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Pharmaceutical Manufacturing: Linking Vision and Decision-Making to Achieve a Roadmap Toward cGMPs for the 21st Century

This article presents the changing manufacturing environment and how companies can develop an infrastructure to continue to meet their strategic objectives.

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Introduction

Despite the innovatory and advanced science nature of many of its products, the pharmaceutical industry has been more used to incremental change in manufacturing rather than quantum leap advances. Now, however, there is the prospect of more rapid change in the industry. Changes in the regulatory stance and compelling business reasons are prompting companies to consider 'big leap' rather than 'small step' changes. But many companies remain wary of drastic change. How can companies judge how best to prepare for the future manufacturing strategy and infrastructure? How fast and how far should they move? Many companies are seeking to implement manufacturing change, but are doing so in sub-optimal ways that do not maximize benefit for the company. This is because, often, changes in manufacturing practice and infrastructure are not being informed by a clear manufacturing vision. Such a vision must address the regulatory, market, scientific, and technological forces that will shape pharmaceutical manufacturing in the future. Changes in regulation and technology are already influencing how existing products are tested. Looking ahead, regulatory, scientific, and technological developments have the potential to produce significant change in the interaction of manufacturing and the market. This article considers this changing context and looks at how companies can develop a manufacturing vision. It outlines four possible manufacturing scenarios that companies may find themselves considering. The IT/manufacturing infrastructure that will be important for each scenario is presented.

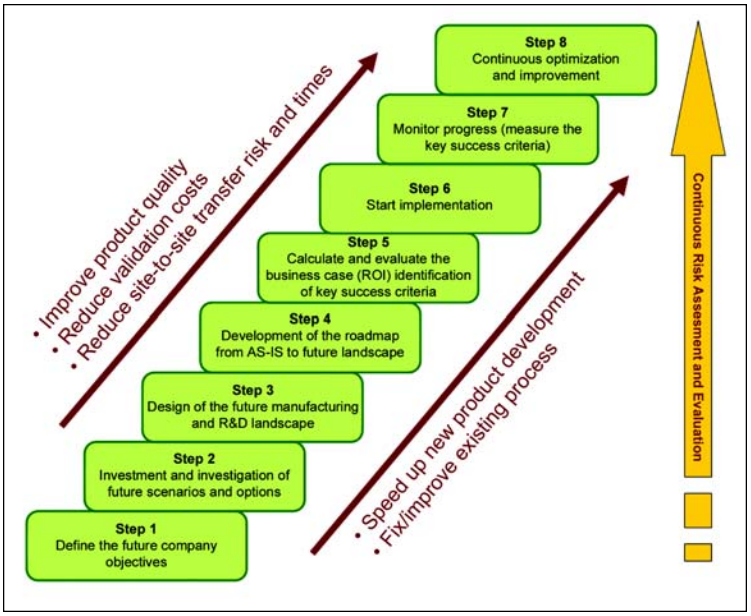

Figure 1. Moving toward the manufacturing vision.

The Changing Manufacturing Context

The pharmaceutical manufacturing sector has been inherently conservative in its approach to manufacturing change. Regulation is a key driver for change. Historically, though, the regulatory framework, with its reliance on batch inspection, has de-

terred manufacturing innovation. Regulation has driven change, but in an 'after the event' fashion with compliance reliant on enforcement and inspection. Now, recent initiatives of the US Food and Drug Administration (FDA) herald an era where regulation can act as a more dynamic driver of change with both quality and regulatory compliance 'designed in' to the manufacturing process. The FDA's PAT framework and its cGMPs for the 21st Century initiative provide significant opportunities for improvement and innovation in pharmaceutical manufacturing. The FDA talks about a 'desired state' of manufacturing with:

- product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- an ability to affect continuous improvement and continuous "real time" assurance of quality[1]

The final report of the FDA's cGMPs for the 21st Century Initiative[2] highlights the choices that pharmaceutical companies face:

> "At the end of the cGMP initiative, the pharmaceutical community has arrived at a cross-road; one path goes toward the desired state and the other maintains the current state. The path toward the desired state is unfamiliar to many, while the current state provides the comfort of predictability. The Agency hopes the pharmaceutical community will choose to move toward the desired state."

