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– There’s more to R&D than meets the eye
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‘Because we can’t redesign thumbs’
A team of engineers and social scientists are working to better understand the needs of people using insulin pens. See what solutions they have come up with.

When uncertainty is part of the equation
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The people driving sustainability
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The power of science

Mads Krogsgaard Thomsen, chief science officer in Novo Nordisk, shares his fascination with science and talks about why we need to ensure a research environment where new ideas can flourish.

From an early age, I could see the promise of science as a way to improve health and well-being. This started out as a determination to establish my own veterinary practice but along the way I met a laboratory scientist. Suddenly, the world of research and discovery opened up endless possibilities to solve health complications in my mind.

In 1991, I joined Novo Nordisk and began a new journey, developing research projects into treatments for diabetes, haemophilia, growth hormone deficiency and women’s health. In 2013, Novo Nordisk’s diabetes products reached 24 million people, giving them the opportunity to live healthy lives free of complications. This is a constant reminder to me that our science is truly powerful and global.

We use this strength to continue to look for new and better ways to address unmet patient needs, and we are dependent on talented health and natural science PhD graduates and researchers to do so. But the number of these people with a high level of talent is not matching demand. In Denmark, home to our global research and development (R&D) organisation, our future need for talented and educated researchers is at risk of outstripping what is available locally.

This year, we published an invitation to the public and governmental research institutions to join us on a journey to bolster the life science research base in Denmark. ‘Invitation to growth – a road to job creation’ demonstrates the case for action, showing how medical discoveries are the result of global cooperation between universities and biopharmaceutical companies and highlighting the positive impact this also has on job creation.

It is indeed in the interest of society, in health terms, that we ensure a strong and sustainable environment for science to flourish.

**A look inside our world of science**

I am a firm believer in the power of science. In my role as head of global R&D at Novo Nordisk, I’ve also come to learn the truth behind Voltaire’s words - with great power comes great responsibility.

This issue of TBL Quarterly demonstrates how Novo Nordisk conducts R&D with a responsibility towards patients, our employees and society at large. And this approach goes all the way back to the 1920s when our company was founded. As early as 1924, the Nordisk Insulin Foundation was set up to manage the company’s profits to ensure part of this was given back to society to scientific and humanitarian causes.

In this issue, we take you through the R&D journey from idea to patient. First, we meet Jesper Lau who works as a scientist in Novo Nordisk’s protein discovery area. He shows us why he is passionate about proteins and how his work in the lab is translated into meeting the medical needs of people with diabetes.

We show the results of global research collaborations. Novo Nordisk owes its 90+ year history to a collaboration between Danish and Canadian scientists and since then we have been giving back through our own collaborations with universities across the globe. Børge Diderichsen and Lars Hovgaard tell about their experiences from China.

Companies like ours need to use animals in R&D. The complicated interplay between a pharmaceutical product and a living organism cannot be replicated completely in a test tube. For issues of safety, it is a legal requirement that all new drugs are tested in living animals before they can be tested in people. This doesn’t mean we can’t find ways to minimise the number of animals used and to ensure that the animals we do use are treated well. In the article ‘Making it all add up: replacing, reducing and refining the use of animals in research’, Christian Hove Rasmussen shows how we work to come up with alternative methods and Lise Holst talks about how we collaborate with NGOs and governments to build and support a 3R culture to Reduce, Replace and Refine the use of animals in our research.

In the development of our products, we must always keep the needs of the people using them as a leading focus. In the article ‘Because we can’t redesign thumbs’, we meet Ida Vesterdal and Jakob Oest Wielandt, who have explored the unmet needs of people using insulin pens to find ways to overcome physical challenges that made daily injections a struggle. What they identified is an engineering marvel.

But successful discovery is never guaranteed. In the article, ‘When uncertainty is part of the equation’, Andreas Linderoth Norlin and Mette Aagaard Hertz show how we handle situations when research projects are closed down.

Lastly, we explore the power of science beyond its contribution to health. In this issue’s ‘People driving sustainability’, we meet Asser Sloth Andersen whose work with optimising yeast strains used for growing insulin cells has led to a reduction in the use of water and energy during production.

"I am a firm believer in the power of science. In my role at Novo Nordisk, I’ve also come to learn the truth behind Voltaire’s words - with great power comes great responsibility.”

When developing new treatments, we want to remove probability and chance, and attain certainty: Certainty that our products are safe and effective, certainty that our products are meeting the needs of the millions of people that rely on them for their health, and certainty that we are living up to the expectations we set for ourselves and society.

I think back to that chance meeting with the university scientist that influenced my career path and hope that we can continue to bring new scientists into the world, increasing the probability that such chance meetings may happen more often.

**Mads Krogsgaard Thomsen**

Executive vice president & chief science officer
A positive contribution to society

The purpose of Novo Nordisk’s research and development (R&D) activities is to make new and better products available to patients. But R&D also makes a positive contribution to society in other ways, namely through job creation and scientific progress. Here are a few highlights:

- 24 million people use Novo Nordisk’s diabetes care products
- Novo Nordisk has more than 100 R&D partnerships across the globe
- In 2013, Novo Nordisk supported PhDs and PostDocs with a contribution of DKK 20.3 million (covering a period of 2-3 years)
- In 2013, the Novo Nordisk Foundation² donated approx. DKK 0.8 billion to scientific, humanitarian and social causes
- Novo Nordisk has more than 40 products on the market within diabetes, haemophilia, growth hormone deficiency and hormone replacement therapy
- In 2013, Novo Nordisk invested DKK 10.9 billion (14% of revenue) in R&D so that new treatments can be developed
- 4,500 employees work in Novo Nordisk’s R&D centres in Denmark, the US, China and India
- Novo Nordisk expects to create 3,000 extra jobs in its R&D organisation by 2022³
- In Denmark, for every 100 people employed in the biopharmaceutical industry, a further 240 jobs are created in the rest of the Danish economy¹

² The Novo Nordisk Foundation owns 25% of Novo Nordisk’s shares through Novo A/S.
Jesper Lau is passionate about proteins and his work in the lab helps meet the medical needs of people with chronic diseases.

