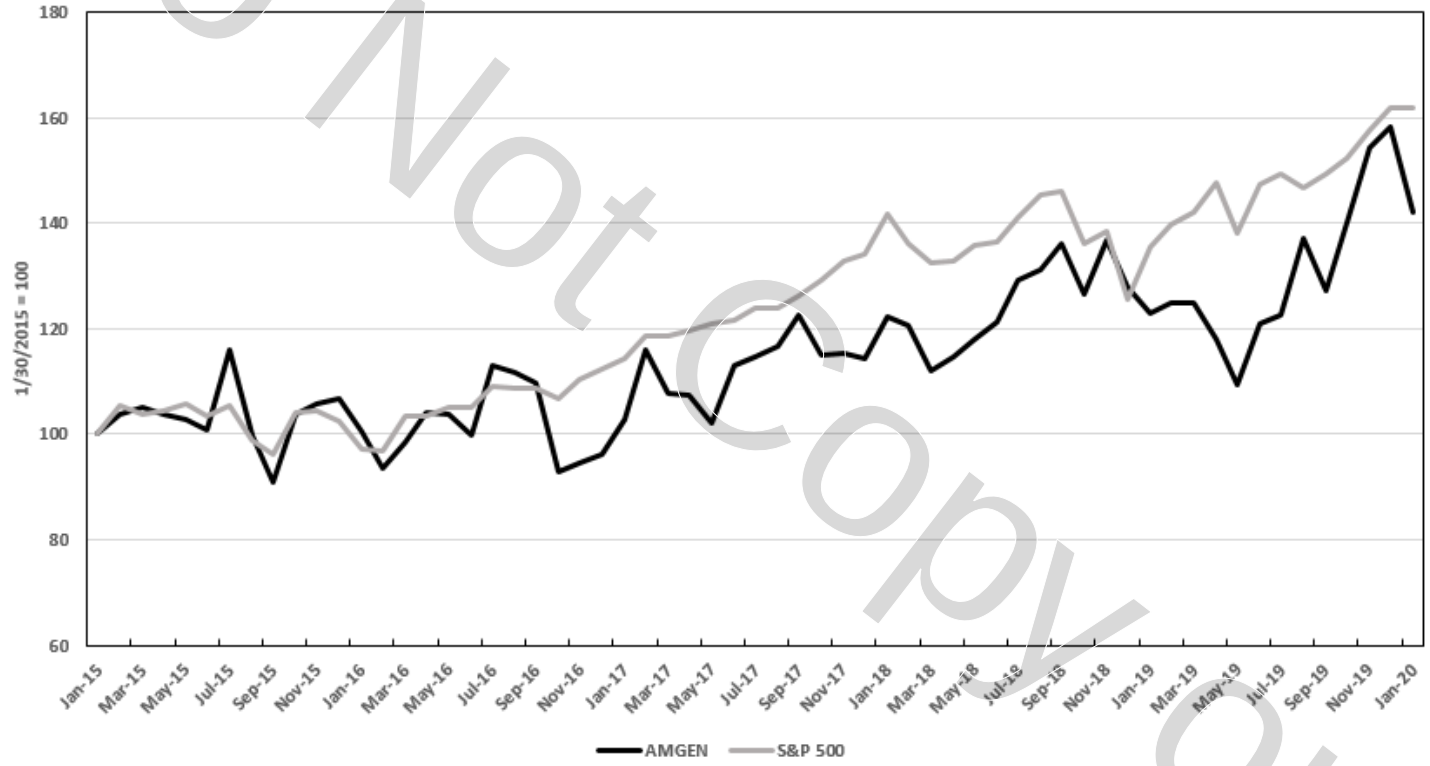
Source: Amgen, Form 10-K, December 31, 2019, p. 44, https://www.sec.gov/ix?doc=/Archives/edgar/data/318154/000031815420000017/amgn-12312019x10kq42019.htm, accessed June 2020.

