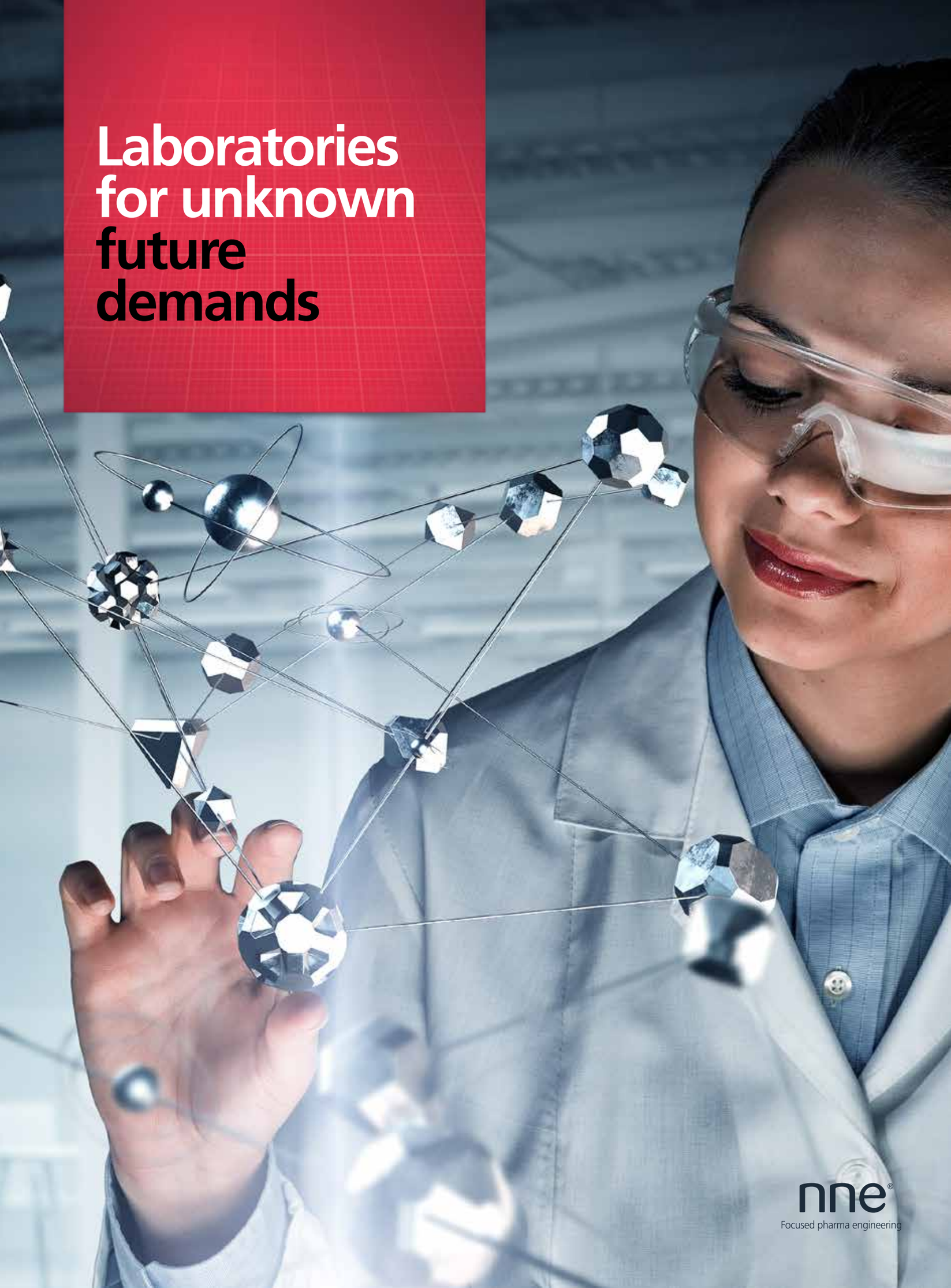
Laboratories for unknown future demands



nne®
Focused pharma engineering

Designing laboratories for an uncertain future

Dealing with unknown future demands and rapid changeability is commonplace in this new pharma reality. Yet laboratories are often planned or even established before it is fully known which processes and technologies they actually need. The answer to this problem? Embracing flexible, modular laboratory facilities that can adapt to future research needs and process development.

The initial phases of a laboratory project are by far the most important. To be successful, you need a thorough understanding of the project, business objectives and motivations behind the design. You need to apply this same focused approach towards compliant and future-proof laboratory operations, whether you're designing biopharmaceutical laboratories for research, development or quality control (QC).

In addition, the relationship between the laboratory product, laboratory processes and how the product is handled in operations is key to design. To approach this in the most efficient way, you need a comprehensive understanding of laboratory work processes, work flows and operations. You should then translate these aspects into programming, concept and laboratory design fit for purpose.

As experienced pharma engineering and laboratory consultants at NNE, we know it takes a frontloaded and focused effort to create a solid basis for decision and design. By definition, laboratory users and customers are the experts, and a major part of a planner's efforts is to drive and facilitate a structured process to uncover the requirements for a specific project.

UPDATING YOUR MINDSET TO AVOID REDUNDANT DESIGN

One current trend is that companies are investing in new laboratory facilities, or refurbishing current facilities, to improve flexibility – where main functions can be switched within weeks or even days. This is where modular concepts of flexible and mobile lab inventory and equipment become relevant.

Another trend is an increased focus on how laboratories are used. Traditionally, one of the fundamental objectives for laboratory design was to create space for a specific number of full-time employees. But severe pressure on the footprint of a laboratory facility means analysts, scientists and researchers can no longer have their own dedicated labs and equipment. There is a clear move away from "my lab" towards "our lab" – and an overall decrease in the size of laboratory facilities and lifecycle cost.

Therefore, staying stuck in an outdated mindset can make laboratory projects redundant from the outset. Organizations must adapt to a new business mindset of productivity, efficiency and creativity. And to match these business goals, they need to ensure future-proof and flexible laboratory concepts, with shared spaces and new ways of organizing.

This could include, for example, having centralized core facilities of high performance liquid chromatography (HPLC) to serve the whole lab facility, rather than decentralized specialty functions with individual expert teams. Overall, it is important to evaluate the relevance and benefits of new technologies and uncover the motivations behind design, laboratory requirements and needs for the future.

TRANSFORM INTO A LABORATORY OF THE FUTURE WITH TECHNOLOGY

Technological development offers new opportunities across the board. For example, it is now possible to integrate QC sampling and analysis directly into process equipment. Therefore, when looking ahead to laboratories of the future, one key trend is a move towards integrating QC activities with manufacturing functions.

Another trend is new technology and operating methods trickling down to laboratory design. For example, the amount of digital data generated from laboratory processes is rocketing, and time spent on data handling is therefore significantly increasing. This influences work operations and laboratory concepts, meaning focused data handling and collaborative spaces need to be integrated into future laboratory models.

In addition, time spent on scientific collaborations and knowledge sharing is increasing and is expected to grow further with information technology and availability. Related to this, automated and integrated lab equipment, including robotics, are now used more than ever. And since robotic equipment rarely sits in work heavy areas, it therefore needs a simple, technical room with equipment to keep it cool.