“What do you want to be when you grow up?” This is a common question that children and young people are being asked and answers can span across anything from policeman to hairdresser. For Jesper Lau, the answer has been “scientist” as long as he can remember.

In fact, he started his career as a child where he experimented with chemistry and in his own words “made a lot of trouble” in his parents’ basement. “I have always been very playful and curious to understand the world and I guess this has followed me throughout my scientific career,” Jesper says when looking back.

Today, Jesper is Vice President of Diabetes Protein & Peptide Chemistry in Novo Nordisk. Working with a team of protein chemists and engineers, his job is to try to understand how nature works in detail in the quest to design proteins and peptides that can end up as new treatment opportunities for people with type 2 diabetes and other chronic diseases.

But what is so special about proteins and peptides? And how can understanding ‘how nature works’ be translated into meeting medical needs?

Building blocks of life
Proteins are large biological molecules that consist of peptides which are chains of amino acids. Proteins are often referred to as the ‘building blocks of life’ since they perform different key functions in living organisms. Many diseases are related to defects in proteins. One example is diabetes where the body no longer produces insulin or uses the insulin it produces ineffectively and therefore is unable to regulate blood sugar.

Protein-based medicine takes its starting point in the body’s own functions and tries to recreate or enhance a process in the body. That’s why it is also known as ‘replacement therapy’. In the case of diabetes, insulin is injected to help move sugar obtained from food from the bloodstream into cells throughout the body to be used for energy. In the case of haemophilia, a bleeding disorder, another type of protein-based medicine is injected that enables blood clotting.

Proteins differ from most other medicines which are based on small molecules, meaning that the active substance is a small chemically manufactured molecule which can normally be processed into tablets and consumed orally. Because it is a small molecule it is not broken down by enzymes in the stomach and the active substance can be absorbed into the bloodstream. From there, the small molecules can reach almost any desired destination in the body because of their tiny size. This is how an aspirin works.

But proteins are more complex. They are large and bulky, which can prevent them from gaining access to the place in the body where they are needed. They are also very sensitive to the enzymes of the stomach and intestines, and therefore cannot be taken as a tablet. This means that protein-based medicine, such as insulin, has to be injected to be useful – at least for the time being.

Decorating peptides with organic chemistry
Ever since the discovery of insulin back in the 1920s, Novo Nordisk has worked to innovate protein-based treatment, and Jesper has been part of this journey since 1990.

According to Jesper, Novo Nordisk made an important decision in 2006 when it was decided to move out of the small-molecule space and focus solely on protein design.
However, the company realised that it needed to work not only on the protein backbone, but that it could add chemical side chains onto the proteins to further enhance their treatment potential. Combining these two disciplines – biology and chemistry – is key in Jesper’s work and for the future R&D pipeline for Novo Nordisk.

Each protein peptide is built of amino acids. When designing a new peptide Jesper has all the amino acids as building blocks and like pearls on strings he put them together one by one in almost endless combinations. But always with a clear purpose.

“We always have the patient in mind when looking for new treatment opportunities,” says Jesper. “For example, it is key for us to find ways in which we can reduce the number of insulin injections needed to improve convenience for the person living with diabetes.”

Part of the job in Diabetes Protein & Peptide Chemistry is therefore to engineer proteins and peptides in a way so that the duration of the active substance in the body is prolonged with the purpose of reducing the number of injections. “What we do is to ‘decorate the peptides with organic chemistry’ which means that we for example take a fatty acid, attach it to the peptide, thereby changing the properties of the peptide, and make it able to last longer in the body,” Jesper explains.

Combining science and art
The new peptides are produced on a so-called peptide synthesiser in Jesper’s lab. And each experiment comes with a wealth of data. According to Jesper, looking at the data can be quite chaotic and you need to approach it in a systematic way and search for trends. To help with this, Jesper and his colleagues use a huge database that stores scientific data from the entire organisation and enables them to filter in the data. “At the end of the day, only very few new peptides pass the filter, and materialise as something that we can work further on,” Jesper notes. “Most of the time nothing new happens, but when there is a breakthrough you are able to see it instantly!”

According to Jesper, designing a new molecule is a mix between science and art. Of course it requires scientific knowledge and experience, but it also calls for intuition, creativity and a little bit of faith. And working with proteins also requires patience. Developing new medicines is a process that takes, on average, 10-13 years. And for every 10,000 molecules studied, only one will become a medicine that makes it to market.

But this does not discourage Jesper. “We know that only very few scientists will make a new drug, but this is not the only motivation,” he says. “It is more about the journey, the scientific curiosity and knowing that together we can make innovative things happen. Being a scientist is like being an adventurer every day.”

“Developing new medicines is a process that takes, on average, 10-13 years. And for every 10,000 molecules studied, only one will become a medicine that makes it to market.”

Watch a video about Jesper Lau and his work: http://video.novonordisk.com/video/6463574/engineering-proteins-is-like
A passion for proteins

So how are proteins used in medical treatments? Protein-based medicine takes its starting point in the body’s own functions and tries to recreate or enhance a process in the body.

In the case of diabetes, the body no longer produces insulin or uses the insulin it produces ineffectively and therefore is unable to regulate blood sugar. By means of gene technology, the naturally occurring proteins like insulin can be produced and used as medicine to treat diseases.

This is how it works:

1) The functional protein from a human cell is identified
2) The genetic code of the protein is identified
3) The gene is modified to develop a pharmaceutical protein
4) The modified gene is inserted into production cells (such as bacteria or yeast)
5) The cells are cultured in large, closed tanks thereby producing the desired pharmaceutical protein
6) The pharmaceutical protein is isolated from the cell through a purification process and then formulated into the desired medicine using advanced technology
7) The protein-based medicine is made available as treatments for...