Exhibit 2 Amgen Product Sales by Type, 2017-2019

	2017 ($21.8 Billion)	2018 ($22.5 Billion)	2019 ($22.2 Billion)
Enbrel®	25%	22%	24%
Neulasta®	21%	20%	14%
Prolia®	9%	10%	12%
XGEVA®	7%	8%	9%
Aranesp®	9%	8%	8%
KYPROLIS®	4%	4%	5%
EPOGEN®	5%	5%	4%
Sensipar®/Mimpara®	8%	8%	--
Other Products	12%	15%	22%

Source: Amgen, Form 10-K, December 31, 2019, p. 3, https://www.sec.gov/ix?doc=/Archives/edgar/data/318154/000031815420000017/amgn-12312019x10kq42019.htm, accessed June 2020.

Exhibit 3 Amgen Stock Chart Relative to S&P 500, January 2015-January 2020



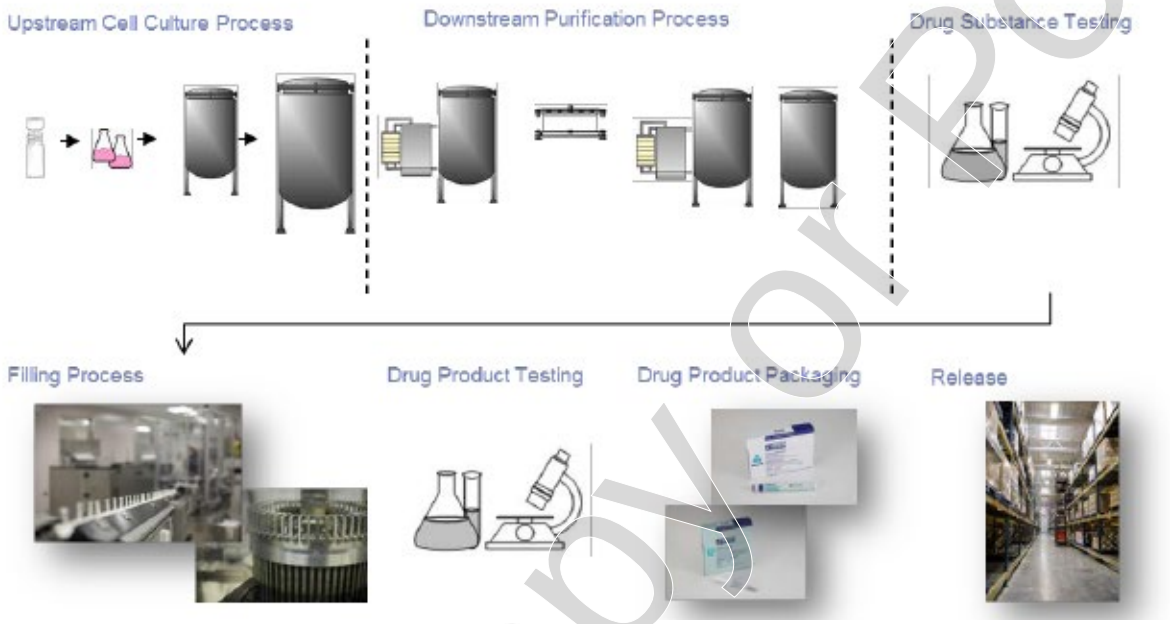
Source: Refinitiv Datastream, accessed 6/23/2020.

Exhibit 4 Amgen Properties and Operations

	Manufacturing	Administrative	R&D	Sales/Marketing	Warehouse	Distribution Center
U.S. Locations						
Thousand Oaks, CA	✓	✓	✓	✓	✓	✓
San Francisco, CA			✓			
Louisville, KY					✓	✓
Cambridge, MA			✓			
Woburn, MA	✓				✓	
Juncos, Puerto Rico	✓	✓			✓	✓
West Greenwich, RI	✓	✓			✓	
Tampa, FL		✓				
Other U.S. Cities		✓		✓		
Non-U.S. Locations						
Brazil		✓		✓	✓	✓
Canada		✓	✓	✓		
China		✓	✓	✓		
Germany		✓	✓	✓		
Iceland		✓	✓			
Ireland	✓	✓		✓	✓	
Japan		✓	✓	✓		
Netherlands	✓	✓		✓	✓	✓
Singapore	✓	✓			✓	
Switzerland		✓		✓		
Turkey	✓	✓		✓	✓	✓
United Kingdom		✓	✓	✓		
Other Countries		✓	✓	✓	✓	

Source: Amgen, Form 10-K, December 31, 2019, p. 41, https://www.sec.gov/ix?doc=/Archives/edgar/data/318154/000031815420000017/amgn-12312019x10kq42019.htm, accessed June 2020.