All of these trends influence how laboratories work. Previously, lab workers spent around 60% of their time in a laboratory and 40% in support-related and write-up spaces. But going forward – with new laboratory design and new technology – only 20% of work time could be spent in the lab, and the remaining 80% on data handling, support functions and working in collaboration spaces.

Ultimately, laboratory automation and the growing emergence of robotics will transform the typical workday for laboratory technicians and scientists, and significantly alter the anatomy of the physical lab space.

HOW TO MOVE FORWARD AND PREPARE FOR AN UNKNOWN FUTURE

With so many changes on the horizon, how can you successfully create sustainable and future-proof laboratory facilities?

First, it is key to take the right initial steps, and create a solid basis for decision and design. This could include using modular and generic laboratory concepts that can integrate future technologies down the line. It is also important to use an overall approach, and avoid the mistake of customizing spaces based on past technologies and ways of working. And last but not least, you should conduct laboratory concept development in close cooperation and interaction with laboratory experts – the users – taking daily operations into all design considerations.

Mega trends

Agile and flexible
Research and development requires laboratories that support multiple products and projects

Automation and optimization
The cost of operations is increasing and so is the length of timelines for drug development. Therefore the key to successfully manufacturing personalized drugs from development is automation and process optimization.

Cross-disciplinary interaction
Working in modern laboratories is a social activity, and therefore requires an environment that facilitates creativity or creates interdisciplinary synergy.

Classified laboratories
Increasing requirements to work with genetically modified or highly pathogenic organisms means more laboratories must be designed for containment or high containment.

Virtual organisms in silico clinical trials

Testing drugs on humans and animals in costly and lengthy clinical trials are the past. "In silico trial" is an individualized computer simulation used in the development phase or in the regulatory evaluation of the products. While completely simulated clinical trials are not feasible with current technology and understanding of biology, in silico trial development is expected to have major benefits such as less use of time, less cost and faster product to market.

Laboratory design development to support an attractive, efficient and integrated workplace:

Supporting the transition from ‘ME’ to ‘WE’

The new pharma reality includes challenges like industry competition, planning for unknown needs and changing regulatory requirements. Attracting and retaining talent is key to staying competitive.

Building an attractive workplace includes many different elements. One focus area should be embracing the diversity of work functions and helping operators feel like a meaningful part of the bigger picture. To get the “we” feeling, transparency is key, as it shows the individual where their value lies and helps them see their role in overall company achievements.

When processes, research, development and product launch are highly automated and digitalized, it helps define operations and ways of working – from compartmentalized functions to the entire value chain. At the same time, it supports a highly attractive, efficient and integrated workplace.

To support increasing capacity, flexibility and improving throughput, the bridging of efficiency and workplace attractiveness should be reflected in physical facilities as well as in the organization. The main disposition of the facility should be optimized so that it reduces complexity and fragmentation. This kick-starts the transformation into an integrated, high performance work culture.

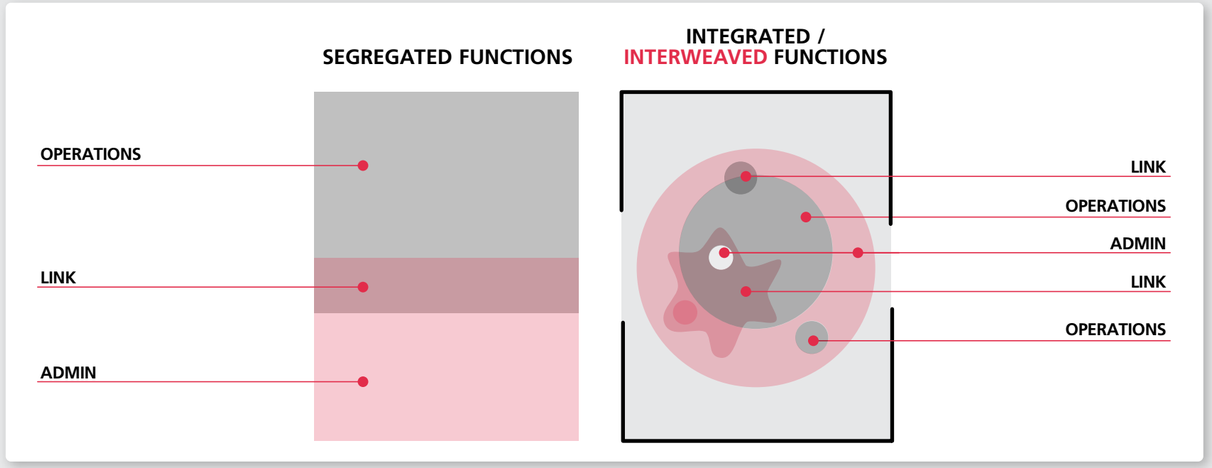
In design development, for example, one focus area should be different workspaces where people can meet formally, informally, get energized, interact or concentrate on deep work. Overall, the facility should be a central hub of knowledge sharing, where different development projects, disciplines and internal organizations can blend and synergize.

Another element in designing a synergetic workspace with a strong social, professional and aesthetic setting, is to use flexible and adaptable modules. These can integrate with nature to encourage interaction and improve the overall working environment for employees.

In addition, to facilitate a “we” culture that promotes local and global collaboration and fast and efficient knowledge sharing, ‘interactive collaborative hubs’ should also be integrated into facility design. These can include smartboards, touchscreens, data handling and global platforms.

Another focus area should be to promote simple and seamless movement between functions in both GMP and non-GMP zones, while also encouraging transparency, cohesiveness and interaction.

Ultimately, the final facility should be an attractive and stimulating R&D universe, where the building’s architecture, process flows and the visual setting focus on the patient and on bringing drugs faster to market.



Incorporating corporate responsibility in design

Creating responsible strategies and a holistic and cross-disciplinary design approach are key drivers for successful integration of environmental, social and financial responsibility aspects. Taking global trends and challenges regarding climate, resource consumption and attracting talent into consideration, this may include zero emission goals, an inspirational and innovative working environment and community involvement.

ME to WE

FROM ME

Internal

- Decentralized organization, focusing on local organization business targets and on overall goals
- Hierarchy in main and support functions lacking understanding of overall targets
- Results based on individual performance – one person, one group, one function, one site, one company
- Data handling as an individual or limited group effort
- Physical and non-transparent facility borders between functions

External

Limited integration with the local community, ‘self-sufficient’ and closed image

TO WE

Internal

- One organization with holistic focus to support the mission of the lab facility as a center of excellence
- Seamless collaboration between main and support functions to support common goals
- Results based on a collaborative approach – collaboration / interaction between people from different-groups, functions, sites, companies
- Data handling/processing based on sparring and knowledge sharing, local and global
- Transparent and seamless transmission between functions to support integration

External

High level of integration and interaction with the local community, open and involving image

Laboratories – creativity for better results

NNE offers a number of services to improve laboratory efficiency, ranging from implementing Lean techniques and reorganizing existing facilities to programming and designing new facilities that support the needs of a rapidly changing business.

