SQ Innovation

Furosemide- How to Make a Leading Drug Better and its Use Wider

Pieter Muntendam, MD
President and CEO

9th American
DDF Summit
Drug Delivery & Formulation
September 9 - 10, 2019 | Boston

www.furosemide.com

Pieter Muntendam, MD – Founder and CEO

- 35+ year career in pharmaceutical and device industry
- Early career:
  - Senior management/executive career in leading companies
    - Johnson and Johnson, Glaxo, Organon (now Merck), Millennium
- Entrepreneurial career:
  - 20+ years as CEO
  - Raised >$300M through private, public and strategic financing
  - Relevant predecessor companies
    - CEO SpringLeaf Therapeutics (Boston) –
    - Founder scPharmaceuticals – sc furosemide for worsening heart failure
    - CEO SQ Innovation AG (Zug, Switzerland)

SpringLeaf Therapeutics

scPharmaceuticals

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About SQ Innovation AG

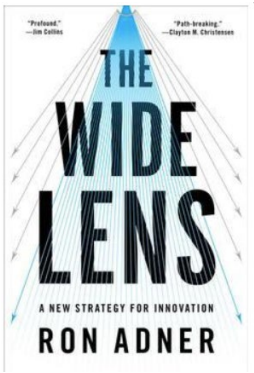
- Recently formed for the purpose of developing novel treatments for subcutaneous delivery
  - Leading Project:
    - Furosemide treatment for fluid overload in heart failure
    - Proprietary high-concentration neutral pH formulation
  - Other Projects:
    - To be announced in Q4 2019
- Fully capitalized through FDA & EU approval
- Partnership with Gerresheimer AG
  - Leading global supplier of primary packaging and drug delivery devices

Our Fascination with Subcutaneous Drug Delivery

- Our Fascination
  - Subcutaneous delivery enables treatment where and when needed and by lay caregivers
  - Subcutaneous delivery by wearable infusors creates a half-life independent pharmacology model
    - The Infusor can provide the desired systemic exposure profile regardless of the elimination half-life
  - Large volume infusors eliminate the need to further concentrate biologicals
    - Reduced development time
    - Reduced pharmaceutical risk

Consider the Eco System

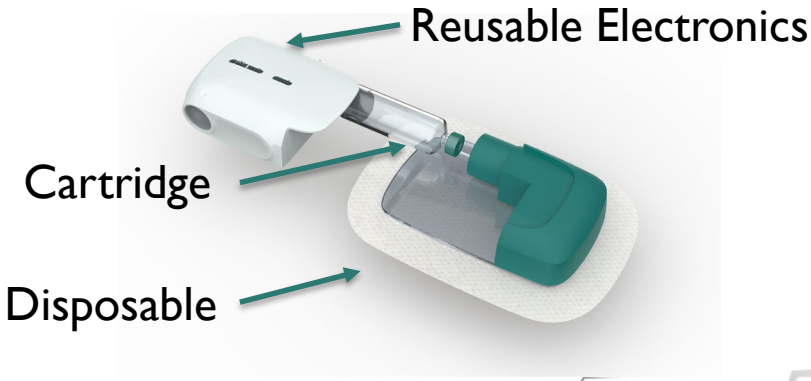
- A drug delivery product requires an enabling ecosystem
  - Infusor
  - Primary container
  - Plunger
  - Accessories
  - Filling equipment
  - Labeling and handling



- Ron Adner book is circulating in our industry to make the point
  - Must read at some companies
  - Many examples in the drug delivery space where this has failed resulting in failures, delays, high cost.

Infusor Archetypes

- "It just needs to get in"
  - Repatha© type – does not matter how slow/fast as long as it is tolerated
- The delivery profile is critical
  - Requires controlled delivery
- Why did we pick the Sensile/Gerresheimer platform?
  - Controlled delivery
  - Cost-effective because of two component structure