This new regulatory approach presents companies with the possibility of new manufacturing visions. It also comes at a time when the risk reward context for pharmaceutical manufacturing is changing. Companies are becoming more exposed to powerful wider market forces. The pharmaceutical industry is at a key turning point in many respects. Historical ways of delivering value will not be sustainable on their own in the future. All the key planks of value are in transformation – drug development pipelines are drying out, pricing is under pressure, and generic competition is more intense. Cost containment is the name of the game both for the government customer bodies that play a lead role in the pharmaceutical market around the world and the private insurance customers in mar-

Case Study 1: Manufacturing Vision Development

Background

A pharmaceutical company has a product that will soon run out of patent and generic manufacturers are becoming strong competitors. Reducing manufacturing costs has been defined by this pharmaceutical company as a key business objective.

A Typical Response

The company decides to appoint a team of experts whose task is to review manufacturing and propose optimization proposals. After a couple of months, this team presents the cost reduction initiatives to their management. A list of suggestions have been made, such as better planning to remove Work In Progress (WIP) and to lower inventory; optimization of manufacturing yields and costs by enlarging the batch size (higher filling levels in manufacturing equipment); in-line inspection instead of manual inspection; and installation of process analyzers to detect batch end-points, for example for drying and blending. The team shows that these measures will deliver a reduction in manufacturing costs.

A 'Manufacturing Vision' Response

Another company takes a different approach. Instead of appointing a team to look for optimizations and improvements, it first organizes a high level meeting with representatives from a range of departments - R&D, manufacturing, sales and marketing, regulatory affairs. The aim of the meeting is to investigate what will be needed in five to 10 years time, taking account of business challenges, technological options, and regulatory opportunities.

The group has already looked at their current product portfolio and future portfolio, based on their pipeline. It has investigated the consequences of this new portfolio on the current manufacturing infrastructure. It has considered what the future manufacturing landscape will look like to be able to cope, not just with the new product portfolio, but also with the future market and environmental requirements, business model requirements, regulatory changes, etc. A scenario planning exercise has supported the exploration of possibilities and future scenarios. This study results in the identification of a manufacturing vision, which describes the future required manufacturing landscape that will best fit with the most likely scenarios.

This vision makes it easier to identify the gaps between the current "as is" manufacturing situation and the future "to be" one. It also helps to indicate the improvements and changes that the company can already start to implement. A roadmap linking the "as is" and the future "to be" situation enables the company to focus on the improvement and optimization projects that help it move to the future situation. The company can avoid investments which, taken in isolation, might have a sufficient Return On Investment (ROI) to implement, but when looked at in a fuller context, would not achieve a more sustainable advancement for the company. This broader perspective enables the company to move forward in the knowledge that it is not just investing in little islands of optimizations, but is linking them to a wider and bigger quantum leap forward.

kets such as the US. Double-digit sales and income growth has come to an end under pressure from patent expirations, generic competition, and Over The Counter (OTC) switches.

Alongside these trends, we are not so far from a future where it will be possible to develop drugs that are tailored to the individual genetic and proteomic profile of the patient, making the therapy more effective and having less side-effects by optimizing dosage and drug composition for each patient. An investigation by the national academy of science of the UK concluded: "personalized medicines; tailoring drug treatments to a person's genetic profile, also known as pharmacogenetics, have a promising future,"[3] predicting that "over the next 10 to 20 years, we expect to see several pharmacogenetic products enter mainstream healthcare."[4] The report pointed out that "industry will continue to favor drug candidates that avoid the effect of genetic variation, but where that is not possible, the development of drugs with an associated diagnostic test is expected to become routine in the next 10 to 20 years."[5] In part, mainstream pharmaceutical M&A companies have reflected this future with repeated acquisitions of biotechnology companies. These moves have been designed to boost drug pipeline portfolios in the short to medium term and build capacity for a more genetically-driven industry of the future in the medium to long term.