Diabetes
Haemophilia
Growth hormone deficiency
Hormone replacement
Globally, Novo Nordisk has more than 100 R&D partnerships. See how a partnership with the Chinese Academy of Sciences helps Novo Nordisk build knowledge and networks in China.

Børge Diderichsen spends a lot of time in the air. With an impressive professional network spanning the globe, he is in constant motion to keep connected to colleagues, ministers and prominent scientists in Europe, the Americas and Asia.

As Head of Research & Development (R&D) Outreach in Novo Nordisk, Børge’s job is about building relations – a corporate diplomat one could say – and he travels the world to facilitate contacts between Novo Nordisk’s R&D and academic partners abroad. With more than 30 years in the company, he is no stranger to the business! He admits that his time in Novo Nordisk goes back longer than the date on several of his colleagues’ birth certificates.

But the company’s global scientific collaboration has an even longer history. It is how Novo Nordisk got its start.

Cross-Atlantic collaboration
The foundation of Novo Nordisk’s insulin production came about as a result of cross-border collaboration between researchers. In 1921, the Canadian scientists, Frederick Banting and Charles Best, were able to extract the hormone insulin for the treatment of people with diabetes. On a trip to the US in 1922, Danish researchers, August and Marie Krogh1, heard about this revolutionary discovery and decided to contact the University of Toronto where insulin had been discovered. These talks led to the couple returning to Copenhagen with permission to manufacture and sell the vital insulin in Scandinavia.

This laid the foundation for what is today Novo Nordisk and in the spring of 1923, the first patients were treated with insulin manufactured in Denmark.

To Børge, the history of Novo Nordisk is unique and illustrates a mind-set that still characterises the company today: “It shows global outlook and the desire to use science to solve societal challenges,” he says.

A global challenge
Despite medical progress, the global health challenge of diabetes continues to increase. It is estimated that 387 million people – 8.3% of all adults – have diabetes.2

A challenge as complex as the diabetes epidemic requires coordinated global efforts and sharing of knowledge and resources. Scientific discoveries flow across borders and are increasingly the result of companies, governments and academic institutions working together. A strong research environment is good for all parties involved and Børge’s experience shows this, not least in China where he just returned from. And China has a special place in his heart.

Børge has for many years had a deep interest in the relations between Europe and China in the field of biotechnology and he has travelled extensively in the country. China is also the country in the world with the highest absolute number of diabetes cases – 96 million adults are living with diabetes.2

Being on the forefront of this development and acknowledging that research is increasingly done across borders, Novo Nordisk established an R&D centre in Beijing in 1997 - the first R&D centre in China set up by an international pharmaceutical company. Ten years later, Novo Nordisk’s relations in China were further strengthened through a partnership with the Chinese Academy of Sciences (CAS). CAS is the top academic institution in China within science and technology. It has 104 research institutes, two universities and some 60,000 professional staff and 45,000 graduate students.3

Tying the knots to advance research collaboration
In 2007, Novo Nordisk and CAS established the NN-CAS Research Fund by a donation of USD 2 million from Novo

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1. August Krogh was a professor at the University of Copenhagen and awarded the Nobel Prize in medicine in 1920. Marie Krogh was a medical doctor and the fourth Danish woman to earn a doctorate in medicine.
Nordisk. The purpose of the Fund is to support projects of interest to both CAS and Novo Nordisk in the fields of diabetes, biopharmaceuticals, and protein sciences that are jointly submitted by scientists from CAS and Novo Nordisk.

“The Research Fund demonstrates our long-term commitment to build capacity and advance research achievements to the benefit of both Novo Nordisk and the Chinese research community – and ultimately to people living with diabetes in China”, says Børge.

“The Research Fund demonstrates our long-term commitment to build capacity and advance research achievements to the benefit of both Novo Nordisk and the Chinese research community – and ultimately to people living with diabetes in China”

The projects include research projects, workshops, PhD fellowships and Postdoctoral fellowships. The Fund also supported eight CAS-NN Great Wall Professorships in Protein Sciences to build relations to rising stars at CAS. Since 2007 Novo Nordisk has granted additional donations, reaching a total contribution of USD 4.3 million leading to 55 projects engaging scientists from 10 different CAS Institutes and from Novo Nordisk in China, Denmark, and the US.

Building knowledge and network
One of the people benefitting from the Fund is Lars Hovgaard, who works as Principal Scientist in Novo Nordisk. Together with Professor Yong Gan, Shanghai Institute of Materia Medica, and Associate Professor Mingshi Yang, Copenhagen University, he is investigating the mechanisms behind how oral protein-based drugs are absorbed in the body. In addition to the academic benefits, Lars highlights the valuable network he has built with Chinese researchers from early master students to senior professors.

“A project between China and Denmark is built on personal relations, trust and respect. If this triple foundation is established at the beginning of a project, the network will last a life time,” Lars says. One example is his encounter with a Chinese PhD student, Lisa, who showed incredible skills and motivation and spent part of her studies in Denmark as a result of the collaboration. She may even end up working for Novo Nordisk in the future.

Professor Ming-Wei Wang, Director of the National Center for Drug Screening affiliated to CAS and active member of the Board of the NN-CAS Research Fund, also highlights the mutual benefits of the collaboration. “This is a ‘win-win’ partnership where sciences are advanced and my academic life is enriched,” he says. “With the support of the Fund, my group has published 16 research papers and a number of young scientists have been trained. I am sure that we can even do better in the next phase of our collaboration.”

Renewing the commitment
In November 2014, Novo Nordisk announced that it increased its donation to CAS. At a NN-CAS board meeting in Beijing, Novo Nordisk signed the official documents increasing the donation by USD 500,000. To mark this and to celebrate the achievements of the Fund so far, Novo Nordisk and CAS hosted a joint research symposium on ‘Translational Research in Biopharmaceuticals’ in Tianjin. The purpose was also to give selected CAS and Novo Nordisk scientists the opportunity to report on progress of their projects as well as to present competencies and interests of CAS and Novo Nordisk departments to facilitate joint research projects in the future.