Laboratory operations – mapping of workflow

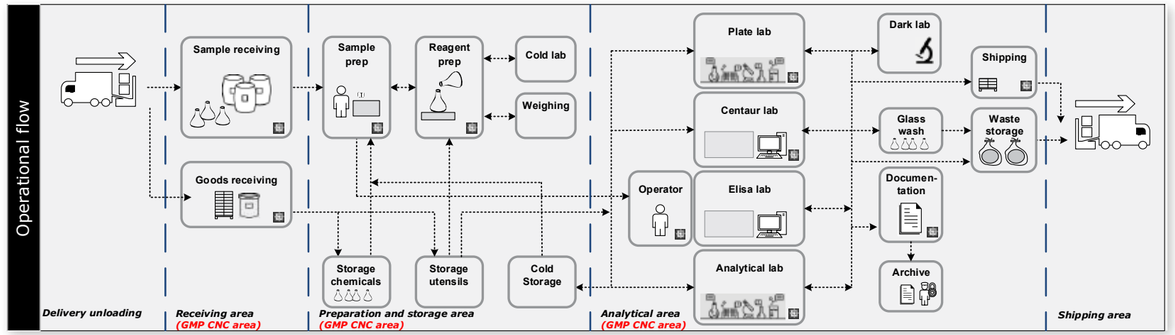
Mapping of operational workflows should be part of the project initiation phase and is an essential tool to ensure full alignment between all project stakeholders. Furthermore, using this powerful visual planning tool facilitates is key to creating a mutual understanding of the laboratory workflow. Furthermore, it enables us as consultants to challenge critical processes and base our assessment and recommendations on factual data.

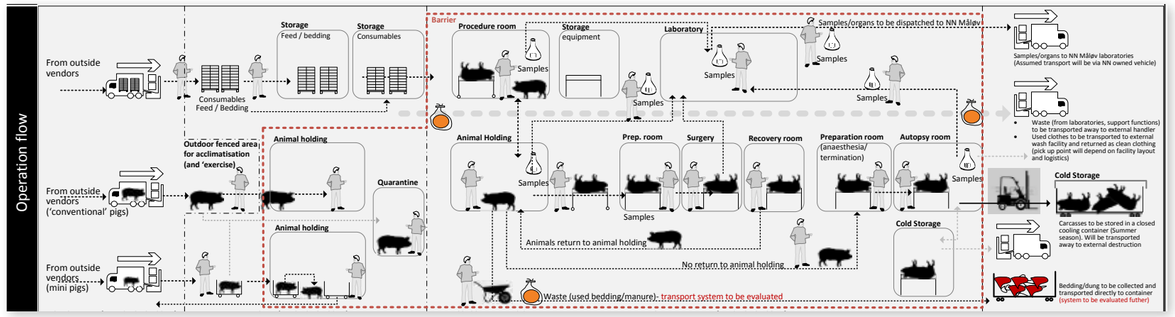
Using laboratory workflow mapping not only ensures a common picture of the main work activities and processes, but also addresses process risks related to workflows, activities, processes or equipment at an early stage of the project.

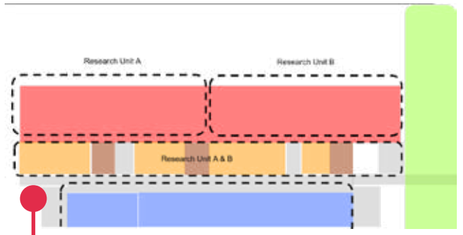
Workflows and operations mapping may also be used to analyze specific complex or critical areas of laboratory operations, for example, specialized operations to analyze the more detailed steps of operations and potential alternatives. The purpose of analyzing selected areas in more detail is to ensure a common understanding between consultants and customer/users and it allows the analysis and understanding to be used directly in concept design development.

To form the basis for laboratory concepts, it is useful to conduct laboratory typologies of typical laboratory and support functions. A typology is a project-defined, generic type of laboratory that may be used as a repeatable stamp in the laboratory planning and subsequent design. The typology defines the overall uniform characteristics of area need, access principles, equipment and main utilities.

The purpose of preparing these typologies is to define functional 'LEGO' bricks of typical laboratory functional units, for example product sample reception and related analysis laboratories and support. Another example is an animal research suite including a procedure room and other support functions.







Our methodology for laboratory operations

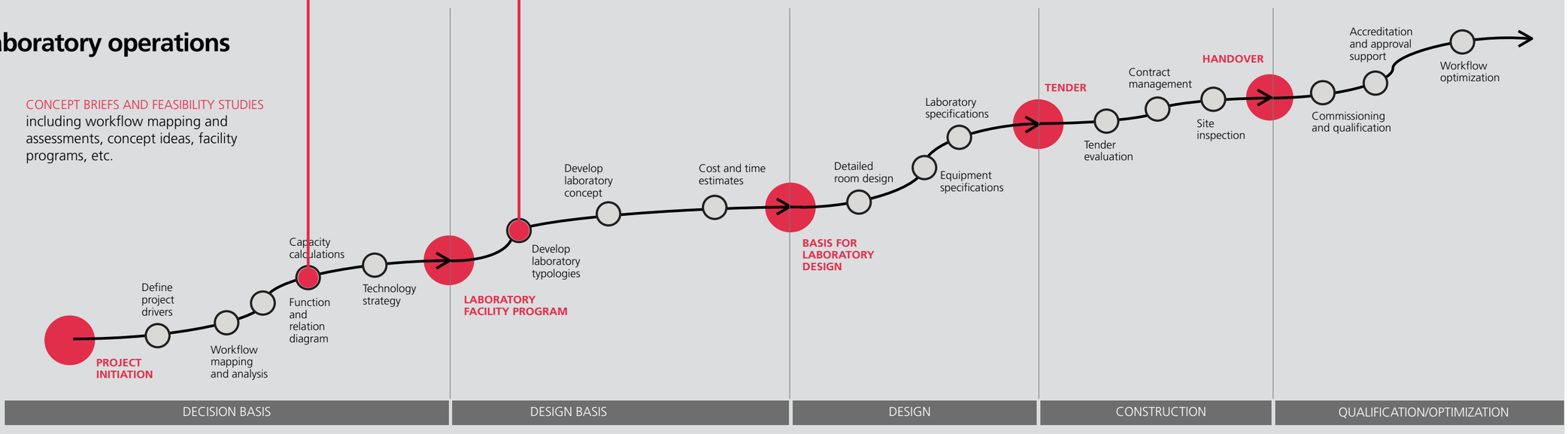
– FULL LIFECYCLE

We focus on understanding our customers' challenges, opportunities and business and translating them into compliant, flexible and future-proof solutions.

We provide:

BASIS FOR DECISON MAKING
By developing business cases, technology strategies, operational due diligence, demand, capacity and localization analyses.

CONCEPT BRIEFS AND FEASIBILITY STUDIES
including workflow mapping and assessments, concept ideas, facility programs, etc.



Digital transformation of lab operation

Today, most development and production laboratories in the pharmaceutical industry are operated in a manual/semi-automatic way and burdened with tedious paper-based documentation.

The frontrunners in the industry have, however, started to digitially transform lab operations to increase efficiency and decrease lead time in laboratories. The potential benefits are huge.

