

# angle

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Quality by Design  
– The Promised Land



Dear all

Welcome to a new issue of Angle, our magazine about NNE Pharmaplan and the world around us.

There are many aspects to engineering for a healthier world. This time we have had the courage to go one step beyond what surrounds us today and look into what we believe will surround us tomorrow. We will focus on one of the most important new trends in pharmaceutical development and manufacturing: the concept known as Quality by Design (QbD).

Many of you have heard about QbD, but it has not yet become mainstream. However, this may soon change.

We mean QbD in a broad sense - not just the narrow sense of product development, but a broad understanding of how it will impact patients, manufacturing, development and other areas.

In this issue, we take you through some of the interesting angles on this new concept. We have included the views of the industry, regulators, patients and our own specialists in an attempt to give a broad picture of what we see today and what we expect in the future.

Please take the time to be inspired with us.

Best wishes

Morten Nielsen  
CEO NNE Pharmaplan

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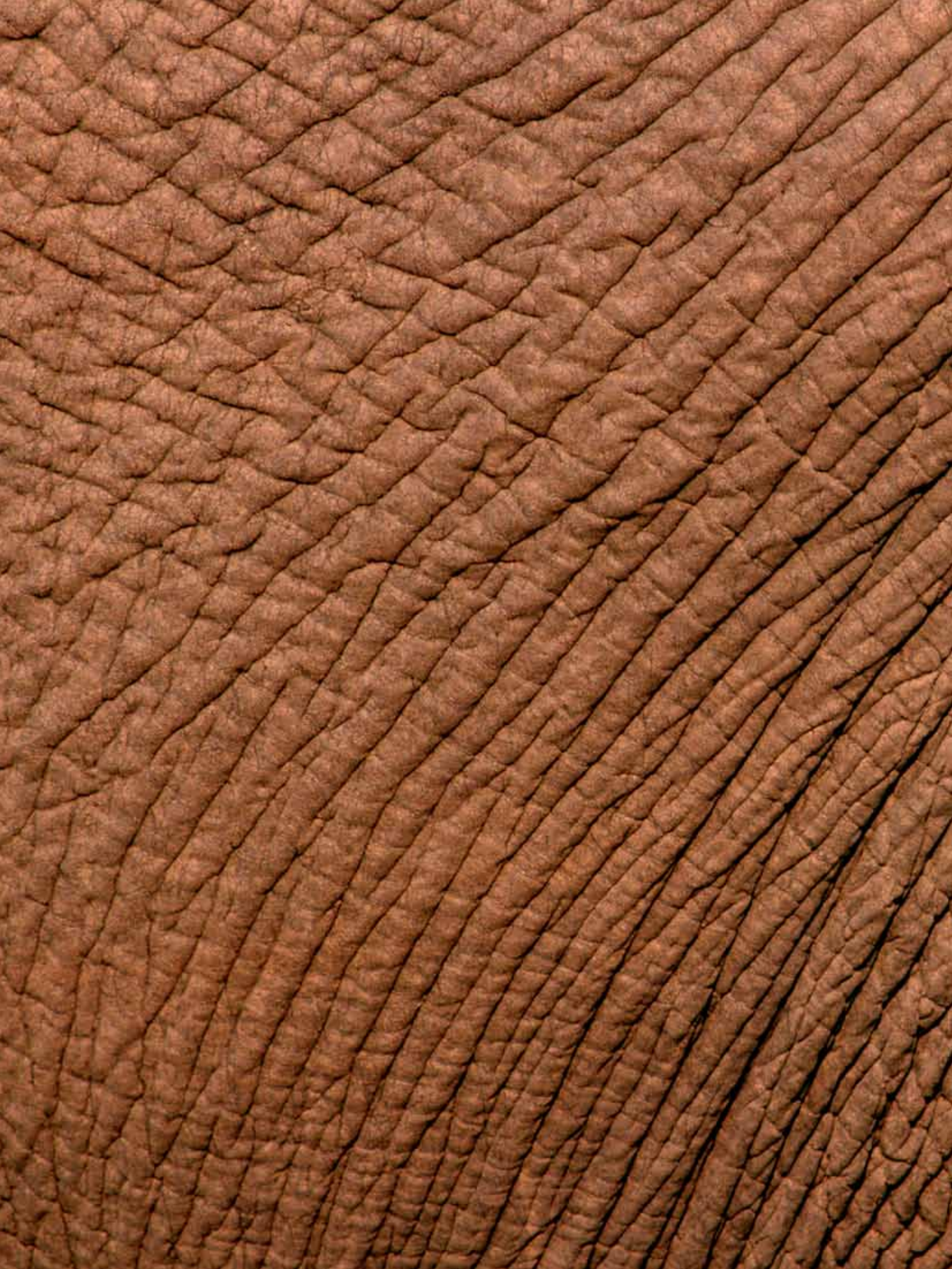
To put it simply, Quality by Design is about focusing on the product and the patient from the outset.

The big misunderstanding, page 6

QbD is no longer just a vision. It is here and many of our customers have already demonstrated significant results using this new framework.

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# The big misunderstanding

The pharmaceutical industry has not yet started to exploit the full potential of Quality by Design (QbD). The reason: fundamental misunderstandings about the nature of QbD.



As in the old fable of the blind men touching different parts of an elephant and then producing conflicting accounts, misconceptions about the nature of Quality by Design (QbD) add up to a fragmented understanding. A part is taken for the whole, and the unity that permeates all of the parts – the elephant in its entirety – remains unseen.

To put it simply, QbD is about focusing on the product and the patient from the outset. Understanding the quality risks of a pharmaceutical product to the patients – and then systematically tracing back into what is critical. Initially, what is critical about the product and then what is critical in the raw materials and in the manufacturing processes.

### **QbD is not only about development - it has far wider applications.**

There is a clear tendency in the pharmaceutical industry towards using QbD to develop medicines in a much smarter and cost-effective way. But QbD is not only about development – it has far wider applications.

The main reason for the industry's sluggishness in implementing QbD is regulatory fear, i.e. the risk of not getting the product approved by the health regulating authorities. But the fact is that the industry itself is responsible for the bottleneck. The regulators in the US Food and Drug Administration (FDA) and the European Medicines Agency have often expressed their dismay at how slow the industry is to adopt QbD.

Since the FDA in 2004 released 'Process Analytical Technology (PAT) - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance', its significance to the industry has been discussed.

QbD is not only an integral part of PAT but in fact subsumes PAT under the larger principle of designed-in quality. Further, the FDA made it clear from the beginning that the goal of PAT is not the technological automation of process control, but comprehensive process understanding. As the PAT guidance says, "a process is generally considered well understood when all critical sources of variability are identified and explained; variability is managed by the

process; and, product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions.”