As co-chairman of this NN-CAS symposium, Børge participated in and spoke at the event which gave him the opportunity to connect with old friends and form new contacts in the Chinese research community. And when sitting in the plane on the way home, he already had new ideas to reach out to the world.

Changing Health through Science in Argentina
Another R&D Outreach project, ‘Changing Health through Science’, has been launched in Argentina with the support of the Argentinian Ministry of Science, Technology and Productive Innovation, endorsed by the Danish Ministry of Science, Technology and Higher Education and funded by Novo Nordisk Argentina with DKK 10 million over three years.

The project covers activities such as prizes for leading Argentinian diabetes researchers, training fellowships at Copenhagen University for Argentinian scientists in the fields of diabetes and biotechnology, training of Argentinian diabetes doctors, and an epidemiological study of diabetes in Argentina.

Novo Nordisk is also running R&D Outreach projects in Turkey and Iran.

Watch a video about the R&D Outreach project in Argentina: http://video.novonordisk.com/video/9907159/research-exchange-between-argentina-and
In the pharmaceutical industry, the journey from idea to patient for a new product is highly complex and time consuming. Industry estimates that out of 10,000 ideas that start off in the lab, just 10 will reach the clinical trial stage. From these 10, it is likely that only one will be approved as a new product. The process for a successful new product takes 10 to 13 years from initial start to finish.

Along the R&D journey, there are ethical issues related to the use of life science technologies for the discovery, development, and production of pharmaceutical products. See how Novo Nordisk deals with some of them here.

**RESEARCH & DEVELOPMENT (R&D) PROCESS**

The R&D process includes activities through which innovation is transformed into patient care.

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<th>Stages</th>
<th>RESEARCH</th>
<th>DEVELOPMENT/CLINICAL RESEARCH</th>
<th>COMMERCIALISATION</th>
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<tr>
<td>Process</td>
<td>Laboratory and animal studies</td>
<td>phase 1</td>
<td>Approval</td>
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<td>Discovery</td>
<td>phase 2</td>
<td>phase 3</td>
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<tr>
<td>No. of people studied</td>
<td>Up to 10,000</td>
<td>Launch</td>
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<tr>
<td>Time</td>
<td>~ 5 YEARS</td>
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<tr>
<td>No. of molecules</td>
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**Research:**
In the first step in the journey from idea to patient, researchers at Novo Nordisk work with clear guidelines to balance ethical concerns related to the use of animal in research and testing, the use of human materials, stem cells, and gene technology.

**Development/clinical research:**
When a compound is proven to be safe and effective in animals, it starts the clinical trial phases. To ensure that the rights of individuals are protected, the trials are safe and the outcomes transparent, Novo Nordisk applies the same rigorous procedures wherever the company sponsors clinical trials.

**Commercialisation:**
When a new product receives regulatory approval, the launch begins. From marketing to medical affairs representatives to the sales force, everyone involved adheres to strict ethical policies related to interactions with healthcare professionals and organisations. Additionally, phase 4 trials are conducted to monitor possible long-term side effects, new indications, treatment experience or specific safety concerns.
Zooming in on clinical trials – the what, the how and the why

Clinical research is a collaboration
Clinical research is a complex and highly regulated process where multiple stakeholders work together, including the pharmaceutical industry, hospitals/clinics, patients, healthcare professionals, and governments/healthcare authorities.

Global standards
Clinical trials are approved by national health authorities and ethics committees. Novo Nordisk applies the same ethical standards wherever the company conducts clinical trials. The company will only conduct trials in countries where these standards can be met, and where we intend to seek approval for and market the new product.

Conducting a clinical trial
A healthcare professional (HCP), also known as an investigator, conducts the clinical trial on behalf of the sponsoring pharmaceutical company. The main role of the investigator is to serve and protect the interests of the trial participants and ensure their safety, rights and privacy are maintained.

Clinical research is a collaboration
Clinical research is a complex and highly regulated process where multiple stakeholders work together, including the pharmaceutical industry, hospitals/clinics, patients, healthcare professionals, and governments/healthcare authorities.

Trial protocol design
- HCPs give scientific and operational input
- Health authority gives input
- Novo Nordisk writes protocol with the primary investigator

Patient recruitment
- HCPs agree to screen patients at hospitals/clinics for inclusion
- Novo Nordisk supports the conduct of the trial

Patients in trial
- HCPs treat and educate patients at hospitals/clinics
- Patients follow the treatment as described in the protocol
- Safety and efficacy data from patients are sent to Novo Nordisk by HCPs

Results reporting
- Novo Nordisk analyses data and shares it with the HCPs involved
- HCPs write publications in collaboration with Novo Nordisk

Participating in a clinical trial
Participation in a clinical trial is always voluntary and participants may withdraw from the trial at any time, without providing a reason, and without this having any consequence for their future treatment.

Sponsoring a clinical trial
During the execution of a clinical trial all parties involved – including the company sponsoring the trial – have specific responsibilities to ensure adherence to ethical principles. For every trial sponsored by Novo Nordisk, a clinical trial protocol is written by Novo Nordisk incorporating comments and suggestions from investigators, ethics committees, and health authorities.

To share knowledge and ensure transparency, Novo Nordisk communicates clinical trial results through scientific journals, at conferences and via publicly available websites. We publish the results of our clinical trials irrespective of outcome and in 2014 we decided to go beyond regulatory requirements when it comes to ensuring the results of Novo Nordisk’s clinical trials are made publicly available. An overview of all the Novo Nordisk sponsored clinical trial programmes worldwide can be found on novonordisk-trials.com.