For example, manually operated instruments can be replaced by computer-controlled instruments. These are automatically fed plans on what to analyze before execution and send test results automatically to central systems for documentation or further analysis. These instruments can be combined in laboratory cells with a limited number of related analytical instruments, where robots transfer samples from one instrument to another.

In addition, samples can be transferred between these cells by automated guided vehicles, and samples can be tracked with matrix codes of RFID chips.

To optimize highly automated lab instruments, the lab can be supported by an advanced finite scheduling system. The analytical results can then be uploaded to a central data repository, where advanced data analytical tools can exploit recent developments within artificial intelligence.

A typical example of a system architecture for advanced digital operation of development labs is shown below. Automated and integrated lab solutions can increase faster launch of products and cut down cost for development/production of products. However, the actual solution must be adapted and aligned with company specific business objectives and strategies.

This can be ensured by developing a digital transformation strategy for lab operation as shown in fig. 2.

NNE can help you with this strategy for lab operations and assist with implementation based on our vast experience from multiple other projects.

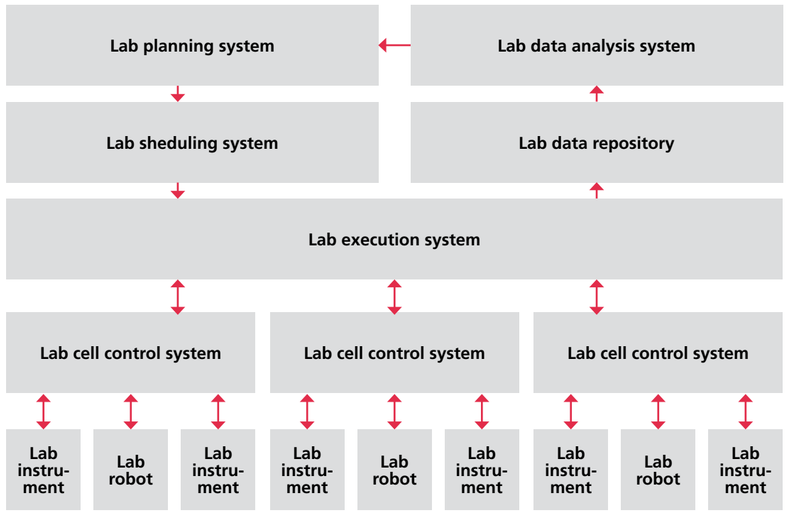


Figure 1. Architecture for highly automated and integrated lab operation

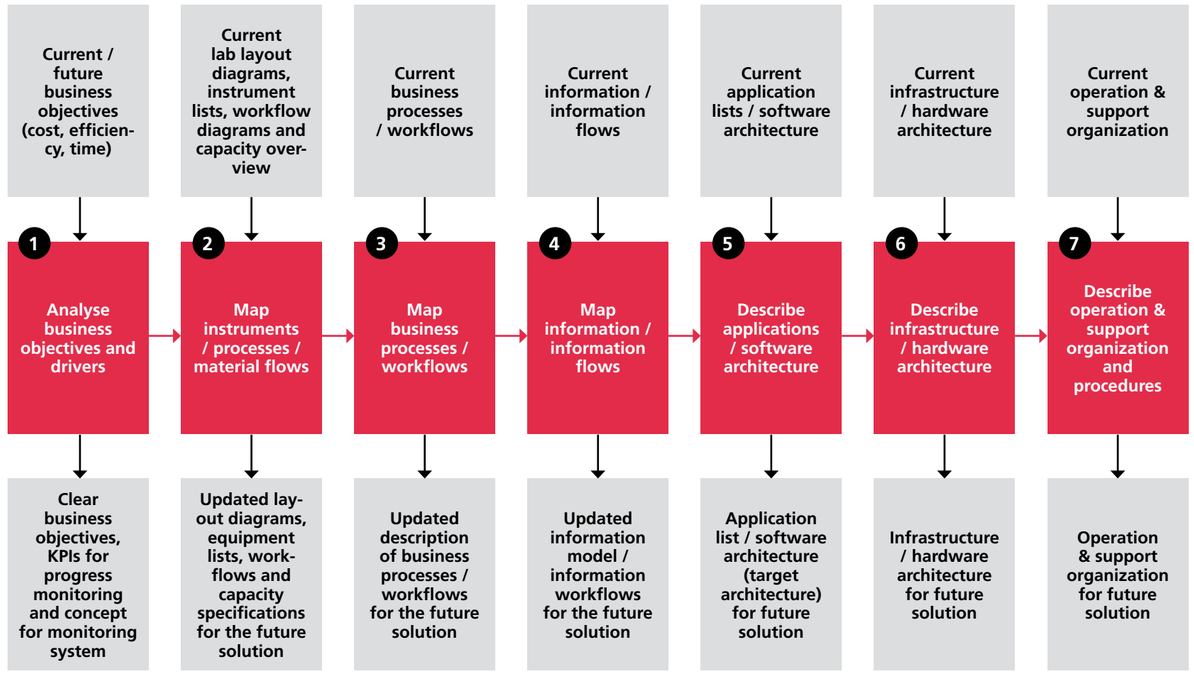


Figure 2. Model for development of digital transformation strategy

Cell therapy journey – from research to clinical manufacturing

The rapid development of advanced therapy medicinal products (ATMPs) comes with a lot of unknowns – both when it comes to research and clinical manufacturing. ATMPs are very different from traditional API or biotech products and require a different manufacturing setup. Hence, a different approach is needed for the novel research and transition to clinical manufacturing.

For manufacturers of traditional medicinal products, moving into the ATMP market entails a number of challenges. Here are a few of the major ones – and some possible solutions:

- ATMPS are a new area and complexity is very high - both development and regulatory requirements are a moving target. Therefore a flexible and adaptable approach is essential to futureproof equipment and facility design.
- When transitioning from non-GMP R&D to cGMP manufacturing, GMP resources need to be involved very early on and facilities designed with a multi-phase/multi-product approach
- Fast to market often means that processes are not fully developed when the equipment is purchased and the facility constructed. Process changes will therefore happen and may cause delays. A modular, generic and adaptable design approach is key to execute the project on fast track.
- Process development and facility design overlap in a fast-track approach. This increases the risk of inconsistencies and a final result that is far from optimal. An opportunity to prevent this is to detach process and equipment from facility design to ensure maximum flexibility and adaptation when manufacturing.

ATMP equipment availability and maturity
It may be necessary to initiate process equipment for ATMP manufacturing using a stand-alone approach. This requires manual handling until feasible industrialization of these processes and equipment become available in the future.

CASE: **GMP compliant facility for cell therapies**
One of our customers has entered the complex segment of ATMPs and cell therapies and is transitioning from development to early clinical phase for cell therapies targeting a range of chronic diseases.

Manufacturing facility considerations were triggered very early on in the project due to global competition within ATMPs and with the desire of being first to market was a top priority. As a response to the fast track approach, contract manufacturing organizations and mobile GMP modules were utilized. Partnering and leasing an existing ready-to-use GMP facility was also the perfect match in this case.

NNE helped develop a generic, flexible and adaptable facility design concept for tech transfer and clinical manufacturing. The multi-product/multi-phase concept for the GMP facility will directly support these ambitions, enabling the future expansion of the customer's cell research portfolio into the clinic.

