

Novo Nordisk

A focused global healthcare company

Defensive seminar in Copenhagen
Focus on Drug Delivery
September 2002

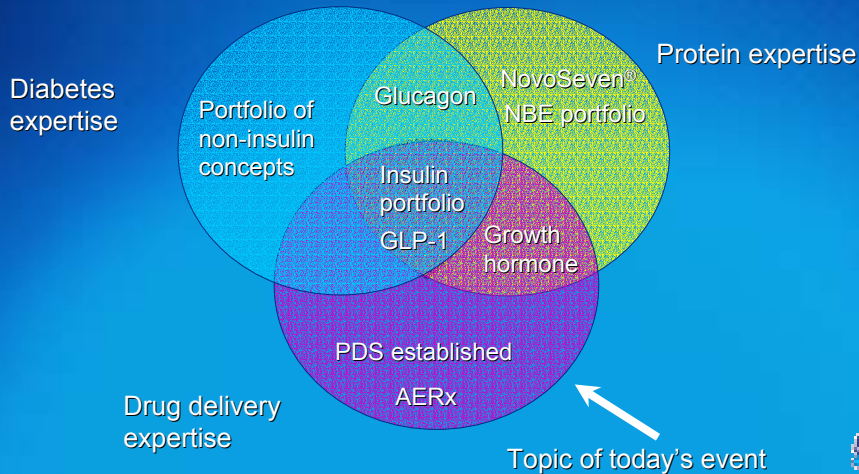


Agenda

- Drug delivery – an introduction
- Novo Nordisk and drug delivery
- Drug delivery in diabetes care - insulin
- Selected potential future concepts
 - Gene therapy
 - Islet replacement



Novo Nordisk's core competencies



Why will new means of drug delivery be of interest?

- Increasing number of proteins being approved by FDA → Need for novel techniques to deliver proteins
- Drug delivery technologies are increasingly being viewed by drug developers as an attractive route to develop differentiated products; also for off-patent proteins
- Increased scope for branding and (in EU) also marketing
- Patients demand increasingly convenient protein delivery
- Convenient delivery drives compliance = interest of payers/society



Where is “drug delivery” useful?

New means of drug delivery are useful for eg the following purposes:

- Frequency of dosing (ease of dosing)
 - Insulin, growth hormone etc.
- Short half-life (possibility of prolongation)
 - Insulin, growth hormone etc.
- High systemic toxicity (causing side effects)
- Expensive drugs
 - Increased bioavailability leading to less waste
- Home/ambulatory treatment



Medical errors can be addressed by devices

- UK Government report from June 2000 on medical errors:
 - Around 1 in 10 people admitted to hospital will be harmed every year
- US Institute of Medicine estimate:
 - >100,000 deaths annually in the US due to medical errors
 - 30-50% of all prescriptions are taken incorrectly
 - 11% of all hospital admissions are due to improper drug administration



Can to some extent be addressed by new delivery technologies



Drug delivery – patient focus

- Medicine and devices
- Education and information
- Diagnosis and monitoring
- Intelligent systems



Scope for individualised treatment and compliance monitoring of patients



Factors affecting drug bioavailability

Physiological factors

Physico-chemical factors

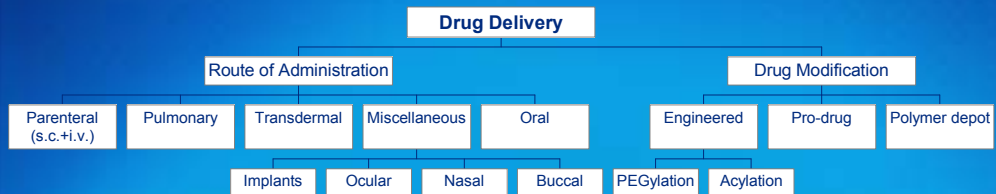
Systemic absorption

Formulation factors

Deposition factors



Drug delivery routes



Delivery preference

| Priority | Patient's preference for route of delivery |
|----------|--|
| 1 | Oral solid (tablet, capsule) |
| 2 | Liquid |
| 3 | Transdermal patch or inhaled |
| 4 | Injection |
| 5 | Infusion |

Source: Credit Suisse First Boston (ref. Scrip)



Delivery preference: Priority no. 1 vs. no. 5

Infusion – no. 5:

- Fast action
- No bioavailability issues
- Cumbersome and poorer patient compliance
- Fast clearance of drugs