Such a future is very relevant to a company's manufacturing vision. As a consequence, drugs will need to be manufactured or produced in smaller batches that are formulated on request to match the profile of certain segments of patients or even a single patient. There will be fewer big blockbuster drugs and more personalized medicines. To accommodate these changing production needs, new flexible regulatory approaches and batch control strategies have to be developed. Moreover, since the treatment is formulated on request and is intended for a patient who may urgently need the medication, product development and manufacturing lead time and release times will have to be drastically reduced.

Developing a Manufacturing Vision

Therefore, pharmaceutical manufacturers face a complex and in some respects, contradictory set of demands. On the one hand, they have the opportunity to make significant investments in automation and process technology, but on the other hand, they face cost pressures, meaning that such investments must deliver the maximum benefit. They face a future drug market that may be more personalized, posing key dilemmas for whether the manufacturing plant development should be large scale or small scale.

Mergers and acquisition activity has made it easier for some companies to close or modify existing outdated plants. In our practical experience, we see companies starting a lot of investment projects both as part of post acquisition activity and elsewhere. They are called various names, such as improvement projects or cost containment projects, but they have in common the aim of manufacturing modernization. However, they are rarely informed by a real look at the bigger picture of where the company wants its manufacturing to be in five to 10 years time (see Case Study 1). Classically, when companies consider investment in Process Analytical Technology (PAT) for example, they often see it as replacing one form of testing with another form of testing without considering its full potential. No wonder Dr. Ajaz S. Hussain, who at the time of being quoted was Deputy Director at the Office of Pharmaceutical Science CDER at the FDA, was prompted to remind companies: "you've got to remember that PAT is not about just throwing in-line sensors at a production line. It is more about understanding the sources of product variability during production and controlling your processes in a flexible way to allow you always to produce a quality product."[6]

Investment tends to be on a limited scale and fragmented, focusing perhaps on one production unit or process, but not making connections across the manufacturing software and infrastructure which, often, remains standing alone or only present on isolated production units. This often results in sub-optimizations instead of an overall optimization. In the future, the requirement will be for all the supporting software and different applications to be interconnected. As Graham Cooke, Director Technology and External Supply EMEA of Wyeth, has emphasized, companies need to avoid developing isolated islands of innovation: "'Islands' of PAT (need) to be tied together as part of an overall strategy. Feed back and feed forward controls. (Companies need to) develop the 'integrated plan' first and then create focus and dive deep into individual unit operations before extending to other unit operations."[7] In addition, whether it is PAT or other innovation, the infrastructure will need to be of high quality and reliability because the recourse to running the production manually will not be an option.

How can companies judge how best to reshape their manufacturing strategy and infrastructure? In the context of PAT, Cooke emphasises the need for 'wider company' multi-disciplinary thinking: "…a number of success factors have been identified for implementation of PAT. These include the need for multi-disciplinary project teams, a clearly defined implementation process, and a strong business rationale."[8] Companies need to address the culture change implications of investments such as PAT which include breaking down silos within organizations and also rethinking job roles. Far-sighted companies seeking to capture the full competitive advantage potential of PAT will, for instance, be looking at the links outside of manufacturing into the consumer-facing functions of product development and marketing. Skill-set requirements will change significantly. Enterprise-wide data management, retrieval, and querying will be vital. Pharmaceutical scientific skills will need to extend into understanding the supportive database structure and be capable of managing knowledge retrieval systems in an efficient, usable, and timely manner.

In our view, the starting point has to be the manufacturing vision and all parts of the business need to be in-