Exhibit 5 Biologic Manufacturing and Packaging Process, Amgen



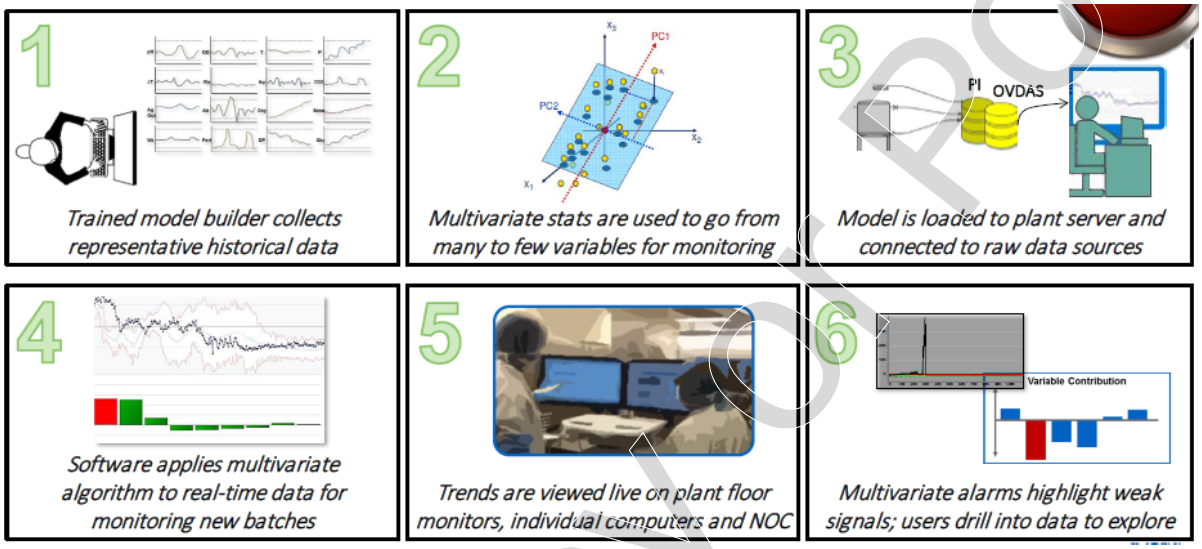
Source: Cenk Ündey and Chris Garvin, "Real-Time Multivariate Statistical Process Monitoring," UMetrics User Meeting, May 8, 2019, Slide 15, https://landing.umetrics.com/hubfs/User%20Meeting%20Presentations%202019/Amgen.pdf, accessed June 2020.

Exhibit 6 Primary Causes of Batch Failure, based on 144 Responses from a Biotech Survey, 2008

Reason for Batch Failure	<1,000 liter capacity facilities	>1,000 liter capacity facilities
Contamination	2.3%	0.8%
Operator Error	1.5%	0.3%
Equipment Failure	1.4%	1.7%
Failure to Meet Specs	1.0%	0.7%
Material Failure	0.6%	1.9%
Cross-Product Contamination	0.4%	1.1%
Other	0.4%	0.1%

Source: Eric S. Langer, ed., "6th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production," 2009, BioPlan Associates, Rockville MD, accessed November 2020.

Exhibit 7 Steps Involved in Building an RT-MSPM Model, 2019



Source: Cenk Ündey and Chris Garvin, "Real-Time Multivariate Statistical Process Monitoring," UMetrics User Meeting, May 8, 2019, Slide 25, https://landing.umetrics.com/hubfs/User%20Meeting%20Presentations%202019/Amgen.pdf, accessed June 2020.

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