Oral (tablets, capsules) – no. 1:

- Ease of administration
- Patient compliance
- Exposure to acidic pH
- Degradation by enzymes
- Poor absorption of large molecules



Novo Nordisk in drug delivery

• Novo Nordisk's technological core competencies:

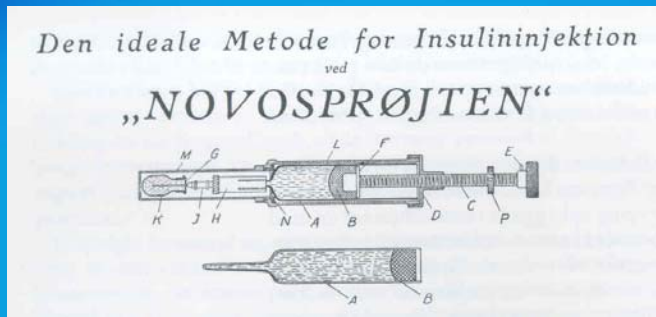
- Molecular biology
- Protein chemistry
- Biologics development
- Large-scale production
- Drug delivery systems

- The challenge is to leverage these competencies to the benefit of Novo Nordisk



Drug delivery in diabetes care - insulin

- Insulin is extracted from bovine pancreases
- Patients, however not all, are successfully treated
- In 1924 the 'Novo Syringe' for injection of insulin is developed
- Novo Nordisk enters a long search for the ideal insulin therapy



Novo Nordisk's drug delivery ambition

*One new delivery system
every year!*



Challenges within insulin therapy

- Bioavailability with/without absorption enhancers
 - Absolute
 - Variability
- Timing and pharmacokinetic profile
 - Onset of action
 - Basal vs. bolus requirements
- Safety and specificity of absorption enhancers
 - Tissue damage
 - Influx of toxins, pathogens and other environmental hazards



Novo Nordisk's devices in diabetes care



Devices Important to Novo Nordisk

↑ **total insulin market**

- facilitate intensification & initiation

↑ **market share**

- differentiation
- clear competitive advantage

↑ **profitability**

- leverage price premiums
- more profitable than vials

Part of NN Vision
(Show leadership, commitment, care, control)



Modern Insulin Pen and Dosers

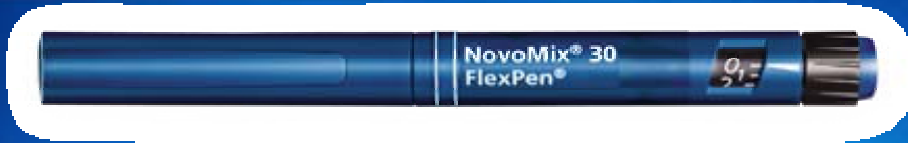
↑ **Simple & Convenient**

↑ **Compliance**

↑ **Control**



FlexPen® – currently being rolled out



- Marketed together with NovoMix® 30
- Perfect for insulin initiation, GP's, passive patients
- Enhanced safety – large clear scale & visual confirmation
- Enhanced simplicity – single-step dose setting & easy dose correction
- Discreet, pen-like & portable

NovoMix 30 FlexPen[®]
(Biphasic insulin aspart)



InnoLet® – The insulin doser that enables patients with complications to manage insulin therapy

- Enables people with eyesight problems to manage insulin therapy
 - Most legible dose-selector scale
 - Large clock-like dial
 - Enables people with manual dexterity problems to manage insulin therapy
 - Compact size and large push button
 - Support shoulder
 - Low push button resistance
- Enables people with difficulty in learning new techniques to manage insulin therapy
 - Familiar kitchen timer-like interface



Pulmonary delivery – the next step



- Historical standard

1921



- Patient friendly
- Single unit increments
- Precision dosing

1980s



- Patient friendly
- Single unit increments
- Precision dosing
- Needle free

>2005



Pulmonary devices in diabetes care

- Pulmonary delivery of systemic drugs is emerging as a viable, rapid absorption route; also for large molecules
- Long-term safety could still be an issue for certain compounds, notably growth factors, but those safety concerns may diminish as more human data is generated
 - FDA's reaction to long-term exposure of insulin to the human lung still awaited



AERx NN1998 – Pulmonary Insulin

☛ Pulmonary insulin opportunity

- ☛ Non-invasive insulin delivery
- ☛ Mainly poorly controlled Type 2 diabetes patients
- ☛ Expanded insulin sales