### **The FDA also encouraged improved process understanding and continuous improvement of manufacturing processes for products already in the market.**

Because the PAT initiative and the concept of designed-in quality appeared at first to be focused on drug development, the misconception arose that QbD was also primarily for use in developing drugs and the manufacturing processes that would be used to produce them. But the FDA also encouraged improved process understanding and continuous improvement of manufacturing processes for products already in the market.

QbD applies to all phases of the product life cycle: drug development, scale-up, manufacturing of both new and in-market products and technology transfer of processes and products to other sites. In drug development, for example, the potential of design space understanding leading to robust manufacturing processes is perhaps the most widely understood aspect of QbD. But QbD offers a further advantage here. Because development usually takes place over a long period of time and often involves many people, it can sometimes result in misunderstandings, errors, and redundant activity. QbD keeps an understanding of design space at the forefront of development efforts, providing the coherence and continuity that trial-and-error approaches lack. QbD can also help maintain ‘lifetime development’ – the continued gathering of data after a product is already

in production. Because only a limited amount of data accumulates during initial development, additional data, framed by the product’s design space, can be helpful in deepening process understanding and continually improving the process.

In January 2011, the FDA published a new guideline on process validation that builds on many of the concepts of QbD. It is already being enforced by FDA investigators during inspections. However, with or without the new process validation requirements, QbD is a new manufacturing paradigm in the pharmaceutical industry. But when we strip away all the hype and slang, we see that the concept has been around in other industries for many years.

Other industries have done it without any regulatory involvement, simply because it makes good business sense. So when an article in *The Wall Street Journal* in 2003 claimed that “The pharmaceutical industry has a little secret: its quality principles lag behind those of laundry soap or potato chip manufacturers”, it was a sign that the world was about to change. Today many of the business benefits that these industries have enjoyed for years are becoming available to pharmaceutical companies. QbD is here. It is time for the industry to remove the blinkers.





# Quality saves lives

Quality assurance of pharmaceuticals is a major public health challenge, particularly in the light of growing cross-border health issues and the international dimensions of trade.

The pharmaceutical industry and its regulators are strongly focused on all quality issues because at the end of the day, drugs often make the difference between life and death. It is therefore crucial that patients can trust the producers of their medicine. The approach to quality management in the pharmaceutical industry is slowly starting to change. And the industry now sees the advantages that other industries have enjoyed for years of developing much more advanced and cost-effective quality techniques.

Although they seldom make headlines, the quality assurance tools and systems for medicines developed under the WHO Expert Committee on Specifications for Pharmaceutical Preparations help a broad spectrum of public health actors to meet that challenge and to work towards ensuring that all essential medicines, including those used in treating large populations, are safe, effective and of good quality.

For the pharmaceutical industry, Quality by Design is not only about adjusting to a new set of requirements - it is an opportunity to import modern quality management techniques and use them for more cost-effective manufacturing and quality management.

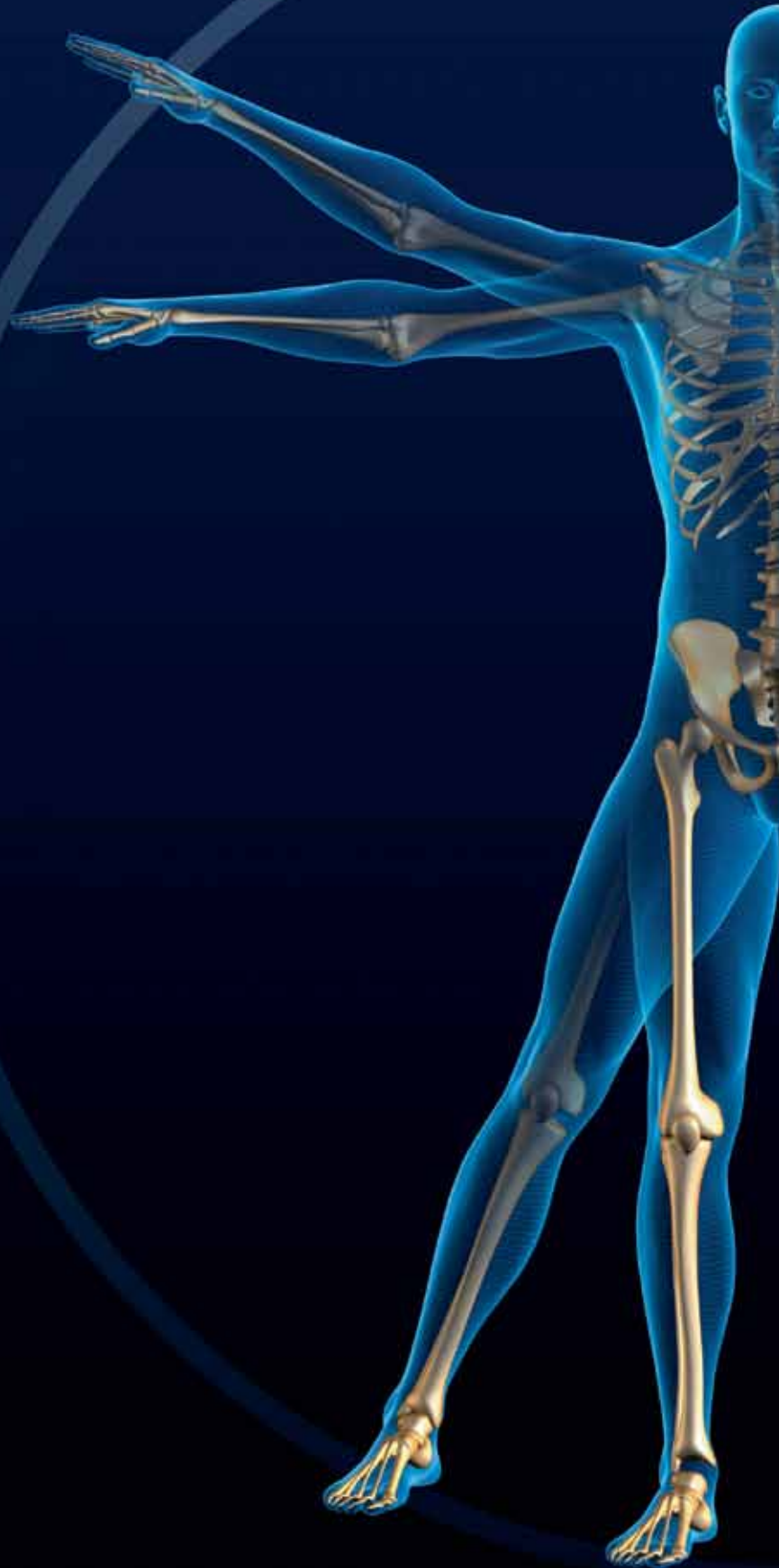
Across Europe, the USA and Japan, the pharmaceutical industry as well as regulators, agencies and organisations including WHO have agreed through the International Conference of Harmonisation (ICH) to follow the principles of Q8 (pharmaceutical development), Q9 (quality risk management) and Q10 (pharmaceutical quality systems).