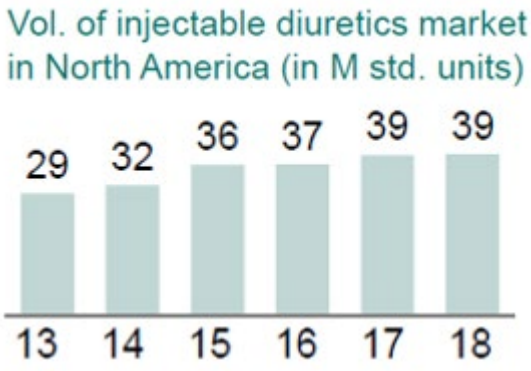


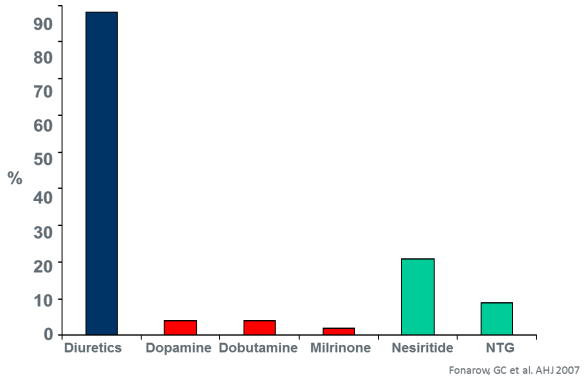
Electronic Controls vs Fluid Path Restriction

- Fluid path restriction has a dramatic effect on drug delivery times
  - Function of diameter and length
  - We were able to achieve a reproducible >2hr delivery time
    - Requires extremely tight (unrealistic) tolerances for the diameters since a slight increase will have dramatic effect on delivery volume
  - Major concern
    - Damage to biological through extreme shear stresses when fluid path restriction is used to slow delivery
- Electronics avoid the shear force concerns
  - Solution needs to be cost-effective which requires some way of re-using the electronic components

Why Furosemide?

- Most widely-used cardiovascular injectable with approximately 40M units in the US alone
- IV furosemide treatment is often the sole treatment a HF patient gets when admitted
- Exceptional economic story
  - An inpatient episode of furosemide treatment costs approximately $20,000 and removes 8.3L fluid (18 lbs)
  - Less than $100 is the cost of the drug
  - Cost per liter of fluid removed is $2,000+
  - Approximately $14b or 3.9% of Medicare budget
- A subcutaneous self-administration of furosemide has the potential to radically change how edema/fluid overload in heart failure is managed.