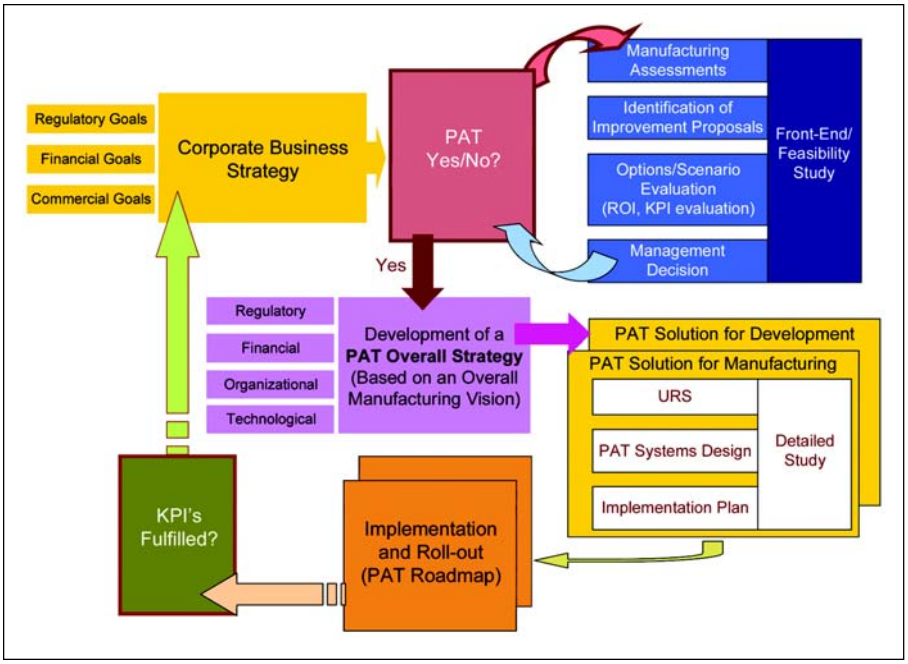

Figure 2. The pharmaceutical manufacturing change context.

volved in looking ahead on a 10 to 15 year time frame. The following case illustration highlights the importance of framing decisions in such a context and contrasts that with the typical approaches that we, as authors, see many pharmaceutical companies taking.

The approach outlined in Case Study 1 allows companies to prioritize specific problems within the context of long-term change. The range of specific concerns could include a need to fix or improve existing processes, speed up new product development, reduce site to site transfer risk and times, reduce validation costs, or improve quality reliability. Most companies are likely to want to realize a blend of these benefits. Their immediate priorities will be determined by the current state of play of their manufacturing and its fit with their regulatory compliance, market and business goals. Most importantly, though, they need to combine this review of current wider concerns with the type of longer-term wider scenario planning outlined in the case illustration above. Figure 1 outlines the steps companies might take to put this process into practice.

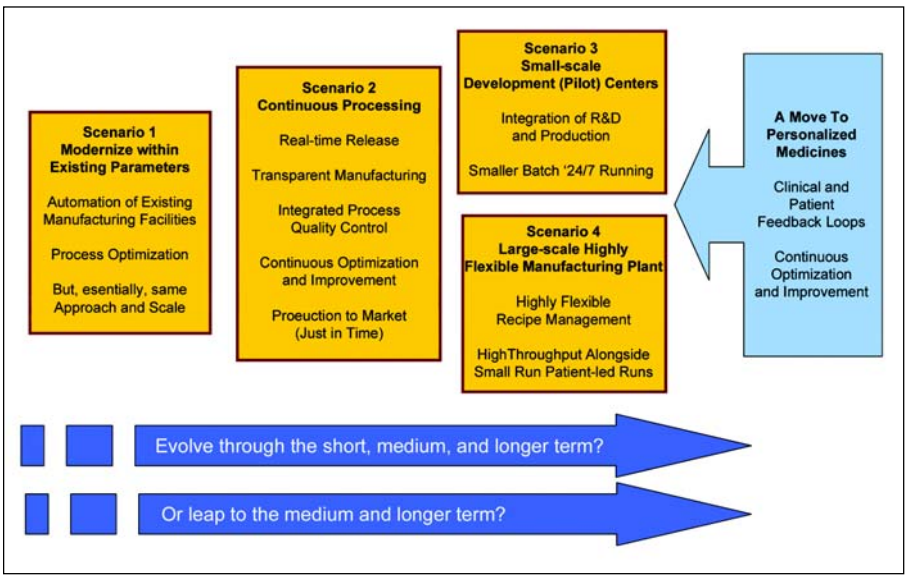

Figure 3. Four change scenarios.