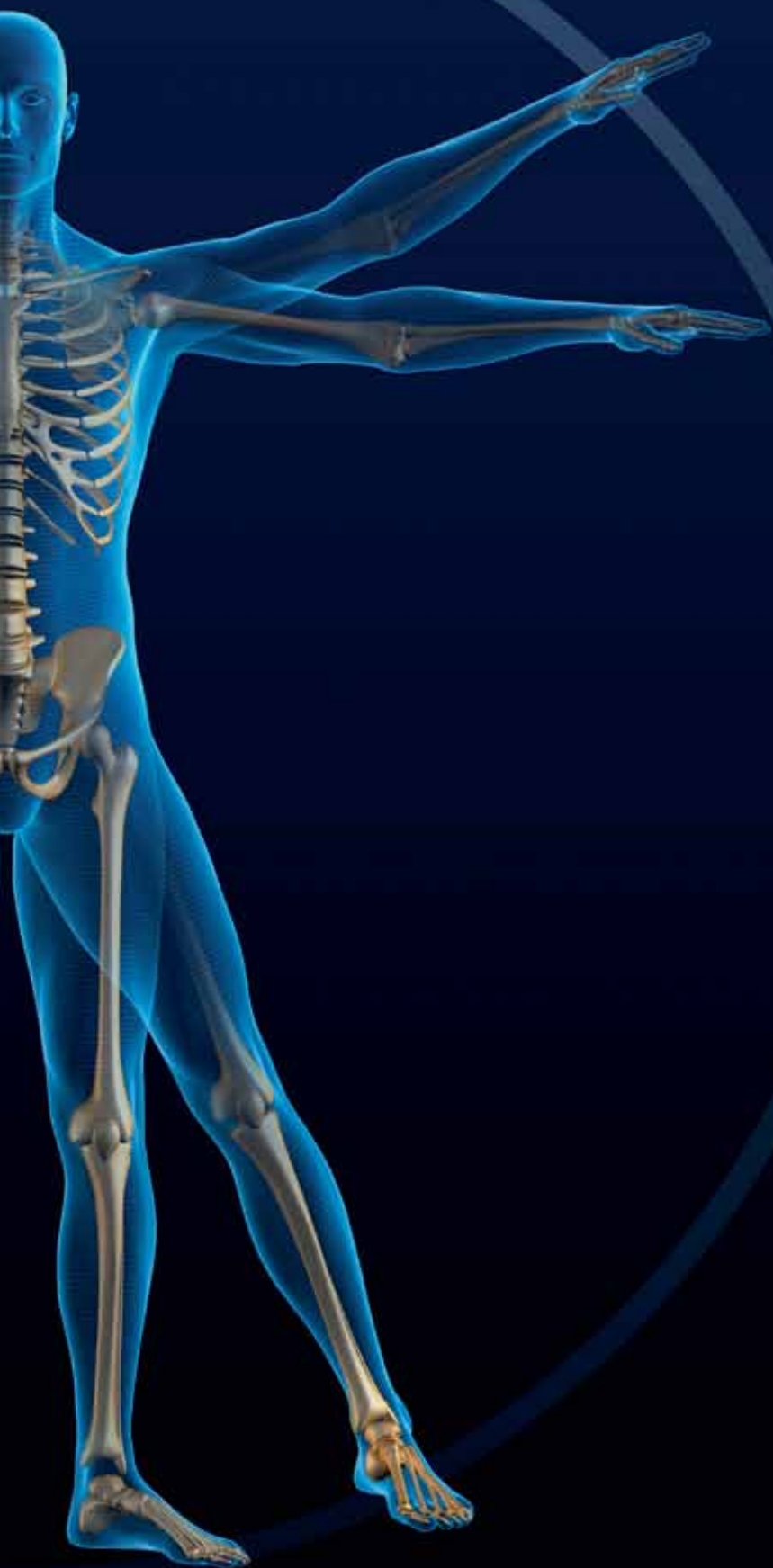
They do so on the common understanding that this is a better way to control quality than using the traditional pharmaceutical quality methods. The principles of the ICH should be encouraged – and will perhaps become statutory in the future.

European regulators accept both the traditional and the new approach, also called the ‘enhanced approach’. The US Food and Drug Administration (FDA) calls the new concept the ‘desired state’ and both Europe and the FDA promote the application of quality risk management methods, statistics and other scientific tools.

But whatever the subject, the aim remains the same: to promote production quality and better pharmaceuticals. For the sake of patients.

**MODEL TRIAL.** During the development of drugs, clinical trials are where 'the rubber meets the road' in connecting the new drug to real patients. But clinical trials may not always be the only way to demonstrate drug safety and efficacy. The FDA and other regulators have shown great interest in new science that supplements or even partly replaces some of the clinical trial activities. The US-based life sciences company Entelos has developed a virtual research lab for simulating clinical trials of new treatments for a range of diseases. Scientists can model the impact of a therapy using multiple variables, for example in genotype, phenotype and pathophysiology. The virtual lab has already proved its worth. When Johnson & Johnson wanted to design a phase I trial of a diabetes treatment with a novel mechanism of action, Entelos simulated the effects of using various dosing levels. As a result of this work, Johnson & Johnson redesigned the trial, resulting in a 40% saving in time and a 66% saving in the number of patients on whom the treatment needed to be tested.





# The sleeping beauty

When it comes to Quality by Design (QbD), the big question is: how soon will the pharmaceutical industry change its approach to development and manufacturing?

In 2004, the US Food and Drug Administration (FDA) raised a major concern in a report under The Critical Path Initiative named Challenge and Opportunity on the Critical Path to New Medical Products.

The FDA said: "Today's revolution in biomedical science has raised new hope for the prevention, treatment and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients."

The Critical Path Initiative has been a landmark in the FDA's effort to stimulate innovation and enable more affordable drugs, and the industry is undergoing major change. Global demand for medicine is growing and increasing healthcare costs will force the industry to look at productivity. Over the last 10-15 years there has been a huge focus on specification, qualification and validation. The regulatory demands have generated far more paperwork and

documentation than any other industry. The pharmaceutical industry has traditionally been very conservative in the use of modern technology, in part due to strict regulatory rules. However, things are changing and in theory the industry supports new improvements to productivity such as PAT (Process Analytical Technology), QbD and ASTM E2500 (a Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment and in line with the ICH Q8, Q9, Q10).