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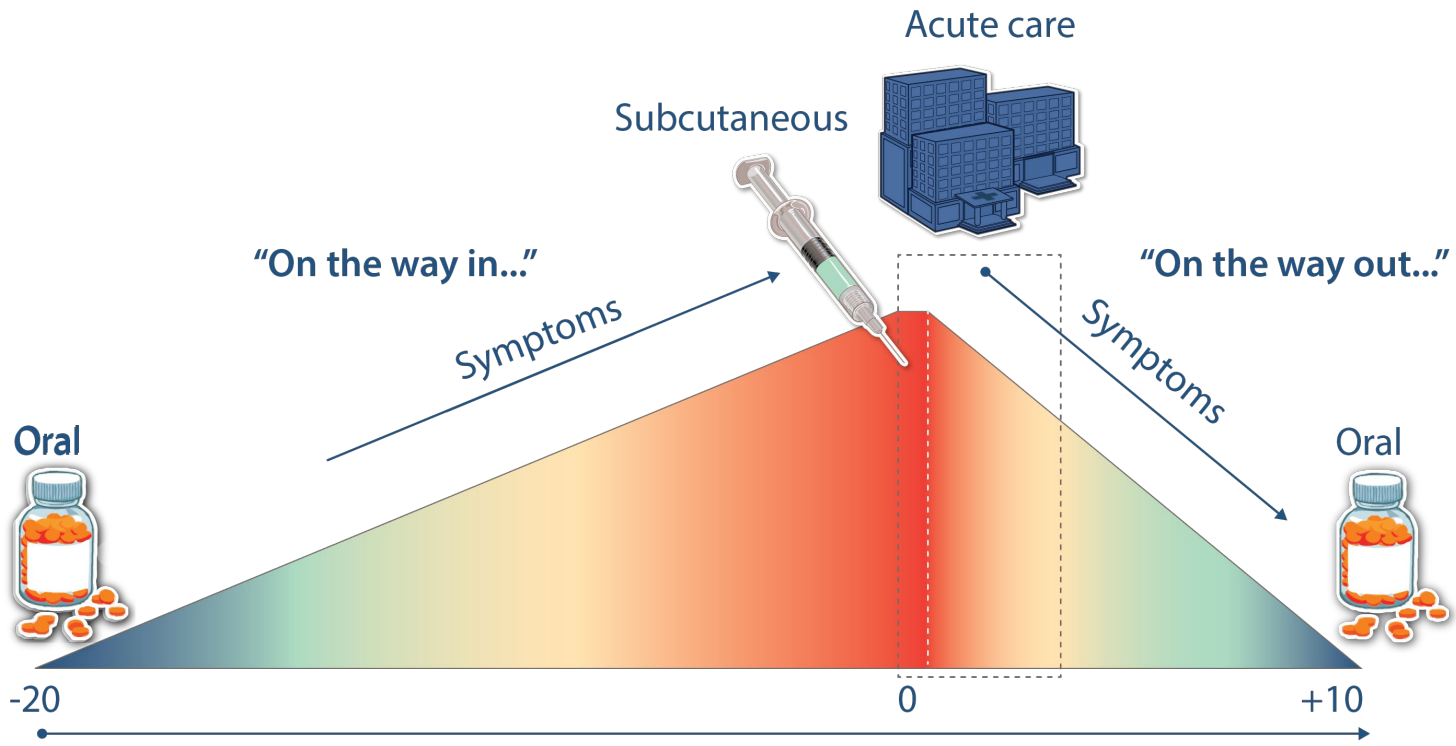
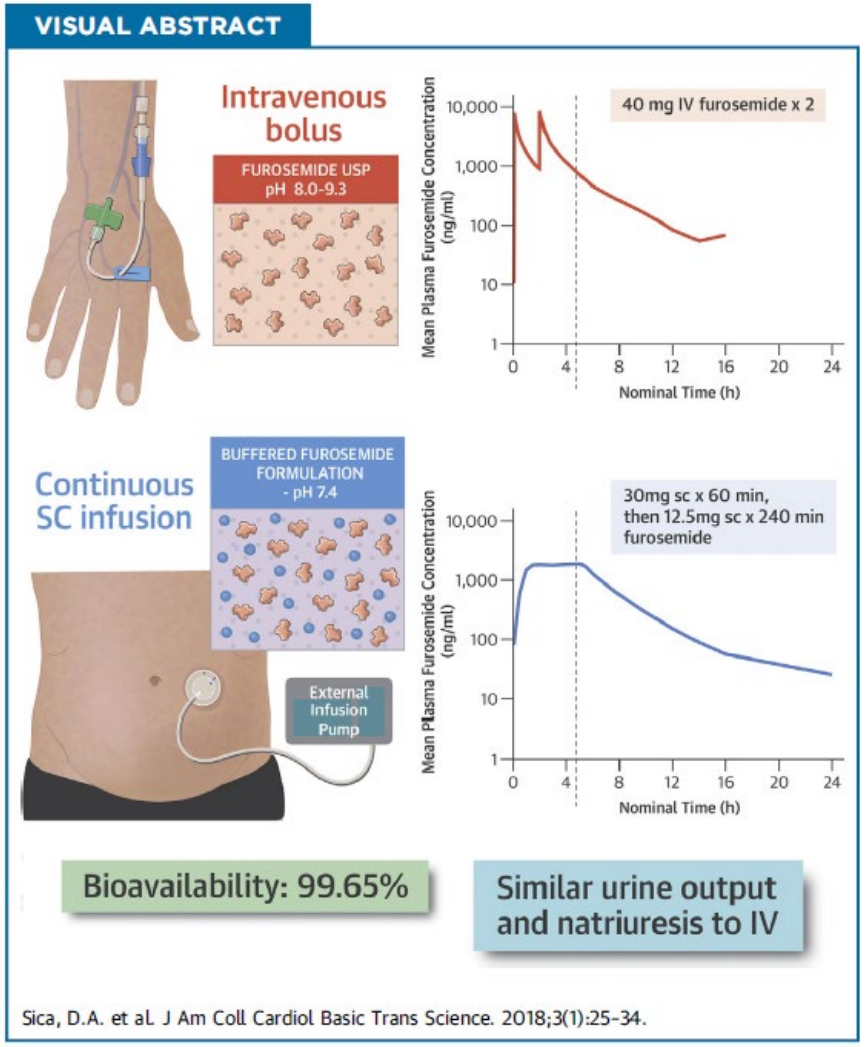
Episode of Worsening

- Now "Oral to IV to Oral"
  - IV almost invariably means in an Acute Care Hospital
- Subcutaneous offers an in-between solution for a patient who clinically does not need to be in an Acute Care setting



How well does this subcutaneous use work?