☛ Product requirements

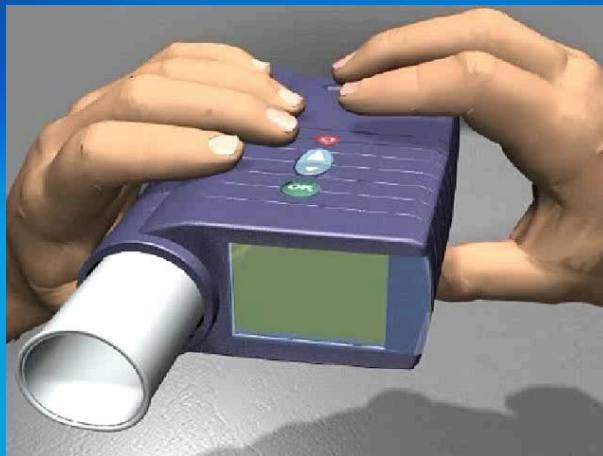
- ☛ Accuracy, precision, dose adjustment
- ☛ Patient friendly device interface
- ☛ Scalable manufacturing

☛ Aradigm is the optimal partner

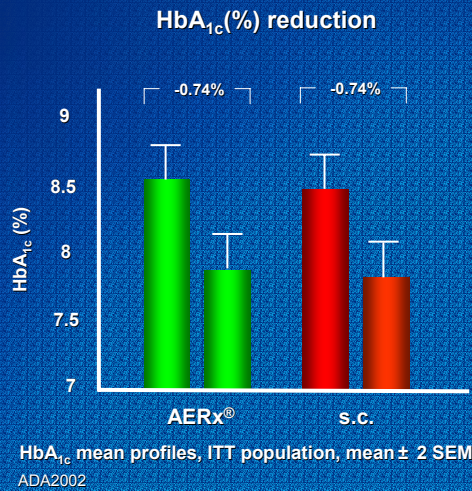
- ☛ Liquid insulin formulation
- ☛ Breath control
- ☛ Increments of single insulin units
- ☛ Performance monitoring



NN1998 (AERx) – How it works



Our inhaled insulin – as effective as injected



Key observations:

- Deep lung deposition of aerosols
- “Breath Check”, one unit increments, highly reproducible delivery
- Rapid-acting profile, one unit increments and patient-friendly features
- 1 oral presentation and 4 posters at ADA
- 3 posters presented at EASD



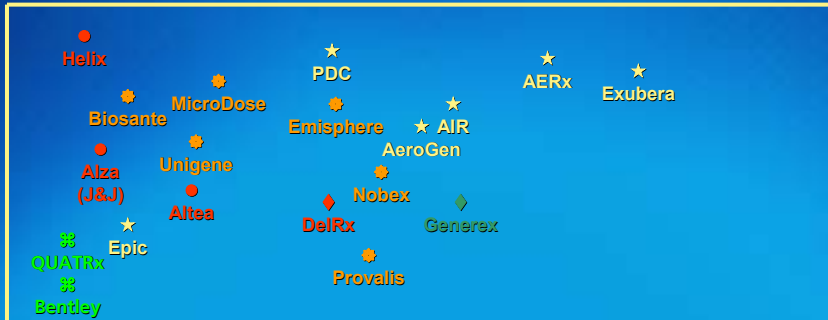
NN1998 (AERx iDMS): Pros and cons

| | AERx® iDMS | Exubera™ |
|-------------------------|---|--|
| • Dosing (per load) | Insulin strip (partial dosing from 2 to 10 UNITS) liquid | Insulin blister (3 UNIT or 9 UNIT blister) powder |
| • Dosing (eq. Units) | 1 UNIT | 3 UNITS |
| • Dosing regime | “UNITS” | “MG” |
| • Breathing pattern | Controlled by “Breath Check” | No control |
| • Mealtime delivery | YES | YES |
| • Compliance monitoring | YES | NO |
| • Absorption enhancers | NO | NO |



Overview, non-invasive concepts

(Development stage, April 2002)