Despite this, critics could argue that the industry doesn't yet have what it needs to develop and make products as safely and efficiently as possible. One could argue that high profit has never forced the industry to urge for new productivity standards. On the other hand, strict rules from authorities have certainly played a role in the sluggishness of the industry to adopt QbD.

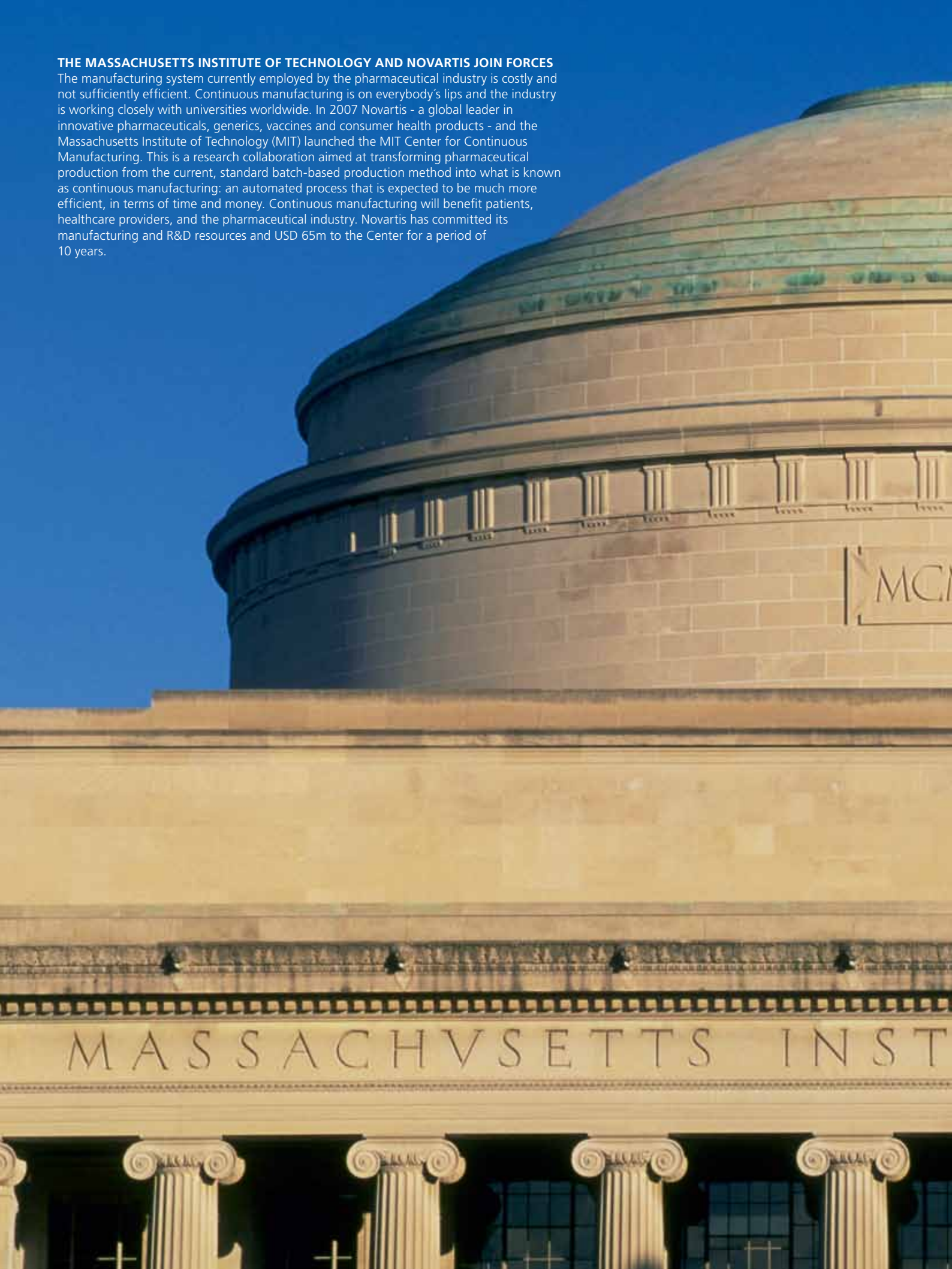
What will be the impact on the pharmaceutical industry? Are we now about to see the big changes experienced by e.g. the electronics, food processing, chemical and automotive industries?

The pharmaceutical industry seems to be awake and one thing is certain: new standards for drug manufacturing are on the horizon.



**THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY AND NOVARTIS JOIN FORCES**

The manufacturing system currently employed by the pharmaceutical industry is costly and not sufficiently efficient. Continuous manufacturing is on everybody's lips and the industry is working closely with universities worldwide. In 2007 Novartis - a global leader in innovative pharmaceuticals, generics, vaccines and consumer health products - and the Massachusetts Institute of Technology (MIT) launched the MIT Center for Continuous Manufacturing. This is a research collaboration aimed at transforming pharmaceutical production from the current, standard batch-based production method into what is known as continuous manufacturing: an automated process that is expected to be much more efficient, in terms of time and money. Continuous manufacturing will benefit patients, healthcare providers, and the pharmaceutical industry. Novartis has committed its manufacturing and R&D resources and USD 65m to the Center for a period of 10 years.



MXVI

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A photograph of a desert landscape. In the foreground on the left, a portion of a patterned blanket with orange, green, and blue diamond shapes is visible. The background shows a vast, flat, sandy desert floor leading to a row of makeshift tents or structures made of various materials, including what looks like cardboard and fabric, under a clear, bright sky.

# Patients first

Development in the pharmaceutical industry has always been a careful balance between the need to get safe, efficacious and hopefully profitable new products into the pipeline and doing so in a way that is both timely and cost-effective. Compliance has often won the fight against innovation when it comes to investing in new production facilities. But as Bob Dylan sang in 1964: “Times they are a-changin”.

Interview with two NNE Pharmaplan QbD experts.



Chris Watts, Senior Technology Partner at NNE Pharmaplan, BSc in Biomedical Engineering and PhD in Pharmaceutical Sciences.

In his former job, Chris Watts was an integral part of developing the US Food and Drug Administration's (FDA) current science and risk-based approaches for cGMP inspections and the CMC (Chemistry, Manufacturing and Control) review of pharmaceuticals, including biotech, generic, and new drugs. Prior to joining the FDA, Chris was responsible for the development and manufacture of products at Dura Pharmaceuticals and Shire Laboratories.

At NNE Pharmaplan, Chris has a consulting role. He is responsible for quality and regulatory projects in addition to leading various strategic projects related to the development and manufacture of pharmaceuticals using a 21st century approach, i.e. Quality by Design (QbD) and Process Analytical Technology (PAT).