Watch a video that shows the activities from when a drug candidate enters clinical trials until it becomes a product ready for approval: http://video.novonordisk.com/video/9190110/from-research-to-submission-clinical
Making it all add up: replacing, reducing and refining the use of animals in research

The discovery and development of new medicines involves the use of living animals for both research and safety testing. This comes with a huge responsibility to address issues ranging from ethical considerations to the reliability of results. Novo Nordisk adheres to the 3R principles to Replace, Reduce and Refine the use of animals. Using mathematical models to think out of the box is just one of the company’s innovative approaches.

From designing a new car to landing a space craft on distant planets, the use of models has helped identify if and how something works. In the development of new medicine, models that provide better predictions on its safety and efficacy save time, money and most importantly, can reduce the risk to people who volunteer to participate in clinical trials and reduce or replace the use of animals.

However, despite how well models are constructed, they are still challenged to capture all the highly complex processes happening in the human body and cannot fully predict how well a new medicine will treat a disease or the side effect. That’s why animal research cannot be replaced in the foreseeable future.

Looking back, animals have been used in medical research and development since 300 years BC and for more than 2,000 years has played an important role in the advancement of life science research. In 1921 insulin was tested for the first time in a dog with diabetes, revolutionising the treatment of diabetes. Not only has the use of animals in research led to important discoveries and development of new medicines, but for many years it has also been a requirement from regulatory authorities.

But through new technologies, Senior Research Scientist Christian Hove Rasmussen is working to reduce the number of animals needed in research. His job is to improve Novo Nordisk’s models by pooling research data and combining human and animal data. In this way, he creates more predictive mathematical models which also enhance our understanding of the human biology as well as the correlation between the results found in animals and humans. It’s called biosimulation.

Understanding human and animal biology

By definition, biosimulation is a computer-aided mathematical simulation of biological processes and systems. Though some people, even after having read the definition a few times, may still be in the dark, biosimulation is about improving understanding. Christian sees it in even simpler terms, “It’s about building better models.”

A good model is one that tells the researcher what works and what doesn’t, for example when a new medicine is injected into the body. A model can give insights into how quickly the medicine is taken up into the blood stream or how long it takes to diffuse into tissue. This not only saves time and money, but in the development phases of early drug research, a good model also helps reduce the number of animals needed for research and regulatory testing.

Christian explains how this has worked in practice. “We have been able to use models and data analysis to increase the understanding of how the drugs are absorbed and how they act on the organism. This, in turn, has allowed us...”

1 Clinical trials are a mandatory step in the research and development (R&D) process. Before a product can be approved by the regulatory authorities, it must be evaluated for its efficacy and safety in people.
to increasingly utilise in vitro methods\(^2\) as a supplement or replacement for animal studies, as well as to improve the bridging from animals to humans. Overall, we are therefore making better use of the animal studies.”

**Making it all add up**

Having a mathematician like Christian working alongside scientists and researchers in the preclinical phase of new drug development is unique. It is also a strong asset in the quest to reduce or replace the use of animals in research. Christian’s journey to Novo Nordisk began during his time working on a huge EU sponsored project called BioSim.

When BioSim started, there were 26 academic partners, nine small and medium sized enterprises, the regulatory agencies in Denmark, Sweden, Spain and the Netherlands, and only one pharmaceutical company, Novo Nordisk. The objective of the network was to demonstrate how the use of modern simulation techniques, like computer models, together with a deep and qualitative description of the underlying biological processes can lead to a more rational drug development process and an improved treatment of diseases.

At the same time, the techniques also offered the possibility of reducing or replacing animals used in research. Christian, who studied Engineering Physics at the Technical University of Denmark, was one of the project members helping to design and test the models and soon caught the attention of researchers working at Novo Nordisk.

We had a lot in common when it comes to the benefits of biosimulation,” says Christian. “We both saw the potential of biosimulation to improve the safety and effectiveness of new medicines, to make the development process more efficient and to be smarter when conducting animal experiments.”

“**We both saw the potential of biosimulation to improve the safety and effectiveness of new medicines, to make the development process more efficient and to be smarter when conducting animal experiments.**”

Since 2008 Christian has been working at Novo Nordisk to turn the complexity of biological systems into simplified models. But as Christian is quick to point out, models still need a human touch. “A model alone can’t tell you everything, it is a collaborative effort,” says Christian.
A 3R centre of excellence

First introduced in 1959 by Professor William Russell and Rex Burch, the 3R principles have helped guide research companies, universities and organisations worldwide on the ethical use of animals in research and testing. They have become widely accepted internationally and in many countries legislation governing animal use in research has followed the 3R principles.

Novo Nordisk works to reduce the number of animals used to obtain the same results, refine the conditions for the animals and replace the animals by using in vitro methods which means that cells or biological molecules are studied outside their normal biological context.

“We only use animals where no alternative exists and recognise that not all animal research can be replaced in the foreseeable future,” says Lise Holst, Director of Bioethics at Novo Nordisk. “We see it as our responsibility to integrate the 3R principles in our work and to collaborate with external partners to further the work.”

In June 2013, the Danish Ministry of Food and Agriculture established a new 3R Centre to explore alternatives to animal research and improve the conditions for research animals. Novo Nordisk joined the Ministry in bringing together the pharmaceutical industry, animal welfare groups and the public sector, all of which have a common interest in replacing, reducing and refining the use of animals in research.

“We have high hopes for this step in advancing the 3R principle,” says Lise. “Novo Nordisk is committed to the reduction, refinement and replacement of animal use in research and the 3R Centre brings key stakeholders together in a unique and high impact constellation.”

Since its launch, the 3R Centre has been focusing on collecting and sharing knowledge on 3R alternatives to animals, supporting research on the development of alternatives to animals and collaborating with similar centres around the world.

The Danish 3R Centre is funded by the Ministry of Food and Agriculture with contributions from Novo Nordisk, LeoPharma and Lundbeck as well as the Danish NGOs, Dyrenes Beskyttelse (The Danish Animal Welfare Society), Forsøgsdyrenes Værn (an NGO focusing on alternatives to and protection of research animals) and Alternativfondet (a foundation supporting, publicising and promoting the development and use of alternative methods to reduce or eliminate the use of animals). Novo Nordisk will contribute DKK 300,000 annually for three years starting in 2014.

