

Replacement and Reduction examples from Novo Nordisk

22nd European Congress on Alternatives to Animal Testing, 10-13 October 2019, Linz, Austria

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Outline of presentation

- Facts on diabetes
- Novo Nordisk's approach to Replacement
- An example of a full Replacement achievement
- Examples of partial replacement

Novo Nordisk at a glance

Novo Nordisk is a global healthcare company with 95 years of innovation and leadership in diabetes care.

This heritage has given us experience and capabilities that also enable us to help people defeat other serious chronic diseases: haemophilia, growth disorders and obesity.



PRODUCTS MARKETED IN
170 COUNTRIES



RTM PUSANT 2020 - Session 9.1
AFFILIATES IN COUNTRIES 80



R&D CENTRES

IN CHINA, DENMARK,
INDIA, UK AND US



OBESITY



EMPLOYS APPROXIMATELY

43,200 PEOPLE

STRATEGIC
PRODUCTION SITES

IN BRAZIL, CHINA, DENMARK,
FRANCE AND US



GROWTH
DISORDERS



APPROXIMATELY

207,000

SHAREHOLDERS

DKK 112
BILLION
IN TOTAL REVENUE



SUPPLIER OF NEARLY
HALF OF THE
WORLD'S INSULIN

29,200,000

PEOPLE USE OUR
DIABETES CARE PRODUCTS

TODAY, 425 MILLION PEOPLE HAVE DIABETES.¹
BY 2045, IT IS ESTIMATED THAT

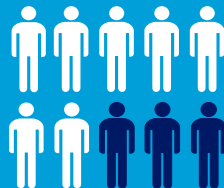
736 MILLION

PEOPLE WILL HAVE DIABETES GLOBALLY²



1 IN 2

PEOPLE WITH TYPE 2 DIABETES DO
NOT KNOW THEY HAVE IT¹



7 in 10

PEOPLE WITH DIABETES DO NOT ACHIEVE
DESIRED TREATMENT OUTCOMES³

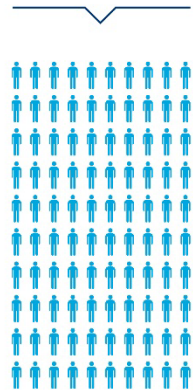
4 MILLION

DEATHS ARE CAUSED BY DIABETES
ANNUALLY¹

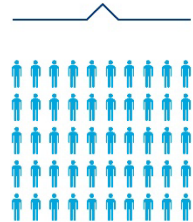


The one rule we need to change

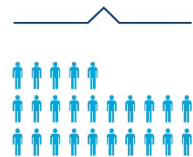
OF THE
ESTIMATED
425 MILLION²
PEOPLE WITH
DIABETES...



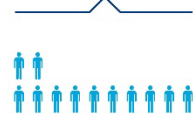
ABOUT
50% ARE
DIAGNOSED...



OF WHOM
ABOUT 50%
RECEIVE
CARE...



OF WHOM
ABOUT 50%
ACHIEVE
TREATMENT
TARGETS...



OF WHOM
ABOUT 50%
ACHIEVE DESIRED
OUTCOMES.



‘The Rule of Halves’¹ illustrates the global diabetes situation. Only around 6% of people with diabetes live a life free from diabetes-related complications.

*Actual rates of diagnosis, treatment, targets and outcomes vary in different countries.

1. Hart JT. Rule of Halves: implications of increasing diagnosis and reducing dropout for future workload and prescribing costs in primary care. Br J Gen Pract 1992; 42(356):116–119.
2. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. International Diabetes Federation; 2017.

Replacement and the EU Directive

- Recital 10:
 - However, this Directive represents an important step towards achieving the final goal of full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible to do so.
- Recital 11:
 - When choosing methods, the principles of replacement, reduction and refinement should be implemented through a strict hierarchy of the requirement to use alternative methods.
- Article 27
 - Tasks of the animal-welfare body
 - advise the staff on the application of the requirement of replacement, reduction and refinement, ...
 - follow the development and outcome of projects, ... identify and advise as regards elements that further contribute to replacement, ...

Novo Nordisk's approach to Replacement

- Why is Replacement so difficult?
 - To replace an animal model you must understand the scientific barriers.
 - Each study has its own nature and objective.
 - In-vivo scientists and scientists applying non-animal methods are often located in different areas of the organization. Knowledge and communications as well as 'match-making' is required.
 - It takes time and resources to develop replacement methods.
 - Legal requirements on the safety of a product are based on information from animal studies. Changing this in a global setting is a long term process.

Novo Nordisk's approach to Replacement

- Novo Nordisk reviews animal models on a continuous basis for replacement with in vitro methods and uses human cells and tissues instead of living animals whenever possible.
- Replacement workshop

Idea storming catalogue
Based on the replacement workshop
June 2016



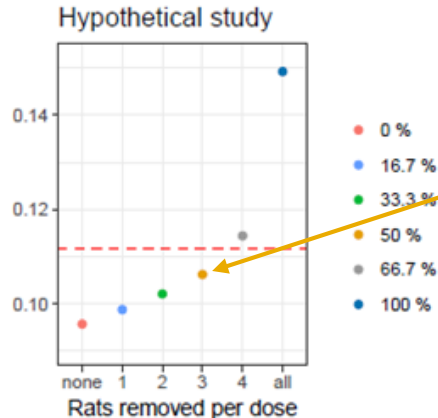
Topic	Subtopic	Feasibility (low, medium, high)	Time horizon
Support functions	Establish a replacement focus group	high	2017
	Science days and workshops	high	running
	Collaborations	high	running
Identify simple readout projects that can be replaced by in vitro methods	Find a biomarker to replace the acute readouts on clotting time		
	Blood glucose in vivo read outs		
	GH in vivo read outs		
	UCP-1 brown fat	high	2017
Screens for side effects	Pigmentation assay		
	Injection site reactions		
	Use of lower species		
Optimise existing in vitro systems	Replacement of some SC administration studies by the Sirius	High	
	Sensor system or similar technology		