Figure 2 provides an overview of the type of overall decision-making process that a company needs to undertake. The current manufacturing infrastructure has to be assessed in the light of the future manufacturing vision (in line with the global company's objectives). What are the current bottlenecks and what are the improvement possibilities? The resulting list of improvement proposals have to be evaluated to judge just what they bring to the company and whether they help achieve the manufacturing vision and its objectives. Depending on which market the company is in, the regulatory constraints need to be superimposed in order to make sure no surprises are encountered. Even for those countries that are actively driving changes (such as the FDA in the US), it is important to involve the regulators early on in the process.

Four Change Scenarios

The outcome of this type of process will be a view about what type of manufacturing strategy and plant the company needs in a more medium to long term timeframe, say five to 10 years time. The answer may be different from plant to plant and many companies are likely to need to plan for a mix of scenarios. For example, a company may choose to implement relatively modest improvement investment in a plant that is manufacturing a product that is nearing the end of its patent period (scenario one in Figure 3). Elsewhere it may choose to plan for a rapid and full scale move to PAT enabling full realization of the FDA's vision of real time product control and release, based on continuous manufacturing operations (scenario 2 in Figure 3).

Companies also will be mindful that a possible trend toward more personalized medicines will increase manufacturing complexity, and in turn, pose challenges for Manufacturing Execution Systems (MES) and quality systems. A larger variety of products and variation of the same products will require greater flexibility of production as well as closer integration along the whole pharmaceutical chain - R&D,

manufacturing, sales, and the end customer.

Scenarios three and four in Figure 3 highlight how companies will face a choice between big plant with flexible recipe production versus small-scale development (pilot) plants which also will be production facilities with dedicated lines. For both models of production, industrial IT systems will play a strategic role, requiring tremendous flexibility, in the first model, to support the flexibility of production that will be necessary, and in the second smaller scale model, to link production with continuous development and learning from clinical trials. The regulatory stance will be a key factor in this mix and at present, regulators are investigating how to support this evolution with the appropriate regulations and guidelines.[9]

A key influence will be the demand side and we are likely to see a mix of large scale, very high throughput facilities handling generic production, and micro-process centers concentrating on higher end personalized medicines. Therefore, pharmaceutical companies need to investigate the investment in planning for a potentially very different manufacturing future as well as responding to pressures on their current manufacturing set-up.

Choosing Between Scenarios – Evolution or Drastic Change?

A critical issue for companies contemplating scenarios such as outlined in Figure 3 will, of course, be how to make choices between them. The identification of the right evaluation criteria (Key Performance Indicators (KPIs) for improvement) is crucial for evaluating the options and for monitoring progress and achievement of the objectives. Each company's situation will be different and judgements on the focus and pace of change will vary according to the ROI analysis of the different options open to them. For example, some companies may consider that certain plants or processes do not merit investment, others will only need minor investments and others require drastic

Case Study 2: Status Quo vs. Automation vs. Full PAT Implementation in a Vaccine Plant

Background

A vaccine plant was seeking to achieve cost savings through modernization of manufacturing infrastructure. Interviews with different stakeholders and analysis of manufacturing data led to:

- the identification of areas for cost savings through the assessment of possible improvement scenarios
- an outline of operational and financial benefits for these various scenarios
- assessment of the impact of different scenarios on the following KPIs:
  - labor (people)
  - manufacturing throughput time
  - quality
  - waste
  - inventory levels

Improvement Scenarios

Three improvement scenarios were identified. Each of these scenarios describe the various steps toward optimal PAT-enabled manufacturing, delivering the maximum benefits in terms of cost savings.

The scenarios are built up in such a way that maximum benefits are realized with minimal investments. They start with the quick wins followed by a sequence of medium to longer term improvement investments. Each improvement investment goes hand in hand with benefits which are displayed as an effect on the Key Performance Indicators (KPIs).

- Some of the scenarios can be executed in parallel; however, when activities are carried out in parallel, the necessary skilled resources need to be available in order to deal with the complexity and the project management.
- A timeline was developed illustrating how much time it takes to implement the improvements as well as the resources and skill set needed for each of the improvement projects. The time to get regulatory approval should be superimposed on the outlined project execution time lines.
- In parallel with the timeline, the sequence of investments needed to realize improvements was established.