Challenges and drivers
Cell therapy journey – from research to clinical manufacturing

New pharma reality Get cell therapies first to market	**Deliver R&D results faster and more efficiently**	**High complexity** (not comparable to other processes)	**Cell therapies is a new area** – a moving target incl. regulatory requirements	**High number of variables** Difficult to control	**Need higher productivity and predictability**	**Cell processing is time consuming and complex**	**Be an attractive partner** (for new partnerships)
CHALLENGES • Speed, quality and cost • Process development in parallel with facility design for clinical manufacturing • Process / equipment changes • Transition from non-GMP to GMP • Tech transfer • Research vs. manufacturing culture clashes			CHALLENGES • Speed, quality and cost • Automation/IT strategy • Upscaling • Technologies and equipment fit for upscaling				
(Discovery) Research			**Development**			**Commercialization**	

A new approach to medicine production

To support the process and the required quality it is essential to focus on:
- Integrated quality control laboratory facilities
- Sufficient in-process storage capacity, including cryo preservation facilities

Biotech manfacturing in lab scale

THE PARADOX OF NEW THERAPIES AND THE PHARMA REVOLUTION

Cell and gene therapies represent new and promising hopes for treatment of chronic and severe orphan diseases. The therapies constitute a new paradigm in biotech manufacturing and set new standards for development and commercialization. Currently we are at the beginning of this journey, especially within cell therapies where a patient's own cells or donor cells are used. There is great hope that these methods will provide better treatments and even a cure – but they also introduce new challenges.

The current development and manufacturing concept is based on small volumes and manual operations in laboratories or lab-sized cleanrooms. Yet the future vision and current GMP regulatory requirements and expectations include reliable, viable and robust manufacturing concepts using automated and digitalized solutions. This is truly a paradox. A pharma revolution is here – but at the same time, manufacturing concepts are still evolving. Synchronization between the two is essential. Key to this vision is the use of technology – currently, some technology and automation elements are available but all-in-one packages do not yet exist.

STEPS TOWARDS CELL THERAPY MANUFACTURING OF THE FUTURE

Demand for new cell therapies and speed-to-market are key drivers. This, combined with the reality of limited technology and equipment availability, forces pharma manufacturers to make future-proof decisions. Using a similar manufacturing tech platform as used in development may currently be an inevitable decision, but it should be smart, flexible and adaptable for new integrated and more automated solutions. Equipment should be mobile and detached from the facility as far as possible and utilities should be designed with flexible hook-up points. The facility around these processes should similarly be smart and flexible, e.g. it should be possible to downgrade cleanrooms GMP-wise and resize spaces without major reconstruction.

CELL THERAPIES AT LAB SCALE

Cell therapies can be divided into two major categories:

- Allogeneic cell therapies: the cells of a donor are used for the treatment
- Autologous cell therapies: the patient's own cells are used for the treatment

Both types will typically be at lab scale in the R&D and clinical phases. Autologous cell therapies, based on the patient's own cells, will still need segregation per batch=per patient in commercial manufacturing. This would currently take place in small, individual cleanrooms at lab scale.

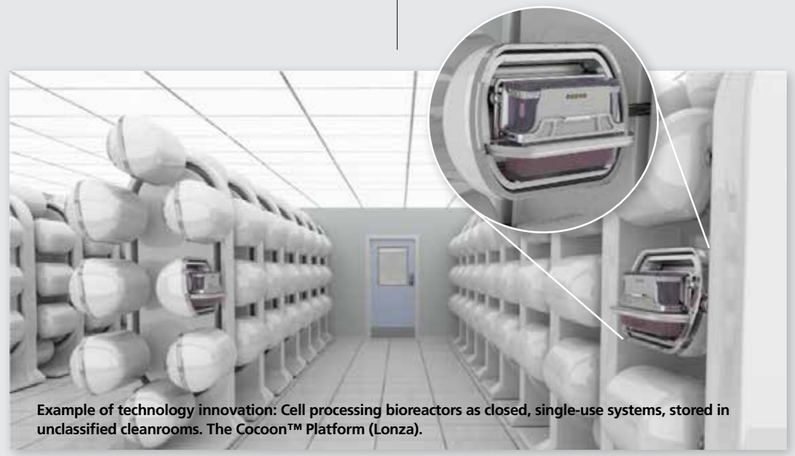
If demand increases, scaling up is not an option - instead, scaling out the process is a possibility. But until the processes can be fully closed and integrated into fully automated solutions, expensive GMP cleanrooms at lab scale are still needed.

The business model is complex. Individual, 100% personalized cell therapies are costly, so affordability is a key concern.

THE VALUE ADD FROM TECHNOLOGY AND INNOVATION

At NNE, we closely follow up to date technological developments and trends, supporting our customers to make future-proof decisions for their current needs. Digitalization and automation of R&D, as well as clinical and commercial manufacturing, requires project specific mapping and analysis. Value stream mapping (VSM) is a collaborative effort and is a key activity towards a digitalization/automation strategy. The VSM often shows that it does not add value to digitalize or automate all processes or work operations and illustrates exactly where real value is generated from using new technologies, now and in the future.

One technology trend for cell processing is closed systems – "GMP in a box". These can be stored in unclassified spaces during processing. When systems like this are fully developed and become off-the-shelf technologies, it it will help close the gap between the pharma revolution and the technology evolution.



Example of technology innovation: Cell processing bioreactors as closed, single-use systems, stored in unclassified cleanrooms. The Cocoon™ Platform (Lonza).

The vision of the future concept
– from manual operations to fully integrated and automated

Traditional concept
- Manual handling
- Open handling in bench
- Product / operator risk
- High GMP classification
- Challenging work environment

Near future concept
- Manual transfer / sterile connections to isolators
- Closed process in each module
- Higher product / operator safety
- Lower GMP classification
- Improved work environment

Isolator Isolator

Future vision concept
- Fully integrated, closed process
- Closed process in each module
- High product / operator safety
- Low GMP classification
- Optimised work environment

Biosafety and biosecurity as design drivers

The worldwide demand for biocontainment facilities for human and animal health is heavily increasing. At the same time, national and international regulations on biosafety and biosecurity are increasingly strict. Consequently, it is crucial to recognize biosafety and biosecurity requirements as a major design driver to ensure compliance and that the design really fits the facility intention, functionality and project mission.

Biocontainment facilities are complex, and planning and designing biocontainment facilities is unlike any other type of project. At NNE, our approach to biocontainment is first and foremost humble. We realize that these projects involve hazardous biological organisms which call for specialized and in-depth knowledge, experience and good international biocontainment community relations.

NEW DEMANDS FOR BIOCONTAINMENT DESIGN

The need for biocontainment grows exponentially with increasing governmental and commercial focus on research, diagnostics and study of known and emerging infectious diseases within human and animal health.

With that, a number of drivers and business assumptions influence the biocontainment industry:

- A growing focus on biosecurity and bioterror sets the scene for biocontainment facilities of the future
- Increasing demand for development of new vaccines for improvement of human and animal health calls for more facilities. And when biological organisms are zoonotic or involve emerging diseases, high containment requirements are a major design driver.
- For universities, attracting top researchers and funding in the future will require flexible environments that facilitate study and research involving high containment, exotic biological organisms and GMOs.