An example of a full Replacement achievement

- Aim: removing authorities' mandatory requirement for quality control of marketed products in living animals.
- Efforts were initiated in 1999.
 - A total of 11 in-vivo tests of marketed products could be replaced by non-animal tests.
 - The number of used animals were gradually reduced from +13,000 per year in the 1990's to 2,078 in 2000 to 772 in 2010. By 28 November 2011, the goal was finally achieved, and Novo Nordisk conducted the last in vivo tests for quality control of its marketed products.
- A group of dedicated employees (13 departments) from across the organization, ranging from science over Quality Assurance to Regulatory Affairs, including R&D management participation in negotiations with authorities.
- It required determination, performing extensive research and collaborating with authorities around the world.
- Novo Nordisk has subsequently implemented procedures to ensure that no more animal tests will be required by the authorities for quality tests of already approved products.

Use of historical controls to reduce current controls in preclinical clamp studies

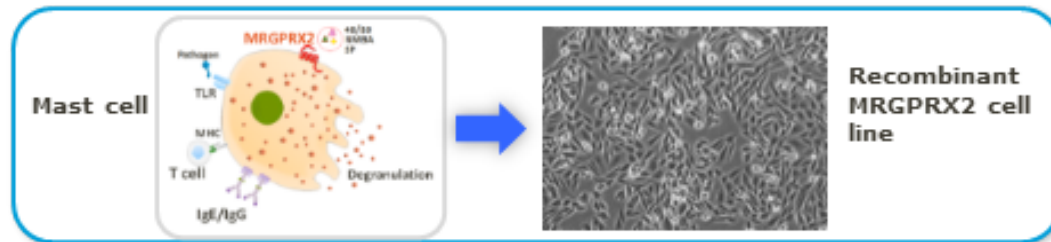
- By investigating 59 historical preclinical clamp studies performed in rats, it was revealed that the reference insulin used in the control rats behave similarly across the studies
- A statistical model that takes historical information into account was applied.
- Using this model, in a future study we will be able to reduce the number of control rats with around 50% without compromising on uncertainty compared to the usual practice.



As the yellow dot is not exceeding the red dotted line in any of the studies, we can thus remove at least 50% of the control rats without compromising on uncertainty compared to the past practice.

***In-vitro* prediction of in vivo pseudo-allergenic response via MRGPRX2**

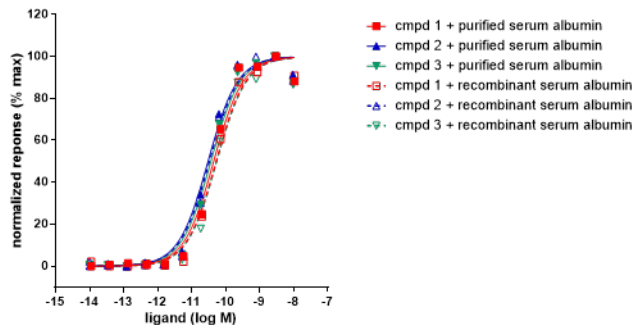
- Some compounds caused injection site reactions after repeated dosing in rodents due to a pseudo-allergic response caused by histamine release.
- Literature reports suggested that activation of the mast cell receptor MRGPRX2 induces the pseudo-allergic response.
- Internal in vitro studies showed a correlation between injection site reactions in rodents and activation of MRGPRX2 of these compounds.
- In vitro screening was implemented using an assay with recombinant expressed MRGPRX2 as a substitute for post-mortem injection site evaluation.



The in vitro assay replaced post-mortem injection site evaluation in rats

Recombinant Serum Albumin Replaces Purified Serum Albumin In Vitro

- Serum albumin is an important reagent in our in vitro assays because it allows us to better estimate the biological effect of the interaction of our drug candidates with the major protein in blood.
- We have replaced the protein purified from mice with a recombinant version produced in yeast.
- The recombinant serum albumin is comparable to the purified protein as shown in one of our typical assays.



The data produced with recombinant serum albumin is equivalent to that produced with purified serum albumin.

Pharmacokinetic results without animal studies

– predictions based on modelling on historic *in vitro* and *in vivo* data

- Pharmacokinetic (PK) studies are studies in drug discovery performed in animals to determine the *in-vivo* distribution, clearance and elimination of potential drug candidates.
- The predictive pharmacokinetic rat model was based on intravenous PK data for more than 1000 potential drug candidates tested in rats over a period of 10 years and data from human receptor affinity assays for the same drug candidates.



Use of human receptor affinity assays in combination with mathematical modelling instead of animals to obtain pharmacokinetic results.

Grey cloud shows cross-validation of training dataset (historical data), blue dots are new drug candidates

A collaborative effort

- EFPIA - The European Federation of Pharmaceutical Industries and Associations
 - Connecting healthcare across the industry and stakeholders to implement the 3Rs



Putting animal welfare principles and 3Rs into action

European Pharmaceutical Industry Report 2019 Update



Beyond Compliance

Practice Science Training

Leading by Example

Sharing Enforcing

Open Communications

Dialogue Reporting

https://www.efpia.eu/media/412869/efpia-report-2019-putting-animal-welfare-principles-and-3rs-into-action_updated.pdf

Acknowledgements

- Thank you - to my Novo Nordisk colleagues:
 - Thóra Brynja Bödvarsdottir
 - Stine Øvlisen
 - Christian Lehn Brand
 - Linu M. John
 - Kristian M. Bendtsen
 - Sif Groth Rønn