Rewarding employees who improve the lives of research animals

One of Lise Holst’s favourite days of the year is the day of the Novo Nordisk 3R Award, where the company pays tribute to employees who bring Novo Nordisk’s commitment to the ‘Reduction, Refinement or Replacement’ (3Rs) principles into action.

This year’s award winner was Susanne Gyldenløve who for more than a year spent many evenings at home in front of her sewing machine to develop a special pig-collar for procedures involving gamma counters to track isotope-labelled peptides. This pig-collar has proven to be a significant refinement initiative, and the pigs no longer have to be put under anaesthesia and experience the side effects of that.

Watch the video to see the external judges’ visit to Novo Nordisk’s animal facilities in Denmark and highlights from the award ceremony:
http://www.novonordisk.com/science/bioethics/animal-ethics/3r-award.asp
A team of engineers and social scientists are working to better understand the needs of people using insulin pens. See what solutions they have come up with.

One key element in any injection device is the source of pressure. In the case of a simple syringe, a plunger is pulled up to bring liquid in the tube and pushed down to expel the liquid. When a healthcare professional is the one injecting, two hands can easily do the job.

For people living with diabetes, where daily injections with insulin are most often given by themselves, a one-handed approach is the most convenient. However, for many people, holding the injection pen and reaching the top of the plunger can be a real stretch for the thumb.

But we can’t redesign thumbs.

The dawn of user design
There was very little customer focus thought into the initial devices used to inject medicine into the body. It started with an early attempt at designing a syringe. One of the earliest recorded procedures took place in the 1600s and used animal bladders as the syringe and goose quills as the needle. Many of the early experiments proved ineffective and some even fatal.1,2,3

It took almost 200 years before a renewed interest in injection devices led to the development of the all-glass syringe and hollow steel needle. With the rise of insulin treatment for people with diabetes starting in the 1920s, needle sizes became smaller. World War II and the Korean War spurred the need for fully disposable syringes that were lighter and sterile.

Then, for nearly three decades, the innovations in injection devices focused on making the syringe and needle safer to reduce disease transmission and disposal. Innovations based on user insights and unidentified needs did not arrive until 1985 when Novo Nordisk pioneered the first insulin pen device, NovoPen®.

Safety, reliability and effectiveness were still at the core of the design but to meet the needs of people who want daily insulin injections to fit with their lives and not the other way around, the new pen device was designed to be discreet, convenient and easy to use anywhere.

A long, long way from the animal bladder and goose quill but the pen device was in its infancy. There were still needs to be met, the question was what was the best way to identify them.

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The engineer and the social scientist

Traditionally, identifying needs involved collecting people's experience with a product through surveys and focus groups. The result often provides valuable insight into what people prefer and what they don't think is so great. But they fall short of offering insight into how they experience the product and are unable to identify unarticulated needs.

Ida Vesterdal heads up a diverse team of industrial designers, design psychologists and anthropologists to better understand the drivers and barriers to living well for people with chronic diseases such as diabetes and haemophilia. By going out and being a part of patients’ lives, Ida’s team visits patients in their homes and spends time with them throughout their daily life. What they discover is often not apparent on paper.

“In our latest study, we gave a family of a child with haemophilia a camera and asked them to record whenever their child had a bleeding episode,” says Ida. “We are then able to see the real situation of a mother or father trying to give an injection to their resistant child, where any step in the process prolongs the parent’s stress and the child’s unhappiness. By watching and analysing the recording, we are able to better see how we can simplify the injection process and lessen the stress and unhappiness.”

According to Ida, many people using an injection device may not be aware of ways their daily treatment could be made easier. In some cases safer, too. Through user insights, Ida’s team helps the project teams to come up with alternative solutions that solve the problem in a way that is intuitive and easy to use.

“The needles on pen devices need to be changed frequently to avoid clogs that can impact the amount of medicine being taken. The needle hassle has been a well-known issue for years. At the same time people think it is a hassle to shift needles and as a consequence of this many people reuse the needle – also to save money. Our role here is to constantly bring the user perspective and concrete feedback from usability testing into play.”

The team, Innovation Facilitation, is responsible for taking user insights from the field and facilitating these insights into the Device R&D organisation. The insights provide strategic input to strengthen the injection device portfolio but most importantly are woven into ongoing projects to ensure that concepts fit the needs of the users.

Before, much of the user insights were being provided by some of the best outside experts in ethnography and user driven design, including RED Associates and the Copenhagen Institute of Interactive Design. But this is now done in-house.

“We believe that this close collaboration between user insight specialists and device projects is the way we create meaningful products to the patients we serve and make sure their voice is incorporated as part of the innovation process.”

A lot of thought goes into designing an insulin pen that fits the needs of the user
Ida Vesterdal works to translate insights from the field into the Device R&D organisation

“Ida Vesterdal works to translate insights from the field into the Device R&D organisation.

“It is not only a matter of understanding the patient – it is also a matter of understanding the organisation and the colleagues who have to work with the insights. We need a shared language and a constant dialogue. Thereby user-driven innovation can take place,” explains Ida.

This is particularly important when it comes to the length of a thumb.

Translating a ‘click’ into design

The first generation of insulin pen devices used the same solution to creating pressure found in the early syringe. On the top of the pen was a dial that, when twisted, would pull up a plunger that filled the pen with the required dose. What user insights showed was that for some people, reaching the top of the push button was a challenge.

Jakob Oest Wielandt, senior project manager in Pre-filled Device Development, was one of the engineers tasked with finding a solution.

“We started by looking for an alternative to the plunger to create a force in the pen. We tried a mechanical spring, pressurised gas, magnetic fields, you name it,” says Jakob. “Then we started working with an internal spring.”