MITIGATING BIORISK IN HIGH-COMPLEXITY PROJECTS

High containment facilities are costly. Changes at a late point or technical errors can potentially cause your facility to exceed planned time or cost. This calls for a different planning and design approach.

At NNE, we start any biocontainment project by building a solid understanding of the facility processes and working procedures, whether it is a vaccine manufacturing facility, a laboratory, an animal facility or a hospital environment.

Our approach to biocontainment projects involves a high degree of frontloading. That means we address biorisk issues in the earliest project phases, and ensure initial biorisk assessments are developed in close cooperation with your biosafety officers and user groups, along with project development. The initial project biorisk assessment will form a robust and holistic basis for addressing regulatory compliance issues as well as biocontainment design solutions.

NNE has developed a work methodology called Biocontainment typologies©, which has proven valuable when more than one biological organism or biosafety level is involved. In general, biocontainment typologies© ensure interdisciplinary biocontainment overview and integration of overall facility procedure requirements.

Through our unique biocontainment project approach, we can reduce the risk of complex biocontainment projects significantly.

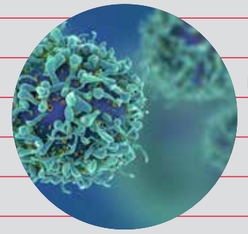
NNE provides interdisciplinary biocontainment expertise to deal with challenges such as:

- How to develop biorisk assessments in close cooperation with user groups balancing the three biocontainment cornerstones of facility design, equipment and working procedures
- How to understand and transform research programs and research mission into biosafety design solutions that match functionality intentions
- How to design for future flexibility without compromising biocontainment engineering solutions
- How to define an adequate or right level of biocontainment in a multiproduct/multipurpose facilities
- How to deal with projects for biocontainment facilities with unknown biological organisms
- How to deal with national biosafety and biosecurity regulations in combination with international standards and guidelines
- How to comply with GMP, biocontainment and GMO requirements at the same time
- How to manage projects with multiple biosafety levels and facility functionalities with zoonotic organisms ranging from laboratories (BSL2/BSL3), small animal (ABSL2/3) and large animal facilities (BSL3AG)
- How to implement high containment facilities in existing premises
- How to design for multifunctional and multispecies animal biocontainment facilities
- How to design compact high containment facilities including waste systems and support functionalities

When bio-containment drives design

Biocontainment facilities are complex, and planning and designing such facilities is unlike any other type of project. These projects involve hazardous biological organisms which call for specialized and in-depth knowledge, experience and good international biocontainment community relations.

Typical design drivers for biocontainment laboratories



- Flexibility
- Changeability
- Scientific mission and vision
- Compliance
- High containment
- Housing principles for research animals
- Multi-functionality
- Operational workflows
- Capacity
- Biosafety and biosecurity
- Cost
- Personal protection equipment

Train the operator upfront

Training on a manufacturing site before production starts is expensive and time consuming. And especially in laboratories, access before the laboratory is fully ready for operations can be very restricted. Instead, simulating training procedures in a realistic virtual environment takes away the need for physical equipment.

Virtual and augmented reality have made it possible to train operators in standard operating procedures (SOPs) in a virtual or semi-virtual environment. VR training is possible for all kinds of SOPs e.g. equipment operations, cleaning procedures, testing, etc.

BENEFITS OF TRAINING SIMULATIONS

- Faster ramp-up time – possible to train off site before facility handover
- Non disruptive training – no need to disturb production to train in physical area
- Faster training completion time
- No risk in equipment damage – safe and controlled environment
- Improved retention and recall – learning by doing
- Training cost reduction
- Easy onboarding
- Social aspect – team building

CASE: Biosafety cabinet loading

Operations in a biosafety cabinet follow a precise code of conduct where each movement made within the cabinet must be controlled and performed correctly. Wrongful conduct can contaminate the product and create a strain on both time and resources.

Thus, it proves an interesting case for a proof of concept on training that was designed for both virtual and augmented reality (VR/AR).

The AR version provides digital information through a HoloLens and makes it possible to interact with the equipment and add to the understanding of the more delicate parts of the procedure.

The VR version provides a completely controllable environment where airflow and warning messages can be simulated. It also makes it possible to train the operator without the need for physical equipment.

The VR goggles are equipped with leap motion tracking that registers the hands of the user. This enables him/her to interact with the virtual elements without use of controllers or gloves.

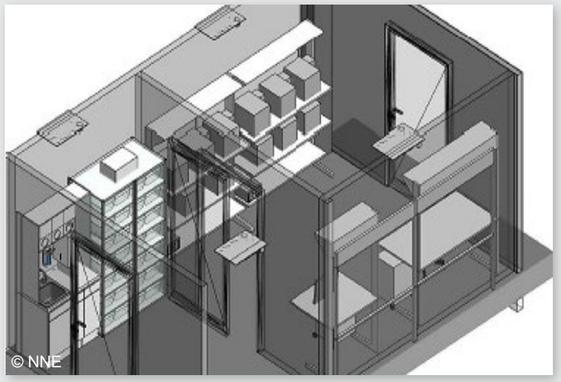
In-vivo research lighthouse facility sets new standards

PLANNING FOR UNKNOWN FUTURE NEEDS – NEW PHARMA REALITY

In many R&D pharma sites, it is not unusual that R&D units are decentralized and operate independently. In this new pharma reality, increased industry competition forces pharma manufacturers to rethink R&D strategies to deliver more drug candidates faster and more efficiently.

Unlike manufacturing of known products, planning what R&D should deliver in the future is more difficult to predict and is basically planning for unknown future needs.

This challenge calls for a completely different way of thinking and designing R&D facilities for the future.



AMBITIOUS REQUIREMENTS BRIEF AS BASIS FOR DESIGN

One of the largest global pharma manufacturers had prepared an ambitious R&D in-vivo project initiation as design basis when NNE became involved as general planner to design and realize the project until handover.

Firmly anchored in upper management, the ambition was to eliminate numerous existing decentralized R&D units and make a transition to long-term, future-proof single state-of-the-art R&D on the same site – an R&D lighthouse. The ambition included an overall program of known and future unknown R&D functions. Another defined ambition was to use new technologies and automation wherever relevant and possible. With unknown future needs within research segments and deriving regulative requirements, it was a defined part of the program to establish BSL2 and ABSL spaces to support the needs of current and future research studies and general flexibility.

The project initiation included an overall site masterplan and was essential as design basis and in terms of setting the first steps right in the project. To exploit the full functional and research potential of the new in-vivo research facility, it was decided early on not to have any storage space in the facility. The site masterplan included a central warehouse to deliver materials, using a just-in-time storage philosophy. This is a major change compared to how most R&D facilities are operated today.

TAKING FLEXIBILITY AND MODULAR TO A HIGHER LEVEL

Establishing a new in-vivo research facility requires a combination of both different types of laboratories animal facilities and general support functions. The split between and need for laboratories and animal holding spaces depend on the need of the individual research studies. The facility program was intentionally downsized compared to the total square meters of the existing, decentralized in-vivo facilities.