"In my work at the FDA, we encountered multiple companies that were actually eager to start working with PAT and QbD. But there were significant barriers, varying from appropriate business cases to regulatory concerns regarding changes to existing manufacturing processes. In general, the pharma industry is not perceived as a leader in manufacturing quality improvements or optimisation. You just don't start chasing the 'newest' quality initiative and often justifiably so. Nonetheless, for many of us at the FDA we sometimes felt that implementation of PAT and QbD could have been faster.

The FDA spent significant resources to ease the regulatory concerns with PAT and QbD implementation. However, I suppose that

many in the industry remained concerned about other barriers, including the economic issues. We experienced a healthy dose of scepticism regarding the business case - whether PAT/QbD efforts would pay dividends, either in terms of improved product quality and risk mitigation or reductions in production costs. Additionally, there were and are organisational barriers within the companies. Is there alignment across the company in the relevant departments and at the right levels? But it now seems that many of these concerns have been addressed and things are changing".

During 2008 and 2009, the FDA's Office of Pharmaceutical Sciences received 99 initial applications that it considers 'QbD related', around 10 percent of the total of 980 applications across new drugs, biologics and generics.

**It would be difficult for me to characterise any one aspect of a QbD programme as more important than any other.**

"Today, I think the industry has a much better idea about what QbD actually means and how it can be used. PAT and QbD provides a way to achieve the necessary balance and, if recent trends at the FDA are an indication, it may also make the difference between receiving an 'approved' letter or a 'complete response' letter, which requires additional information - not to mention the time and effort necessary to assemble the requested data."

"With respect to my experiences at the FDA benefitting our customers, I hope we can do just that ... benefit our customers. A comprehensive understanding of the regulatory requirements and expectations is crucial. Just as important, though, is being able to translate those general, regulatory expectations and requirements into specific, practical solutions that can be implemented throughout the life cycle of pharmaceutical products and processes (from R&D through routine manufacture).

These skill sets are not only important when addressing cGMP deficiencies or issues, but for QbD they would be even more applicable

in an R&D setting when drugs and biological products are being developed.”

Many often ask: “Is there one element of QbD that is most important?” It would be difficult for me to characterise any one aspect of a QbD programme as more important than any other. Consequently, perhaps the most important aspect of QbD is understanding that it is a comprehensive effort that includes a variety of tools: ranging from statistical analysis and DoE (Design of Experiments), to QRM (Quality Risk Management).

These tools can of course be used on their own, but can also be combined for an effective QbD programme. Regulators are providing concurrent training on ICH Q8, Q9, and Q10 for a reason: it is important to consider these approaches as complementary. Of course ICH Q8, or Q9, or Q10 can be applied independently; however, they offer the greatest benefit (from a regulatory and business perspective) when used collectively. What the discussion tends to miss is the fact that the whole idea behind getting pharmaceutical companies to improve their production methods through PAT and QbD is to get better and cheaper medicine faster to the patients.

I am confident that I will be able to do this in my new job here at NNE Pharmaplan,” says Chris Watts.



Line Lundsberg-Nielsen, Senior Specialist, Project Quality Management at NNE Pharmaplan, PhD Chemistry and Spectroscopy.

“QbD is no longer just a vision. It is here and many of our customers have already demonstrated significant results using this new framework. As one customer says: “Our

manufacturing processes are not noisy, there are no emergencies or unexpected events on the shop floor”. Another customer puts it this way: “It is not a matter of estimating the return on QbD investments, but rather of estimating the cost of not implementing QbD!”

## **The end quality of pharmaceutical products is not the issue. Products are of good quality.**

We have lots of supporting tools to use when implementing QbD, such as risk assessment, Design of Experiments, process analysers and various statistical and data analysis methods. There is a clear tendency towards using QbD to develop medicines in a much smarter and cost-effective way. In my opinion, the main reason for the industry’s slow implementation is regulatory fear, i.e. the risk of not getting the product approved by the health care authorities.

As early as in 2003 the European Medicines Agency said: “The end quality of pharmaceutical products is not the issue. Products are of good quality”. Their opinion, like the FDA’s, was that the pharmaceutical development and manufacturing could be improved to avoid batch failures, reworking, long cycle times and rigid manufacturing processes that cannot be changed due to regulatory bindings. “We all know that uncontrolled variability in e.g. properties of the starting materials or the manufacturing process affects the quality of the product, so why not focus on avoiding or reducing this variability by designing the quality into the product and controlling the process using smart, innovative technology.”

We need to move from being compliance-focused, where release of products is based on end-product testing, to a higher degree of product and process understanding that makes it possible to adjust and control the process during manufacturing in real time. It sounds simple and obvious, especially since other industries have done it for decades, but I know that not all in our industry see it this way. Yet, I have to admit that for the last thirty days I have been on the move from meeting to meeting so change has come.”

**UCB FIGHTING SEVERE DISEASES.** The global biopharma company UCB has decided to build a cGMP biotechnological pilot plant including development laboratories on its site in Braine-l'Alleud in Belgium. The aim is to speed up availability of biotechnological drugs for serious illnesses in the central nervous system and immunological problems, concentrating on pilot projects and delivering products for clinical trial activities.

The project is based on risk and science-based verification principles according to the ASTM E2500 as well as the ICH guidelines Q8, Q9 and Q10. The first stone was officially laid on 4 June 2010 and final handover is planned for September 2012. NNE Pharmaplan is supporting UCB under an ongoing Engineering, Procurement, Construction Management, and Verification (EPCMV) contract from the detailed design through construction to verification.

The application of the ASTM E2500 verification approach may seem difficult to handle at first. However, the tools and principles of risk assessments and verification of vendor-prepared tests are well-known and easy to implement. As a result of the verification methodology, duplication of the tests is avoided and focus is intensified on the areas with the highest risk to patient safety, which is a key element of the verification approach. Furthermore, flexibility in project execution is increased by elimination of the non value adding dependencies between Installation, Operational and Performance Qualification (IQ, OQ, PQ). At the same time, resources are used more efficiently and the quality risk assessment process ensures that focus is directed towards the real quality issues.





Bio Pilot Groundbreaking  
June 4th, 2010

# The relentless pursuit of perfection

The story of the high quality behind Lexus is the story of how Japan adopted production principles from American engineers.

Lexus is the luxury vehicle division of the Japanese automaker Toyota Motor Corporation. Established in the early 1980s and launched in 1989, the Lexus marque soon became associated with quality, luxury and superior customer satisfaction.