Discovery

Marketing

● = transdermal ★ = oral ◆ = buccal ★ = pulmonary % = Nasal



Selected potential future concepts

Gene therapy and replacement of beta cells



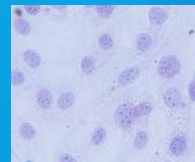
A backgrounder on gene therapy

- Gene therapy involves the genetic modification of cells so that they produce specific therapeutic proteins using gene delivery vehicles called vectors
- For numerous diseases, the product of a single gene can reverse or improve the symptoms of the disease significantly
- Gene therapy has promised much, but has so far delivered no clinical proof-of-concept
- Most gene delivery systems or vectors currently in development have limitations in two areas
 - Safety profile
 - Packaging, delivery and expression of the genes
- The concept is improving as we now have
 - A decade of testing such therapies
 - Improvements in gene delivery systems and their manufacture



Gene therapy in type 1 diabetes: Definitions

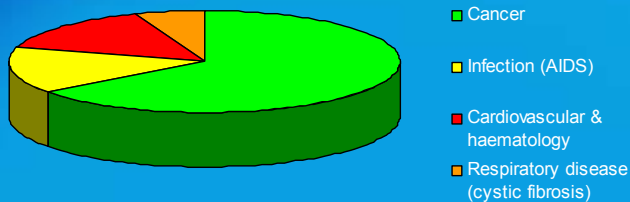
- **Vector-based gene therapy**
 - Genes are inserted in the cells of the patient
 - Safety and efficacy difficult to predict from animal models
- **Engineered endocrine cells**
 - Glucose sensitivity achieved via multi-step genetic engineering *ex vivo*
 - Cells are implanted in patients after careful testing
 - a. Need for encapsulation
 - b. Patients have to receive chronic immunosuppressive medication



Gene therapy - Clinical trials

- Since 1990 approx 425 clinical protocols, involving 3,500*) patients have been approved

Ongoing clinical trials with gene therapy



*) Wood MacKenzie



Gene therapy in diabetes

- Several animal studies suggest that delivery of insulin genes using gene therapy may be better able to mimic the endogenous secretion profiles of insulin from pancreatic beta-cells than conventional pharmacological approaches
 - K-cells and single-chain insulin analogue (SIA),
 - The DNA coding for a genetically engineered insulin analogue is inserted into an adeno-associated virus, and put the entire DNA construct under the control of the promoter region of the L-type pyruvate-kinase gene found in liver cells.
- In general the hope is to test this therapy on humans in four to seven years.



Gene therapy in diabetes (cont)

- If successful, gene therapy could represent a cure for Type I diabetes and could make the use of insulin in these patients unnecessary

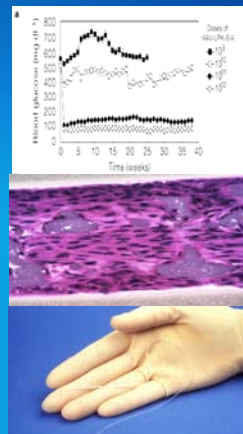
However

- Type I diabetics represent only 5-10% of all diabetics. The gene therapy technique is therefore not for the majority of diabetics and is still 10 years from the market in the best case
- It poses no threat to manufacturers for now



Gene therapy: Novo Nordisk scouts for opportunity

- **Vector-based gene therapy:**
 - Virally-mediated insulin expression in liver cells in diabetic rats and mice
 - Transgenic mice express insulin in gut cells in a glucose-dependent fashion
- **Engineered endocrine cells:**
 - No glucose-dependent engineered cell line with sufficient insulin production
 - Encapsulation techniques from other areas may be used in diabetes



The basic problems of gene therapy

Vector based

- Reproducibility
- Safety
- Proof of concept in man
- Formulation

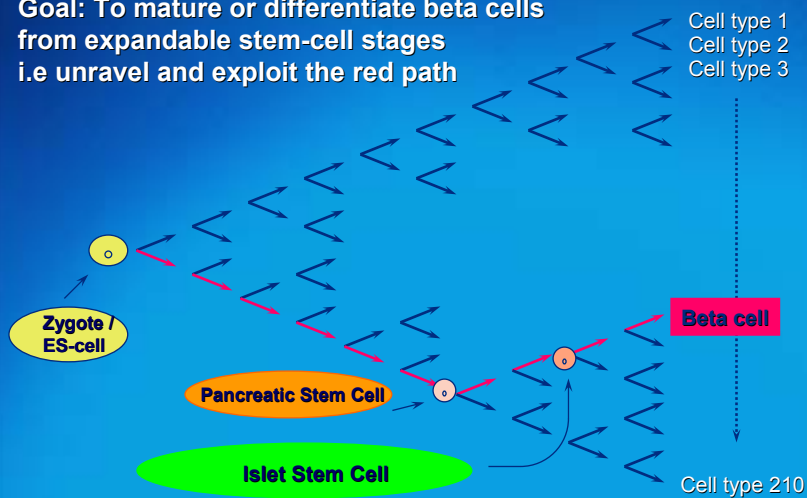
Cell based

- Reproducibility
- Need for immuno-suppression
- Lack of suitable cell lines
- Cell productivity insufficient