Results

The result was a calculation of the optimal scenario (in this case, scenario 3) and its impact on the KPIs:

- Labor: 1/4 of operations people could be re-allocated and 1/3 of the QA/QC people could be freed up for other work.
- Manufacturing throughput time: throughput time decreased with 1/3 freeing up capacity and allowing extra production with the same headcount.
- Quality: 13% of the cost of QA and QC are eliminated because of improvement in right first time.
- Waste reduction: 3.5%
- Inventory: inventory could be reduced by 1/3 (representing about US $14.3 million in this case).

Observations

In terms of PAT implementation, maximum benefits were achieved with a broad PAT definition. This means looking at the full opportunities offered by PAT, as outlined in the FDA PAT Guidance (e.g., real-time product release, manufacturing performance improvement, quality consistency improvement, and regulatory flexibility). This was preferable to a "limited PAT" approach based only on the implementation of an on-line sensor. We found that the feasibility of a broad PAT enabled manufacturing process could be demonstrated with much more certainty.

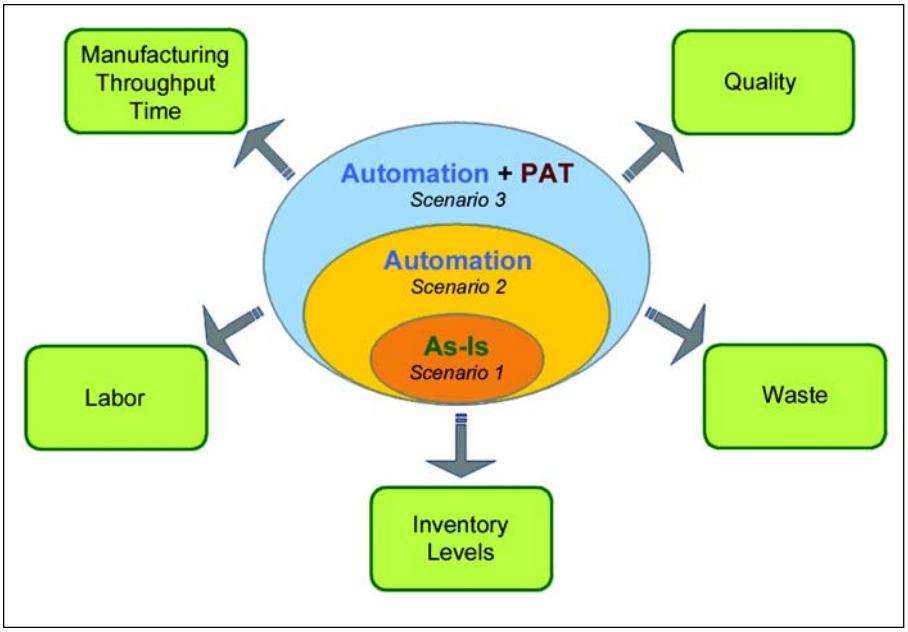

Figure 4. Impact of scenario implementation on various KPIs.

change.

Even in the case of drastic change, it is the authors' experience in many real-life cases that a change, which at first sight may appear quite drastic and associated with big investments, can be shaped into smaller pieces, solving at the same time some technical issues. This allows a step-by-step investment and implementation with each step having a ROI case, providing justification of the investment. The company, although taking small steps, is doing so in the context of a journey toward a manufacturing infrastructure which meets the future business challenges. This will enable companies to be ready for the possible future business scenarios and to take advantage of adopting new technologies early. The critical elements are the selection of the improvement options, the identification of the right KPIs, the size and sequence of the steps, and last but not least, the fit of the future manufacturing vision with the possible future business landscape. Case Study 2 illustrates how this might work in action in a vaccine plant.