The brand reputation grew quickly until, barely a dozen years after its founding, Lexus became America's best-selling line of luxury motor vehicles. But the story behind this luxury car is also the story behind the quality movement in Japan. It began shortly after World War II with the US occupation force's mission to revive and restructure Japan's communications equipment industry. American engineer Homer Sarasohn was recruited to manage the effort by repairing and installing equipment, making materials and parts available, restarting factories, establishing the equipment test laboratory and setting rigid quality standards for products.

The idea behind quality management from the factory to the total organisation was established and stressed. In late 1960, the Total Quality Control concept was outlined: Quality comes first, not short-term profits; the customer comes first, not the producer. Customers are next in the process with no organisational barriers, and decisions are based on facts and data. Management is participatory and respectful of all employees and driven by cross-functional committees covering product planning, product design, production planning, purchasing, manufacturing, sales, and distribution.

The forefathers of Total Quality Control are in fact the forefathers of what we today know as Quality by Design. The early idea behind the work of Homer Sarasohn, Joseph M. Juran and in particular William E. Deming has actually formed the Lexus brand. Today Lexus is known for its highly reliable luxury cars and many credit Lexus' success to aspects of the Lexus production fundamentals. Thanks to the ideas of American engineers.



# Lundbeck knows how to save money

Interview with Lars Bang, Executive Vice President,  
Supply Operations and Engineering, Lundbeck





The financial benefits of Quality by Design (QbD) can be huge. Since 2006, Lundbeck, the Danish pharmaceutical company specialising in treating central nervous system disorders, has saved more than DKK 500m in production costs.

### **To be completely honest, we hadn't expected to find such scope for optimisation.**

In just a few years, Lundbeck has achieved an impressive cost cutting in production. Savings that are so significant, they have even surprised Lars Bang, Executive Vice President, Supply Operations and Engineering.

"In 2004, we were contacted by the FDA. They wanted to gather 10 producers to initiate a series of pilot research studies to show whether QbD could improve and simplify production processes. We went along with the project, but with a fair amount of scepticism in the company. I clearly remember our first internal meeting after we had announced the partnership with the FDA. A few were positive but the majority were astonished. Why should we work with the FDA to change our production process? Wouldn't that just lead to more regulations? More work?"

The pilot project chosen by Lundbeck was a pretty simple project at their production facility in the UK. And it only focused on one specific step in a process. However, the results were surprising.

"To be completely honest, we hadn't expected to find such scope for optimisation. It soon became quite obvious to us that with some pretty basic changes, we

could save more than DKK 20m a year. There is no doubt that the result of the project had a huge impact on our organisation, not least in the area of culture change. And that's important. The exciting thing about QbD from my point of view is the culture change – the positive approach and the will to change something to improve the process. Things that can make everyday situations easier in work processes that are often fraught with rules, regulations and routines. Not necessarily to find errors so you can point fingers but to identify improvements that are to everyone's advantage.

I feel we have a totally revitalised culture today throughout the whole organisation, when it comes to making improvements." The success at Lundbeck's production facility has led to other pilot projects in many other areas of the organisation. And the principles on which QbD is based are in use in many other departments to help achieve savings and improvements.

### **Focusing so uniquely on process improvements as we have done requires a considerable investment.**

"When we experienced the magnitude of the pilot project savings, we gathered all our 110 production managers and conducted intensive training programmes to ensure that we had a shared understanding of QbD. They then communicated the new ideas across our entire production facility to a further 1,000 staff. This process was absolutely essential to the success we have achieved today. Focusing so uniquely on process improvements as we have done

requires a considerable investment. There's no way it could be achieved by simply calling the best consultants in town. What's significant is that you build up a strong knowledge base internally and recruit staff with a knowledge of QbD today. Don't be mistaken, an investment it most certainly is."

### **It also requires a new way of thinking – a culture change.**

Lundbeck has saved DKK 500m in costs across the board, representing a fall in costs from 18% in 2004 to the current level of 13%. The goal is to reduce costs to the realistic target of 10% before 2015.

"In reality, it is a cultural change, where you create transparency in your organisation, so what happens across the organisation becomes visible. In contrast to other industries, we have the obvious advantage of having a mountain of data and batch records on everything we produce. Previously, we largely used this type of data to document production errors to the authorities. Many of us have speculated how we could use this data to better understand the production process and how there isn't just one way of understanding analysis and data. But that also requires a new way of thinking – a culture change."

Despite the initial success of the project, the lack of enthusiasm for QbD according to Lars Bang is attributable to the insecurity associated with the size of investment and the cultural aspect. But things are moving in the right direction.

"Seen over the next five to ten years, there is no doubt that the percentage of costs

will fall. Not only for us, but also for our competitors. It is of course easier for us to achieve fast results. With a staff of 6,000 we belong to the smaller producers in our industry, who are more agile than the larger companies with more than 10,000 staff. QbD will change our processes and production methods crucially.

One day we will have such control of our production processes that the authorities will be able to give their approval without making final inspections because these have been conducted already. The ultimate goal is continuous production. It's not realistic for all processes but it's an ambition for all of us. The day we achieve this, we will achieve far greater savings than those we have seen to date. In principle you can say that, seen in isolation, QbD is unimportant. The sum of the improvements we make and continuous production are what we aim at. Small, effective production that runs 24/7 is the real goal."



Lars Bang, Executive Vice President,  
Supply Operations and Engineering, Lundbeck

# The right incentive

According to the Pharma 2020 survey that PwC published in 2009, new medicines will require totally new organisational structures.

For many years, the pharmaceutical industry has been searching for the next blockbuster - a new strong, global medicine for everybody. But times are changing from mass-market blockbusters to the development of specialist medicines that treat specific disease subtypes. Many pharmaceutical companies have a narrow product range based on batch-based manufacturing.

**Is it because the high profit margin has not forced the industry to press for new productivity standards compared with other business areas like the food and automotive industries?**

The Six Sigma concepts have been used for many years and the principles behind PAT (Process Analytical Technology) and QbD (Quality by Design) have not yet been implemented. Many firms have minimised their risks by 'playing it safe'.

At present all patents last 20 years, regardless of the quality of the intellectual property they protect. Many of the old blockbuster patents are running out and fewer new blockbusters are replacing them. The industry needs to move from a narrow to a wide product range, including diagnostics and delivery technologies. From the Six Sigma-based process to unique manufacturing processes. The need for faster production and more flexible production facilities is greater than ever. For the first time in more than 20-30 years, the focus on optimising and changing production is on a par with the R&D focus. The PwC survey further shows that the industry can save up to 30% of its production costs.

Why have the new ideas behind QbD not yet been implemented in the industry when the need for faster and more flexible production is greater than ever? Is it because the high profit margin has not forced the industry to press for new productivity standards compared with other business areas like the food and automotive industries? It seems there is no excuse for not investing in QbD.