- Cross-over study using low concentration TRIS-based formulation
  - Complete bioavailability
    - 99.65% vs IV
  - Equivalent diuresis
    - 102%
  - Well-tolerated
- Conclusion: Complete bioavailability and equivalent diuresis



Broad Enthusiasm for the Concept

- Enthusiasm
  - Editorials in leading journals
  - Market research conducted over the past 7 years
  - NICE review
- Primary perceived benefits
  - Avoidance of hospitalizations
  - Reduced cost
  - Reduced patient/family burden
  - Improved medical outcomes

JACC: HEART FAILURE VOL. ■, NO. ■, 2017
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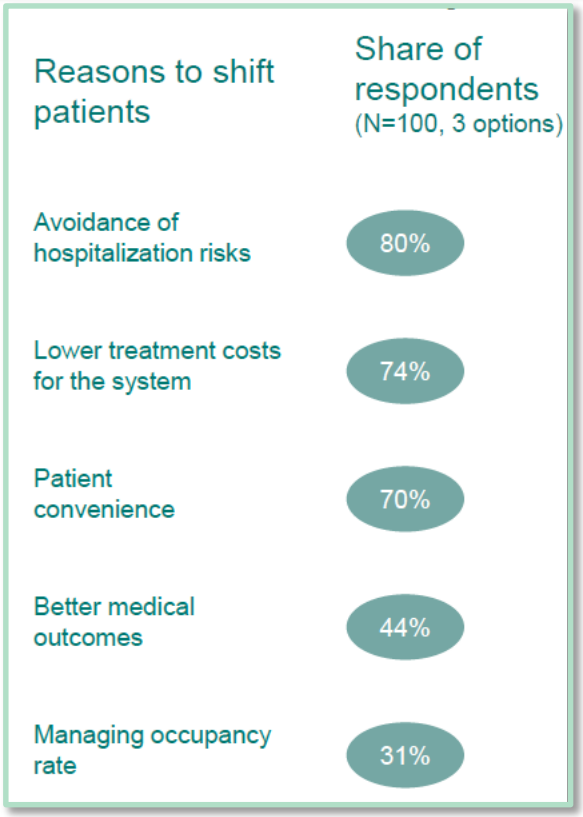
PUBLISHED BY ELSEVIER https://doi.org/10.1016/j.jchf.2017.10.005

EDITORIAL COMMENT

Furosemide Reimagined

Novel Subcutaneous Formulation for a 50-Year-Old Loop Diuretic Agent for the Treatment of Acute Decompensated Heart Failure*

Gary S. Francis, MD, Tamas Alexy, MD, PhD



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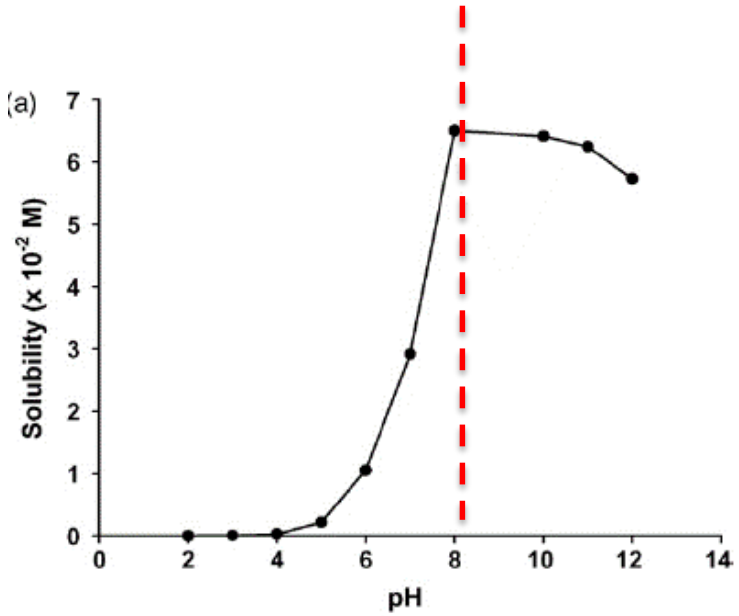
Rationale for New Product Design