After getting the tension of the spring right, with some of the springs in the early prototypes ‘popping’ inside the pen, the newly designed pen worked perfectly. Now when the dosing dial was twisted, the force needed for injecting was created by a spring housed inside the pen.

Once the button is pressed and held, the spring releases the pressure until the full dose is injected (or the person takes their thumb off the button). Without the obvious fully retracted plunger, the team had to find the right signal to tell the user that the injection was complete. The next question was what is the best ‘click’ sound to signal this?

“Making the right click is very difficult. How do you make the right click?” says Jakob. “When we were conducting user tests and focus groups, we included statements related to the click sound. We identified the need to make the click more distinct and we went through a number of iterations and user testing until we hit on just the right click, now heard on the millions of FlexTouch® pens today.”

Seamless collaboration

Ida and her colleagues are firm believers in their approach to user driven innovation. By bringing engineers, social scientists and designers into one room, the project teams at Novo Nordisk have been able to work seamlessly to identify and offer solutions to the challenges facing everyday chronic disease management.

“We believe that this close collaboration between user insight specialists and device projects is the way we create meaningful products to the patients we serve and make sure their voice is incorporated as part of the innovation process. We see ourselves as ambassadors for the users,” says Ida.
Today more than 4,500 people work in research and development (R&D) at Novo Nordisk sites in Denmark, China, the United States and India. They are on a path of discovery, fully aware that sometimes paths may take sudden turns.

The biopharmaceutical industry offers exciting career opportunities, where you can work on the cutting edge of medical science and be part of discoveries that change people’s lives. Scientists and researchers spend the majority of their time making ideas grow, working in a dynamic environment where international experiences are welcomed.

But researching and developing new medicine is also a process characterised by uncertainty. Taking a new medicine from idea to patient is a process that takes, on average, 10–13 years. Along the way, many ideas do not make it to the market. When this happens, projects are sometimes closed down and companies must reorganise activities. Taking care of the patients enrolled in clinical trials¹ and employees working on the projects must then take top priority.

A difficult decision
In September, Novo Nordisk decided to discontinue all its R&D activities within inflammatory disorders. For several years, Novo Nordisk has been working to build up a pipeline within this area, which however has proved challenging. The close-down of the inflammatory R&D activities follows a decision earlier this year to halt development of the company’s most advanced drug candidate used to treat rheumatoid arthritis, known as anti-IL-20.

With the setback for anti-IL-20, the earliest possible entrance into the market for anti-inflammatory treatments was pushed a long way into the future with considerable risk and less chance of developing successful products that would lead to improvements for patients. It was therefore decided that Novo Nordisk instead should focus more on its diabetes core business, including prevention and treatment, obesity and diabetes complications.

Closing down clinical trials with care
When a decision is made to close down R&D activities within a certain area, it has implications for people that are taking part in clinical trials. At the time of the closing, Novo Nordisk had four ongoing clinical trials as part of its development activities within inflammatory disorders. These involve around 620 patients and more than 1,000 healthcare professionals who conduct the clinical trials on behalf of Novo Nordisk in the United States and in selected countries in Europe.

“As soon as the decision was made to close down the inflammation area, all people involved were informed. At the same time, you also look at each individual trial to decide what is the best way to go forward,” says project vice president Andreas Linderoth Norlin, who is responsible for closing down the clinical trials.

One of the trials was so far ahead that it will finalise according to the original plan, two were decided to be discontinued already back in August due to unsatisfactory results and the last one was decided to be closed prematurely as a direct consequence of the discontinuation of the inflammation R&D. All clinical activities are expected to be finalised by July 2015 and Andreas ensures that until closure of the clinical trials, patients will be followed in

¹ Clinical trials are a mandatory step in the research and development (R&D) process. Before a product can be approved by the regulatory authorities, it must be evaluated for its efficacy and safety in people.
accordance with the protocol. After finalisation, all data will be made public so that the results may be used by other researchers in the inflammation area.

Looking to the future

Right now the close-down means that Novo Nordisk is focusing many efforts on clinical trial participants affected by the decision. However, it also raises the question — what will this decision mean for patients living with inflammatory diseases in the future? Many enrolled in trials are hoping for new and better treatments. Ending research can often be hard when hopes are high.

“Although we are discontinuing our R&D activities within inflammatory diseases, we make sure that the valuable knowledge that we have built up over the years is not wasted,” says Andreas.

Going forward, Novo Nordisk will look into possibilities for selling or licensing out some of the drugs from the inflammatory business pipeline, so that other companies can build on this work to the benefit of patients.

But beyond people in the clinical trials, closing down inflammatory research also impacts the lives of everyone working on the projects.

It’s about people

“Our company culture is characterised by long-term thinking and a responsible business approach and compared to the rest of the industry, Novo Nordisk has enjoyed stable growth,” says Mette Aagaard Hertz, who works as head of HR for Novo Nordisk’s R&D organisation. “But uncertainty is part of the nature of the industry and sometimes we have to discontinue activities if we are not convinced they will lead to significant improvement for the patients,” she adds.

When the decision was made at Novo Nordisk to close down inflammatory research, 392 employees were impacted worldwide. For more than two thirds of them Novo Nordisk has been able to offer other positions within the company, particularly those employees who have a skill set that is easier to apply to other disease areas. Such an example is the laboratory technicians in Denmark. For them, Novo Nordisk has established a job centre where they get help with finding new positions within the company.

However, some employees are so specialised which means that it is not possible to rehire them in other parts of the organisation. This has been the case for 17 people in Beijing, 63 people in Seattle and 53 people in Denmark. In Denmark, the people laid off are offered support to find new jobs either inside or outside Novo Nordisk, which includes job fairs where they can learn more about job opportunities.

“It is always unfortunate when we have to say goodbye to good and clever colleagues. However, with these efforts we believe we are doing it in the most responsible and respectful way,” Mette adds.