The good news is that future changes in regulation and patient demand will probably force the industry to make these needed adjustments in order to supply cheaper and faster medicine to the patients. QbD starts and ends with the patients. Could the industry ask for a better incentive?





## THE FDA AND THE EUROPEAN MEDICINES AGENCY

**COOPERATION.** The US Food and Drug Administration (FDA) and the European Medicines Agency have launched a pilot programme that will allow parallel evaluation of the development and manufacturing of new applications that are submitted to both agencies.

The parallel evaluation in this voluntary pilot programme implies that reviewers from both agencies will separately assess the quality/CMC (chemistry, manufacturing and control section of the new drug applications submitted to the FDA and the marketing authorisation applications submitted to the European Medicines Agency. This indicates a clear support to the harmonisation and facilitation of Quality by Design.







# The secret timeline

The FDA approach to new regulations is by no means haphazard. The stepwise introduction of new regulations is intentional and follows a carefully planned timeline.

For years, the pharmaceutical industry has been financially motivated to invest in developing and marketing new drugs rather than revamping manufacturing facilities. And to the FDA, with its mission of protecting patient safety, it has seemed more important to manufacture drugs precisely to specification using tried-and-tested systems than to latch onto the latest manufacturing trends.

However, with a rising number of drug recalls illustrating how quality problems have been slipping through manufacturing systems, change was needed. The US Food and Drug Administration (FDA) therefore decided to elaborate on manufacturing regulations.

**It all started on 21 August 2002** when the FDA announced a whitepaper called 'cGMP for the 21st century - a science and risk based approach', which was a guide to enhancing and modernising the regulation of pharmaceutical manufacturing and product quality. It got attention in the pharmaceutical industry, but many did not understand what this would mean in real terms.

**In July 2003**, the International Conference of Harmonisation (ICH) - an initiative whereby the USA, Europe and Japan cooperate on future, harmonised regulations - announced a new vision to "Develop a harmonised pharmaceutical quality system applicable across the life cycle of the product emphasising an integrated approach to quality risk management and science".

They announced that the new direction would include three new guidelines which Europe, the USA and Japan would incorporate into their local regulation. Today they exist as ICH Q8 on Product Development, Q9 on Quality Risk Management and Q10 on Pharmaceutical Quality System - and local implementation is ongoing. A new Q11 on Development and Manufacture of Drug Substance (chemical/biological entities) is on the way.



Dr. Janet Woodcock

**In September 2004**, a new FDA guide on Process Analytical Technology (PAT) generated some attention and discussion in the pharmaceutical industry on the new PAT concept, and the core concepts were also used by the PAT team of the European Medicines Agency.

**In 2005**, the Deputy Commissioner and Chief Medical Officer of the FDA, Dr. Janet Woodcock, expressed the FDA vision as "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."

**In March 2006**, the FDA accepted volunteer companies for a pilot programme reviewing drug submissions based on Quality by Design. In the following months, the FDA and the life science industry discussed the lessons learned, and the FDA expressed that they liked what they had seen - and wanted more of that in future submissions.

**In 2007**, the FDA, the European Commission, and the European Medicines Agency announced that they had agreed to expand their current cooperative activities in several important areas. Their aim was to reduce unnecessary differences in regulations and to reduce the associated costs to the consumer and the industry.



Head office of the European Medicines Agency

**In 2008**, the FDA announced a new draft guide on process validation, which was finalised in January 2011. It does not require QbD, but shares many of its principles and fits with the QbD approach. In 2011 or 2012, we may start to see the first FDA FD483s - inspectional observation forms and even warning letters on non-compliance with the new FDA process validation regulation - also for existing, legacy products and processes.

**In March 2011**, the European Medicines Agency and the FDA announced a joint pilot programme for parallel assessment of QbD application – an important step towards QbD harmonisation in practice.

Many small steps, but all in the same direction. More focus on QbD – and more harmonisation based on QbD. Just keep watching the timeline.

## NNE Pharmaplan news



### **NEW NNE PHARMAPLAN OFFICE IN CHINA**

In the first quarter of 2011, NNE Pharmaplan opened a new office in TEDA, the Technological Development Area of Tianjin, to respond to the rapidly increasing pharma and biotech investments in China.

The TEDA office, headed by Amir K. Tafreshi, is a satellite office to the local head office in Tianjin and is expected to accommodate some 50 employees by the end of 2011.

Presently, the Chinese office has Novo Nordisk and Novozymes as its main customers, but is expanding its business to other local and international customers located in the TEDA area.

NNE Pharmaplan employs close to 420 employees at its four offices in Tianjin, Shanghai, Guangzhou and TEDA. The Chinese organisation can deliver turnkey and greenfield facilities. It also supports existing customer facilities to comply with new regulations in China as well as with US FDA requirements, enabling customers to export to the USA and European countries.



### **NEW REGIONAL MANAGER AT NNE PHARMAPLAN**

Kim Rasmussen (49) will take up the position as Corporate Vice President and Regional Manager of the Nordic region as of 1 June 2011.

Kim Rasmussen comes from a position as Division Director and CEO for the Ventilation & Indoor Climate of the Danish company VKR Holding A/S. Mr Rasmussen has previously held various executive and managerial positions at Alpine Biomed, Rockwell Automation and Texas Instruments.

“The appointment of Kim Rasmussen as manager of the Nordic region is a valuable asset to our company. Mr Rasmussen has broad international as well as specific Scandinavian work experience. I am confident that his extensive commercial understanding will contribute positively to the continued development of our global company”, states Morten Nielsen, NNE Pharmaplan CEO.

The Nordic region accounts for around half of NNE Pharmaplan’s turnover and employees. In 2010, NNE Pharmaplan reached a turnover of DKK 1,466 million and 1,649 employees.

### NEW NNE PHARMAPLAN RISK TOOL SPEEDS UP THE ANALYSIS PROCESS

A new type of risk tool (RAMM - Risk Analysis Mitigation Matrix) invented by NNE Pharmaplan is used for the first time to speed up the risk analysis process. NNE Pharmaplan is assisting a customer in the development and commercialisation of a new drug. NNE Pharmaplan uses its expertise in Quality by Design, risk management and regulatory filing with the FDA to support the development of a cancer drug that is currently in phase 3 clinical trials and due for launch in 2012. The project is executed at various development and manufacturing sites across North America.

### RUSSIA RULES

Russia is a booming pharma market and at the moment the office in Moscow is probably undergoing the fastest growth that any NNE Pharmaplan affiliate has ever seen. In April 2010, the Moscow office had 15 employees. Today it holds 60 employees and the number keeps growing. To complete a project for a major, international customer, NNE Pharmaplan has also opened a new branch office in St. Petersburg.