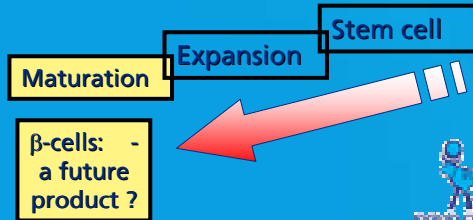
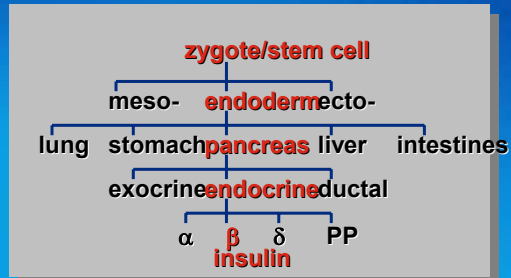
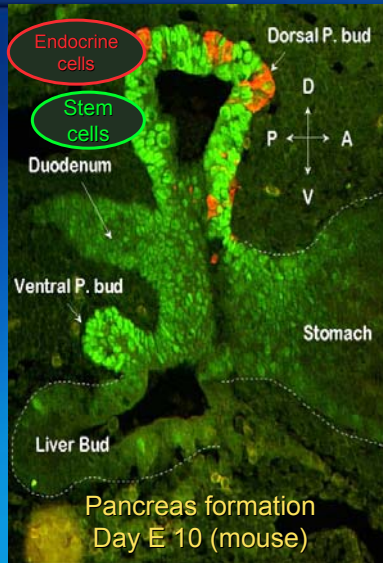


Beta cells differentiated from stem cells

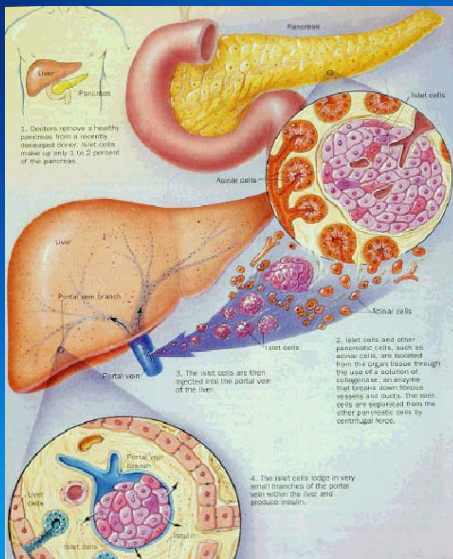
Goal: To mature or differentiate beta cells from expandable stem-cell stages
i.e unravel and exploit the red path



Goal: Mass expansion of β -cells from stem cells



Transplantation of human donor islets re-establishes euglycemia in Type 1 diabetics, but only for the lucky few



- Fifteen patients off insulin for more than 1 year
- New multi-centre US-trial encompassing 40 new patients appears to continue the success, but:
- Life-long immuno-suppression needed
- Much too few organ donors worldwide
- Need for alternative source of functional beta cells

Shapiro et al. N Engl J Med 2000;343:230-8.



Forward-looking statements

This presentation contains forward-looking statements as the term is defined in the US Private Securities Litigation Reform Act of 1995

Such forward-looking statements are subject to risk and uncertainties that may cause actual results to differ materially from expectations, including unexpected developments in the international currency exchange and securities markets, government-mandated or market-driven price decreases for Novo Nordisk's products in the company's major markets and the introduction of competing products within Novo Nordisk's core businesses

These and other risks and uncertainties, are further described in reports filed with the US Securities and Exchange Commission (SEC) by Novo Nordisk and readily available to the public, including the company's Form 20-F, which was filed on 2 May 2000. A Form 20-F for 2000 will be filed by the end of June 2001



Investor Information

Share information

Novo Nordisk's B shares are listed on the stock exchanges in Copenhagen and London. Its ADSs are listed on the New York Stock Exchange under the symbol "NVO". For further company information, visit Novo Nordisk on the World Wide Web at

<http://www.novonordisk.com>

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