The main idea was to completely change the way the new lighthouse facility was used and operated. Flexibility and adaptability were key to this change in operation. In this project, flexibility is defined as a requirement that means it is possible to change laboratory spaces into in-vivo spaces within 2-4 weeks during ongoing operations. It should even be possible to change the size of individual rooms. This is a very ambitious driver that implies a completely different way of thinking and designing.

The key answer to this challenge was to go modular and generic, using a 'LEGO' brick philosophy, enabling generic spaces to be merged or unmerged by implementing or dismounting movable wall systems. In addition, the generic, adaptable modules were designed and equipped with similar flexible utilities as well as automated changeable room-condition systems (temperature, humidity, lighting systems). Last but not least, all spaces were equipped with mobile equipment and casework for fast and efficient change-over.

ROBOTICS AND AUTOMATION TO OPTIMISE IN-VIVO WORK OPERATIONS

The ambition didn't stop there. A focus on creating the most attractive and future-proof research spaces included using automation and robotics for rigid work operations. In a small rodent in-vivo facility, the logistics around cage handling and washing are frustrating, and the work environment for these support functions unattractive. In this project, two existing technologies (AGVs and robotics) were combined to facilitate automated transport, disassemble, wash, autoclave and assemble rodent cages before automated transport to user points. Added benefits included elimination of workplaces in areas with risk of allergen exposure, wet areas and night shifts.

The automation and IT concept allows researchers to focus on research and knowledge sharing activities and operational cost is optimized by replacing rigid work operations with automation/robotics.

'ME TO WE' TRANSITION

Up to now, it is not uncommon for R&D spaces to belong to specific research groups or even individual researchers. Also, dedicated equipment may be 'owned' by a research group. This concept is generally inflexible and does not correspond to current ambitions of innovation, agility and increased knowledge sharing between research groups. Not to mention the challenges deriving from the new pharma reality.

The goals for the new in-vivo research unit not only concerned facility design, equipment and automation. It was also vital to change the working environment, the mindset and the R&D culture. Where the previous work scheme centered around a 'ME' culture, the move towards a more agile and flexible working environment promoted a 'WE' culture. Research groups can now occupy R&D spaces and have access to common support areas in dedicated time periods for specific research studies. At the same time, the just-in-time storage philosophy requires research groups to book and plan ahead. This new type of space occupancy and operations requires a strong and stringent facility management system and management. But most of all, change management is essential for a project like this to succeed.

The high aspirations of increased and value-adding knowledge sharing and innovation takes more than lab and in-vivo spaces. Shared write-up spaces, collaborations spaces and spaces for external researchers are key to fulfill this ambition. Again, these spaces are embedded in the 'WE' culture and concept that responds to the challenges of the new pharma reality.

The new In-vivo research lighthouse facility started operations in 2019 (Central Europe).

Close partnership ensures smooth project execution and joint success

Novozymes' new innovation campus in Lyngby, Denmark will be the company's global hub for research, development and education. NNE merged seamlessly with Novozymes' own organization to provide project management for this flagship project.

Novozymes' new innovation campus is in many ways an investment in the future. Once all phases have been completed, the campus will be the workplace for 2,500 Novozymes employees – or "Zymers" – providing space for future growth in Denmark. Initially, the campus will house 800 Zymers who will be relocated from Novozymes' existing facilities in Bagsværd, Denmark.

But the campus is much more than just additional square metres to house a growing organization. With the ambitious project, Novozymes is introducing new ways of working enhancing cooperation and innovation across functions.

Novozymes knew that they would need help from an external partner to run a project of this magnitude and complexity. At the same time, the company wanted to maintain full control of the project. Novozymes thus asked NNE to provide a project director to join the project organization as part of the internal user owner group.

ONE JOINT TEAM = ONE JOINT SUCCESS

The project is executed as a turnkey project with NCC as turnkey contractor, Rambøll as turnkey consultant (acting as sub-contractor to NCC), Vilhelm Lauritzen Arkitekter as architects, NIRAS as client consultant and Plesner as legal counsel. NNE is part of Novozymes' internal project management team, acting as "Zymers" on the customer side.

NNE's project director, Birgitte Fauerholm Saabye, was in charge of project management with overall responsibility for budget, time and execution strategy reporting directly to the project steering committee. This was only possible due to a strong and trust-based partnership with Novozymes and with Novozymes' project director, Pia Botting Degn, who – with her 19 years of experience in Novozymes – provided invaluable knowledge of Novozymes procedures and relevant stakeholders and experts.

"We have merged into a joint team with Novozymes, forming a strong project team that together has made sure that the project met the planned time and budget and the overall success criteria put forward by Novozymes' steering committee", says Birgitte Fauerholm Saabye.

With our position inside the customer organization, NNE's role has thus stretched beyond the usual design, construction and validation support. We have provided stakeholder management and consulted Novozymes on the entire moving process and the significant change management task that comes with introducing a whole new way of working. In addition, NNE assisted in supervision, construction site safety, validation of autoclave and washing as well as laboratory control.

"Our own project manager group in Novozymes mostly has experience and competencies within construction of production related processes, so in a project of this type, this size and complexity we needed an external project director, says Flemming Funch, Vice President, Supply Engineering at Novozymes. *"However,"* he says, *"we would not give in on having full control of the project due to its importance. Therefore, the project director needed to act and have charge as a Zymer. This requires trust and close cooperation and has proven to be a very successful model in this project. At the same time, we have had the advantage of being able to draw upon other competences from NNE when needed."*

But it is not only Novozymes who benefitted from this setup. Being an integral part of the customer team is a new way for NNE to utilize our core competences within project execution and it provides us with a unique opportunity to understand the customer's perspective and success criteria in depth.

A LEARNING ENVIRONMENT FOR EVERYONE

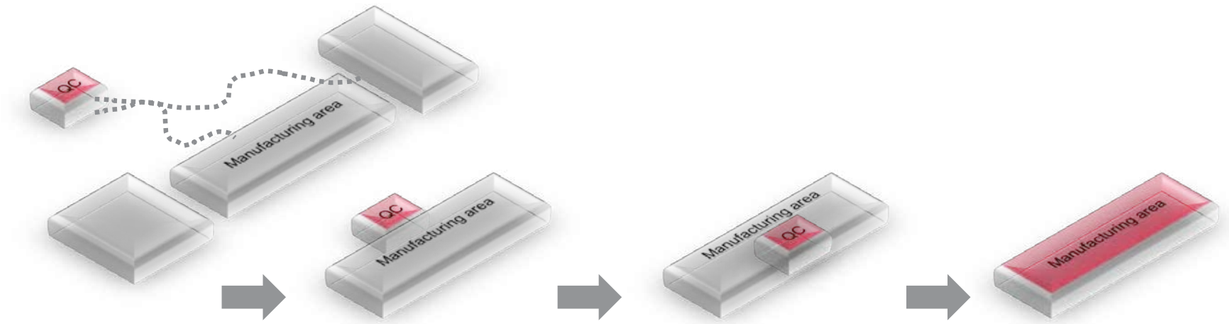
The innovation campus sits on a 140,000 m² site. The first phase of construction entails a ~30,000 m² site with room for 800 employees in research and development and other business areas. This provides sufficient space for Novozymes' operation needs until 2023.