Despite the inflammation close-down, Mette also emphasises that Novo Nordisk is no way slowing down its R&D efforts. In fact, ambitious growth plans means that she and her team are responsible for hiring an estimated 6,000 new people to the R&D organisation in the coming ten years, corresponding to a staff increase of 60% in R&D. They are needed to keep on developing new and innovative treatments for people with haemophilia, growth disorders and diabetes – including prevention, obesity and diabetes complications – where significant unmet needs still remain.
Novo Nordisk uses genetically modified yeast cells for the production of insulin. Production cells are cultivated in large fermentation tanks, where they are given the optimal conditions to grow. This process requires water and energy. But by developing new types of yeast cells, Novo Nordisk is able to reduce its environmental footprint.

Asser Sloth Andersen is one of many researchers whose job it is to create the yeast cells used in the process. He’s a scientist and an environmentalist.

**How did you get interested in protein research?**

I went to University of Aarhus, studying both physics and chemistry. I started out thinking I would be a physicist. But when I got into the science, I really got intrigued by the biology side of things. I started at university in 1978, about five years after all the discoveries that started the field of gene technology. I got quite fascinated on learning more about how the DNA works.

After I graduated from Aarhus, I moved to King’s College in London where I focused on insulin and the insulin receptor which is what insulin interacts with to get the cells in the body to take up sugar. During my research, I started reading a lot of articles on insulin and kept coming across Nordisk Gentofte and Novo. In 1988 I applied and got the job, just before the two companies were merged into Novo Nordisk.

**You work in an area called Yeast and Protein Technology, what is the area’s responsibility?**

We provide proteins or peptides to all the projects that are running in the diabetes research organisation. So whenever there is a new project and they have an exciting new protein that they want to study, they ask us to make it so they can study it. Proteins are complex molecules that can only be produced in living cells. This means that we try to make genetic modifications to different cells that will then produce the proteins we want to investigate.

One of our options is to see if we can make it with yeast but other options such as bacteria or mammalian cells may also be used. However if you want to have a project that is viable in the long run the most fundamental thing is to make sure you can make proteins in processes that are robust.

**How long has Novo Nordisk been working with the potential of yeast to reduce its environmental footprint?**

When I started working with yeast production back in 1991, there were already discussions on how we produce yeast in Kalundborg, Denmark. We were producing more and more insulin and we could see the need to expand the factory and build extra tanks. At some point, people started asking if we could make yeast cells that could produce more insulin using the same number of tanks, or even decrease the number of tanks.

In 1996, these questions were answered by a project called NN729 where we created a yeast strain that enabled us to squeeze down the number of tanks needed to produce enough insulin to provide for the market. You use fewer tanks and you use less water and energy as well as produce less CO₂ emissions. It took many years to go through the proper regulatory filings and clinical studies, but in 2007 you already saw that we were able to decrease carbon emissions although our sales are increasing.
How do yeast strains influence the amount of water and energy needed during the production?
We have these huge tanks in our main production site in Kalundborg, Denmark, where we put liquid growth media and water together with our yeast cells and make them grow. If the yeast cell in a tank produces 1kg of insulin, for example, and we need 10kg, then we need 10 tanks. So the consumption of water and energy will be 10 times more. But if we can produce a yeast cell that produces 10 times the amount in one tank, then we can skip the other tanks and just do the whole process in one or two tanks which will save us a lot of water and energy. That is exactly what happened as a result of the NN729 project.

Do you consider yourself an environmentalist?
Yes, I actually believe I am one. I believe we have to take care of our environment to ensure we have a healthy and liveable earth to give to our children. It’s central that we consider that whatever we do can affect the environment. I think it’s nice that we have an environmental policy here at Novo Nordisk that says you have to think this perspective into all processes. It is this way of working that directs us to make yeast strains that help production in the most efficient and environmentally friendly way.

When researchers come to you with a protein, is it a computer model of a protein?
The research area has a lot of focus groups that are continuously monitoring whether something new or interesting comes up in literature or small companies within diabetes or obesity. Then whoever has the idea will ask us to make a specific protein in large quantities so they can study it in a cellular or animal model that mimics diabetes or obesity to see if there are any effects.

This is really early on in research, where there is an idea. Then you try producing the protein, and if lucky, in 10-13 years, we may have a product. But many proteins never evolve into products.

So your work is the very first step in the process?
The very first step in the process is scouting the world for great ideas, but then, when a new idea comes into Novo Nordisk, the first thing to ask is ‘Can we make this protein or this peptide?’ Then you have to produce a system that can make the protein pure so you can test it. But if you can’t make the protein, then you don’t have a project, so it is the entry point.

If you are lucky, you can follow the project through research and be able to hand it over to the development phase which is the next step in the R&D process when the drug is tested on people for the first time, and then to our friends in product supply who are in charge of large-scale manufacturing. For example, it has been very exciting for me to be a part of the early project work that ultimately lead to the development of one of our long-acting insulins. But it’s not often that you get to follow the project all the way through.

How does this feel?
It’s fascinating and nerve wrecking to develop something new in the lab and to see whether it survives throughout the whole R&D process. But it’s also a driving factor for the people who are working on it to know that if they are successful, their work will be produced on a massive scale to benefit millions of people living with diabetes. It makes it meaningful and worthwhile. It gives us an extra boost to know this.
About Novo Nordisk and the Triple Bottom Line

Headquartered in Denmark, Novo Nordisk is a global healthcare company with more than 90 years of innovation and leadership in diabetes care. The company also has leading positions within haemophilia care, growth hormone therapy and hormone replacement therapy. We believe that a healthy economy, environment and society are fundamental to long-term value creation. This is why we manage our business in accordance with the Triple Bottom Line business principle and consider the financial, environmental and social impact of our business decisions.

2014 marks the 10-year anniversary of the Triple Bottom Line in Novo Nordisk. In 2004, Novo Nordisk’s shareholders voted to amend the company’s Articles of Association to make the Triple Bottom Line an integral part of Novo Nordisk’s objectives.

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