NNE Pharmaplan has a strong market position in Russia since there are relatively few engineering companies with deep knowledge of pharma engineering and GMP (Good Manufacturing Practice) here. The company is currently executing projects for international customers while at the same time servicing major Russian pharma producers.

The Russian offices have become an exciting cultural melting pot, as the rapidly increasing number of local staff are being supplemented with colleagues from Germany, Denmark, Ireland and Malaysia to meet the customers' demand.



### NNE PHARMAPLAN CONSTRUCTS A LARGE FACILITY FOR ASTRAZENECA IN WUXI, CHINA

On 27 April 2011, the ground-breaking ceremony for AstraZeneca's New Injection Solution Plant (NISP) was held at the company's Wuxi site. This is an important milestone for both AstraZeneca and NNE Pharmaplan.

With a total floor area of nearly 4000 m<sup>2</sup>, the NISP facility will comprise two sterile filling lines, three freeze dryers, inspection stations and a packing line. When the facility is at full capacity, it will produce more than 30 million vials annually of Nexium® and Losec®, which are used to treat persistent heartburn and acid-related diseases.

When completed next year, the plant will be a key component of AstraZeneca's global manufacturing capability. It will expand the Wuxi site and enhance its role as a key part of AstraZeneca in China and the Asia Pacific region. NNE Pharmaplan is providing the EPCMV services (Engineering, Procurement, Construction Management and Validation).



### HOSPITALS – A NEW NORDIC FOCUS AREA

Although the hospital sector is a relatively new market for the Nordic region, NNE Pharmaplan is already involved in a number of exciting projects in Denmark. These projects include a new woman-child hospital, emergency wards as well as a new mental hospital.

Being an engineering specialist within the global pharmaceutical industry, NNE Pharmaplan has built up years of experience, which can be directly translated to hospital projects, for example by using the experience with cleanroom design to optimise hospital hygiene and minimise the risk of infection. Moreover, the competences within IT, ventilation and automation as well as personal safety and access control are also applicable when involved in hospital projects.

### NEW BUSINESS OPPORTUNITIES FOR MODULAR PRODUCTION FACILITIES

One of the world's biggest, privately owned companies in the flavour business intends to build a new facility for flavour production in Indonesia. The facility must be suited for very fast product change without affecting the quality of the next batch. Particular attention is paid to keeping off-flavours under control. As the customer intends to build comparable facilities in different parts of the world, a modular facility consisting of fully equipped modules that may also be used for other plants is well-suited for the Indonesian facility. In only five weeks, NNE Pharmaplan did the Conceptual Design (CD) and submitted a proposal for a turnkey project.



### GLOBAL QBD MANUAL BY NNE PHARMAPLAN

NNE Pharmaplan has produced a global QbD manual for a large international pharmaceutical healthcare product manufacturer. The project aimed at creating an aligned corporate QbD approach across various business sections: pharmaceuticals (small molecules), biotech (monoclonal antibodies), vaccines (biologics) and over-the-counter healthcare products.

NNE Pharmaplan helped to develop the QbD strategy, wrote the manual including the IT-based QbD manual and helped to plan the roll-out and training on how to do QbD within the organisation.

### THE YEARBOOK 2010 IS ON THE STREET

The yearbook is an extract of the 2010 annual report and is available as a printed booklet. You can also find electronic versions of both the annual report and the yearbook at [nnepharmaplan.com/Who we are/Media/Download library](http://nnepharmaplan.com/Who we are/Media/Download library).



### EVENT ON TRENDS IN THE BIOPHARMACEUTICAL INDUSTRY

On 7 September 2011, NNE Pharmaplan will arrange a customer event on 'Trends in the biopharmaceutical industry', which will take place in Basel, Switzerland and include a site visit to the Roche Parenterals facility in Kaiseraugst.

Various internal as well as external experts will give lectures on how to map and improve production efficiency by using QbD tools as well as optimisation, technical and regulatory requirements in biopharmaceutical production. Gert Mølgaard, Senior Consultant at NNE Pharmaplan, will talk about recent trends in pharmaceutical manufacturing, quality management and new technologies. Dr. Rainer Schmidt from F. Hoffmann La-Roche AG will present the Roche Parenterals facility project and give a short introduction to the site visit together with Hartmut Schaz, Senior Specialist at NNE Pharmaplan.

The event will be a great opportunity for customers and colleagues from the pharma and biotech industry to meet and discuss with a selected group of experts. For more information and to register for this free-of-charge event, please send an email to: [contact.de@nnepharmaplan.com](mailto:contact.de@nnepharmaplan.com).



### CALENDAR

#### Where to meet NNE Pharmaplan in June – November 2011

##### **Helsinki, Finland** **7 June 2011**

2011 PDA Europe workshop: Advanced therapy medicinal products and next generations medicines: gene, immuno, cell, stem cell therapies

##### **Frankfurt, Germany.** **20-22 June 2011**

10th annual biological production forum 2011

##### **Bethesda, Maryland, USA** **22-23 June 2011**

2011 PDA workshop: Single-use systems workshop on 'Knowledge enables implementation - a consensus approach'

##### **Edinburgh, Scotland** **19-21 July 2011**

Bioprocessing, biologics and biotherapeutics conference

##### **Shanghai, China** **22-24 August 2011**

3rd Annual BioProcess International Conference and Exhibition

##### **Basel, Switzerland** **7 September 2011**

Trends in the biopharmaceutical industry

##### **France** **21-22 September**

POLEPHARMA meetings 2011 Annual Meetings for the pharmaceutical industry's decision makers

##### **Jakarta, Indonesia** **29 September - 2 October 2011**

IPEX: Indonesia international pharmaceutical expo 2011

##### **Nuremberg, Germany** **11-13 October 2011**

TechnoPharm 2011 International trade fair for life science process technologies

##### **Biarritz, France** **18-20 October 2011**

A3P Congress 24th international congress

##### **Berlin, Germany** **19-20 October 2011**

Bioproduction 2011

##### **China** **25-28 October 2011**

ISPE China conference 2011

##### **China** **25-28 October 2011**

ChinaPharm 2011 The 16th China international pharmaceutical industry exhibition

##### **Texas, USA** **6-9 November 2011**

2011 ISPE annual meeting

##### **Russia** **22-25 November 2011**

PHARMTECH 2011 13th international specialised exhibition

GERMANY. Almost one million children and adolescents suffer from hay fever and will do so for the rest of their lives, unless treated.

DENMARK. ALK has started supplying GRAZAX® - the world's first tablet-based grass pollen allergy vaccine - out of their modernized facilities.

**nne pharmaplan®**  
Engineering for a healthier world