The remaining ~100,000 m² area will be developed in future phases. Ultimately, the campus will include laboratories, offices and learning centre featuring teaching labs. The learning centre will provide opportunities for students and visitors to learn about nature and biology. The low-rise buildings will be surrounded by a park, which will be open to the public

FACTS

Customer:	Novozymes
Country:	Denmark
Site:	140,000 m² (total site)
Project duration:	October, 2015 - March 2019
Services provided:	Project management at the customer side

Pharma QC laboratories of the future are:
At-line, in-line and on-line



As-is situation example:
- QC lab in another building than manufacturing on same site
- Separate organisations for QC and manufacturing
- Physical distance
- Risk of 'quality gap'
- Need for speed in urgent trouble shooting in manufacturing may be a challenge

In refurbishment or greenfield projects:
QC lab located in 'trailer' connected to manufacturing and part of same organisation

- Integrated organisations
- Short distance
- Opportunity to close quality gap
- Increased speed in troubleshooting

New Greenfield projects:
QC lab located in same building as manufacturing and part of same organisation ('shop-floor' philosophy)

Semi-integrated QC in manufacturing – same organisation
Shop-floor concept
Use available technologies for relevant real-time release controls

To-be situation:
New Greenfield projects: QC lab fully integrated in manufacturing facility and organisation (full scale 'shop-floor' philosophy)

One organisation, full integraton 80% of quality control is in-line, on-line, at-line, 20% is supported by local QC lab carts
Technologies are available and adaptability is included for continuous implementation of evolving technologies

Digitalization and adoption of new technologies can help increase pharma quality control speed flexibility and efficiency. What would be the relevant steps to gain the benefits from available and evolving technologies?

CURRENT SITUATION

Quality control (QC) is a key function within pharma companies and plays a large role in commercial manufacturing and certain stages in R&D. Put simply, it is impossible to continue on to the commercial process before QC clearance is available. And in the final steps of commercial manufacturing, QC is the final gate before a product is approved for release to the market.

Despite the key role of QC and its close relation to manufacturing, it is often physically located far from from the actual manufacturing premises. Sometimes QC is even located remotely on the same site. This is because QC is traditionally a separate organizational unit to manufacturing.

WHAT ABOUT QC IN THE NEW PHARMA REALITY?

There are several challenges related to the current QC situation. When manufacturing experience production and quality challenges, fast troubleshooting and response time is essential. A separate and detached QC organization, located away from manufacturing, may not be optimal – especially when considering the pharma reality of today. There is now higher industry competition and uncertainty, as well as an increase in batches that tend to be smaller in size.

Finally, new and different treatment areas are a large part of this new reality. These parameters call for an increase in speed, agility and adaptability, but the core role and mission of QC in pharma manufacturing remains the same: to demonstrate and document that manufactured products are GMP-compliant, safe and can be released for patient use.

With the challenges this new reality brings, we are on the cusp of a paradigm shift for manufacturing and R&D QC laboratories. The traditional QC laboratory is different from R&D and development laboratories, where the main objectives of QC are productivity and compliance. These are characterized by:

- Main tasks, such as scheduled sample flows and a large variety of QC testing methods
- A need for specific functional rooms like sterility control
- Being a separate organization outside the pharma manufacturing organization
- Often being physically located outside and with some physical distance to manufacturing

QC OF THE FUTURE IS IN-LINE, ON-LINE AND AT-LINE

Even though the QC objectives remain unchanged, the QC concept must move towards: "In-line, on-line and at-line". What does this mean? QC functions move towards a 'shop-floor' situation (located directly where the manufacturing processes takes place), while at the same time being a direct and integrated part of the manufacturing organization. Physically, QC analysis should eventually be fully integrated in the manufacturing process equipment as real-time release testing. However, speciality and sterility QC analysis cannot be integrated into on- or in-line analysis. Instead, these should be conducted directly in the lab area as part of the manufacturing space and a shop-floor concept. The benefits of this include full integration of manufacturing and QC, a significant increase in productivity, a minimization of human errors and better compliance. At the same time, manual workload can be reduced by up to 80%.

Looking to other industries, the in-line, on-line, at-line concept is already implemented e.g. in the car-manufacturing industry (production line of new cars) and other types of assembly and packaging lines like Sony and PlayStation. Pharma companies like Takeda have taken main steps towards this concept, but are somewhat limited by the fact that they only have around 50% of the technology needed available today.

Although these industries are different, their goals are the same: industries are different, the goals are the same: high quality, speed, flexibility, adaptability, productivity and fast to market. In the mentioned examples, quality control is organizationally integrated into the manufacturing organization, and troubleshooting is a joint challenge and effort.

WHAT ARE THE STEPS TO TAKE TOWARDS THE FULLY INTREGRATED QC OF THE FUTURE?

Taking QC in-line, at-line and on-line will not happen overnight. Depending on the current situation, a pharma manufacturer is likely to have the traditional concept of a physically remote QC lab and a separate area for manufacturing. One first step to consider could be to start the integration of QC and manufacturing organizations. This will increase the common understanding of QC functions and overall manufacturing goals. A second step could be to establish a local QC lab-unit 'station' in the manufacturing area, to increase speed of analysis and QC responses.

In new greenfield projects or refurbishment projects, a simple step could be to locate QC functions directly connected to a manufacturing building – and again ensure an organizational link between them.

When pharma manufacturing equipment and digitalization and integration technologies are fully compatible, the ultimate step for pharma QC would be to go truly in-line, on-line, at-line. In this scenario, there would be no remote QC function. As technologies will continue to evolve, the solutions implemented should still be prepared and ready to integrate new technological solutions for continual optimization.

QC MEGA TREND: QC RESPONSIBLE FOR 50% OF THE CONTROL STRATEGY

When QC becomes a fully integrated part of both research, product development and commercial manufacturing, there is a beneficial side effect: QC can then play a more significant role in developing of control strategies. This is a huge benefit for both process development as well as commercial manufacturing.

TRANSITION TO QC FOR THE FUTURE

To ensure you capture the value of implementing evolving technologies using a phased approach, it is vital to get the first steps right. Each pharma company needs a clear vision and business case to evaluate which technologies and equipment to implement. Part of this analysis should include a value stream mapping, to create an overview of where new technology adds true value. Implementation of digitalization and automation is a significant investment , so it is vital to get it right first time to get the expected value and benefits. Another pitfall is underestimating the time and effort needed for planning and implementation. Apart from technology implementation, the change management process is equally important for success.

Finally, it is key to have an implementation plan, including relevant test and pilot tests, to support final decisions on both technologies, equipment, IT and automation systems, and last but not least how to phase the implementation.

WHO WE ARE

NNE is an international company specialized in pharma engineering. We help pharmaceutical companies bring products to market by providing flexible, compliant and future-proof solutions. We have close to 1,000 professionals delivering global knowledge and best practices, all dedicated to supporting our customers globally and on local sites.

Through focused pharma engineering we enable our customers to deliver on demand.

Visit nne.com

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