- Elimination of need to fill the device from a vial
  - Removal of multiple critical steps, several of them were not intuitive and prone to human error and device failure.
- Work with reduced volume
  - Use of widely available 3 mL cartridges
    - Extensive manufacturing experience with 3mL primary container
    - Cost of goods
- Incorporate industry learnings
  - Several commercial products have become available since we first started in 2012

Requirements for the Pharmaceutical Product

- Primary container:
  - 3mL cartridge to deliver 80mg dose
    - Target 30mg furosemide/mL
- pH: ~ 7.4
- Shelf-life: 24 months at RT
- Biggest challenge is concentration at neutral pH
- Furosemide Injection USP
  - pH 8.0-9.3 – typically formulated around pH 9.0



pH-solubility profile of furosemide in TRIS buffers (0.5M) at 30 + 1 °C.

International Journal of Pharmaceutics 345 (2007) 142–153

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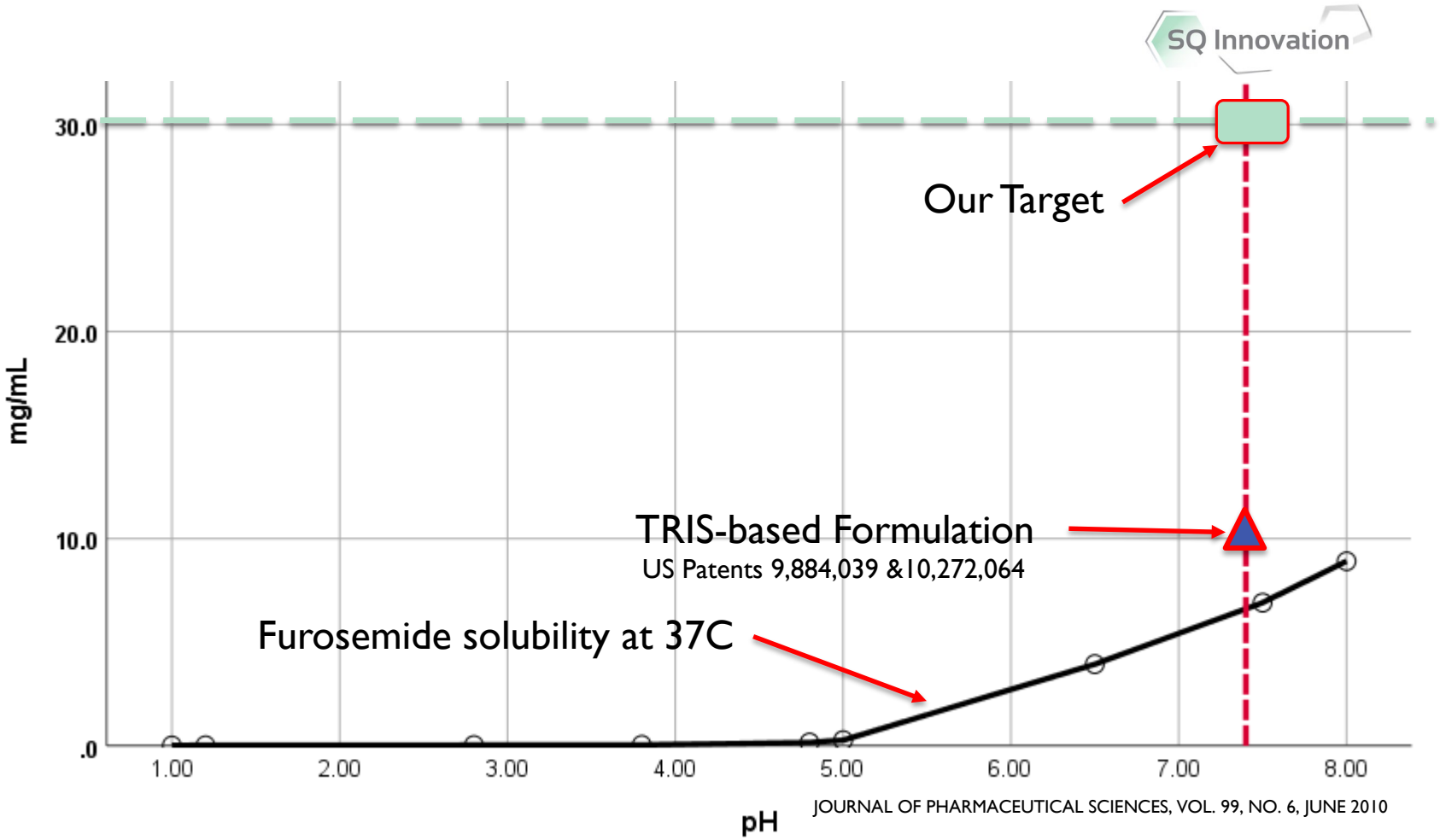
Our Challenge