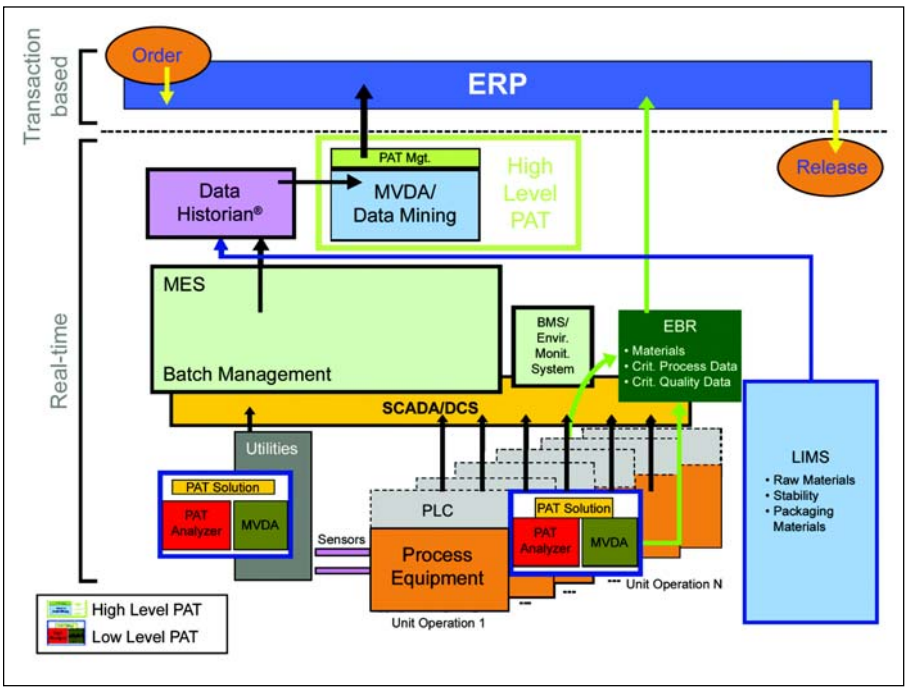

Figure 5. Manufacturing infrastructure scheme.

Manufacturing Infrastructure

Once they have chosen between different possible manufacturing visions and completed some scenario planning, companies will, of course, need to decide on the manufacturing and IT infrastructure that will be required for the chosen scenario. Decisions about the future architecture will differ between the various scenarios, and crucially between those with smaller size process equipment and larger scale manufacturing. As an example, Figure 5 outlines a manufacturing infrastructure scheme corresponding to scenario 2 of Figure 3. The PAT solution has interfaces to the process equipment, the process automation, and will take care of data collection from the process, eventually from extra real-time measurements (PAT Analyser) as well as data storage and retrieval. It consists also of an MVDA engine able to interpret quality data and translate this into control and correction actions. The high level PAT solution will combine various unit operations and will take care of the overall product release of the final product.

In general, the role of the quality management system will shift to the manufacturing floor and will be of more strategic importance, as it is essential for real-time product release. Greater integration of multi-disciplinary teams will be an important factor alongside the hardware and software. The quality management system will consist of a LIMS system and PAT systems (on unit and on line level). It will allow Production Performance Analysis (PPA). In turn, for faster time-to-market, a closer link between development and manufacturing is required that allows for continuous improvement. Figure 6 outlines the wider architecture that is needed. A central role will be occupied by knowledge management systems and data portals, but also by advanced data mining techniques. The

role of knowledge management systems and data portals will be essential for this change.

Conclusion

A combination of regulatory, market, scientific, and technological forces is likely to mean that pharmaceutical manufacturing will undergo rapid change in the next five to 10 years. Many companies are already investing in change projects, but they are often piecemeal and not accompanied by a clear manufacturing vision. The absence of such a vision also means that companies sometimes feel caught between 'big leap' and more incremental changes. In fact, incremental change is vital to achieve a longer term 'big leap.' But, in the absence of a manufacturing vision, companies find themselves with no roadmap. The consequence is that changes are made in relative isolation without maximizing their potential incremental contribution to longer term improvement or, worse, moving the company further away from the manufacturing it will need in the future.

We have shown how companies can use a range of tools – scenario planning, ROI analysis, KPIs – to construct such a roadmap to ensure changes are linked together, thereby avoiding piecemeal and sub-optimal change. There is a need for companies to more consistently align investment in IT and manufacturing with their vision of the manufacturing that will be needed in the future. In doing so, companies will be able to ensure that investments don't just deliver specific gains, but also help accelerate the company's progress toward longer term goals.

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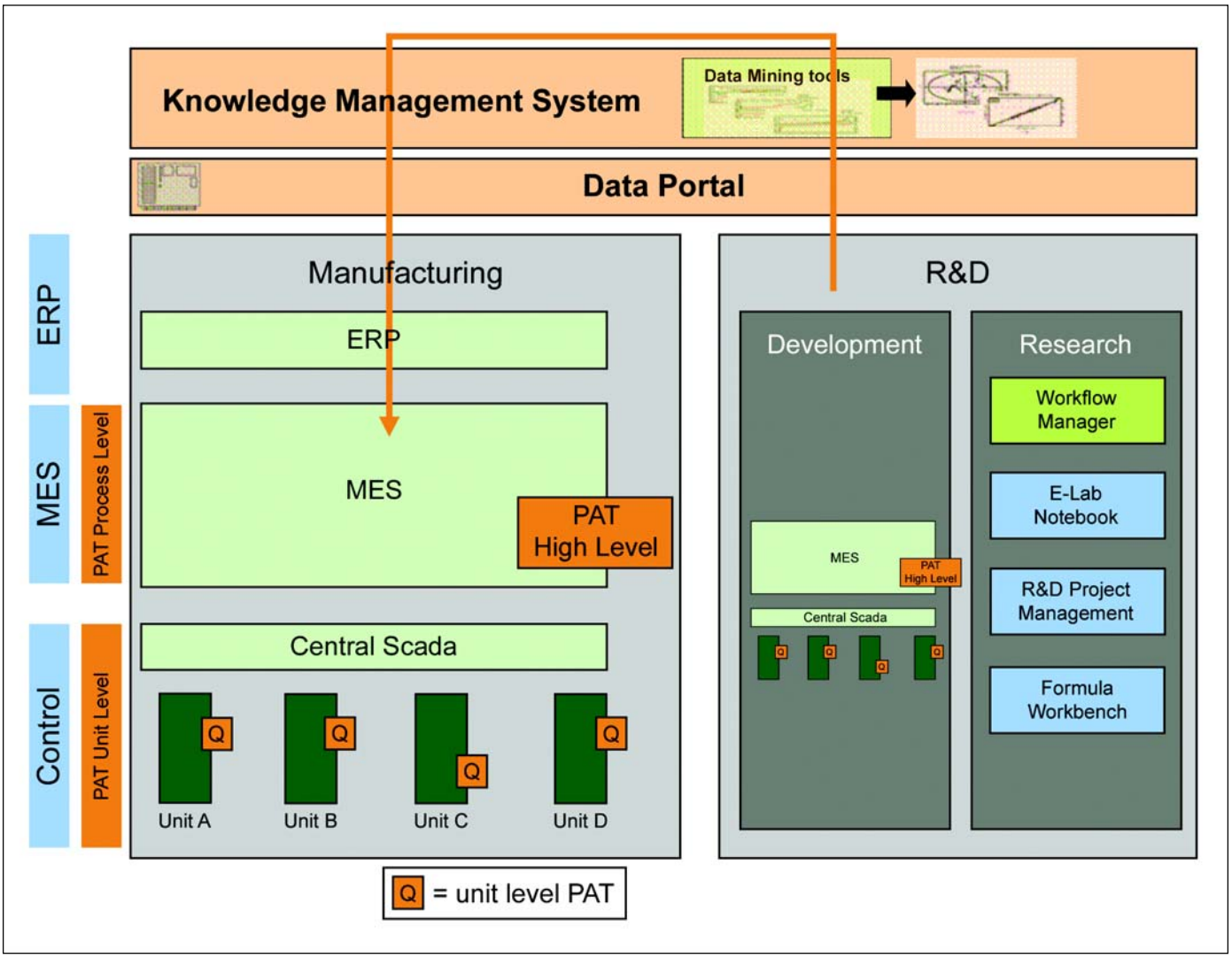

Figure 6. Tighter integration of development, manufacturing and knowledge to achieve continuous improvement.

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