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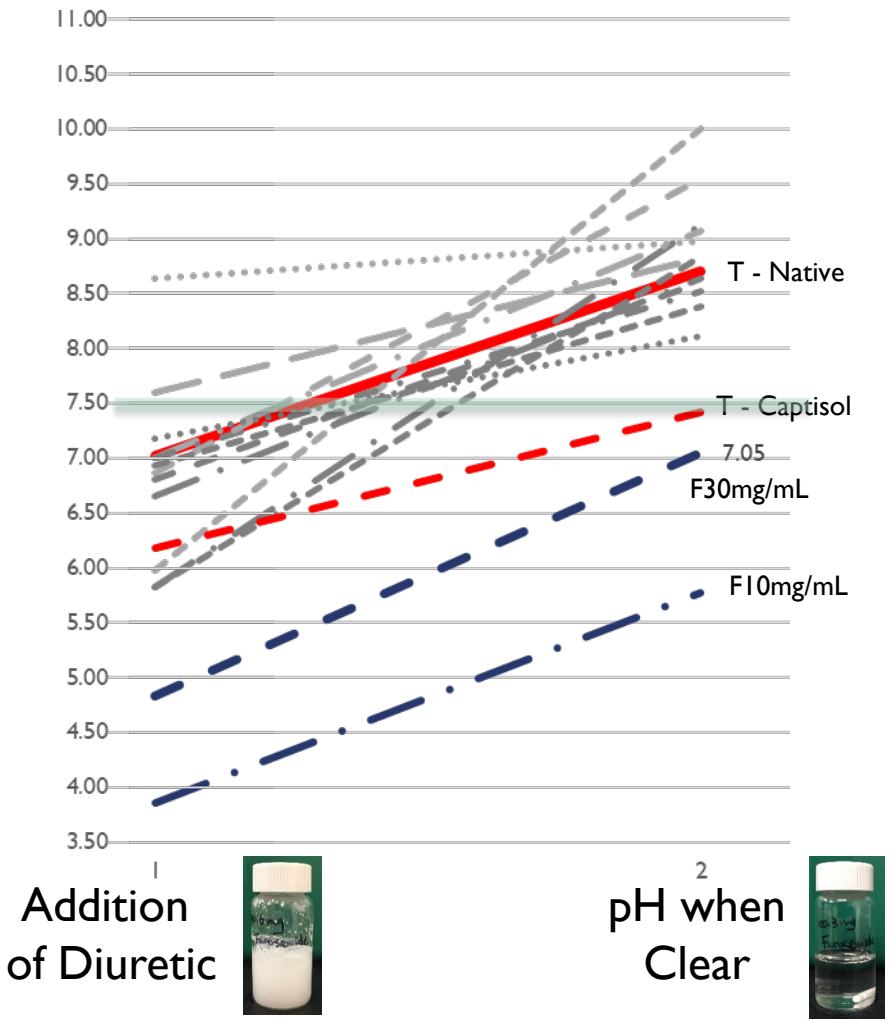
Our Formulation Research

- We screened a long list of buffers and solubilizers (grey lines)
- None had noticeable effect except 40% Captisol which reduced pH at solubility from 8.7 to 7.4
- The Furosemide line was even more dramatic with solubility of 10mg at pH 5.8
- Additional experiments confirmed stability of solution at 30mg/mL with pH of 7.4
- Multiple IP filings



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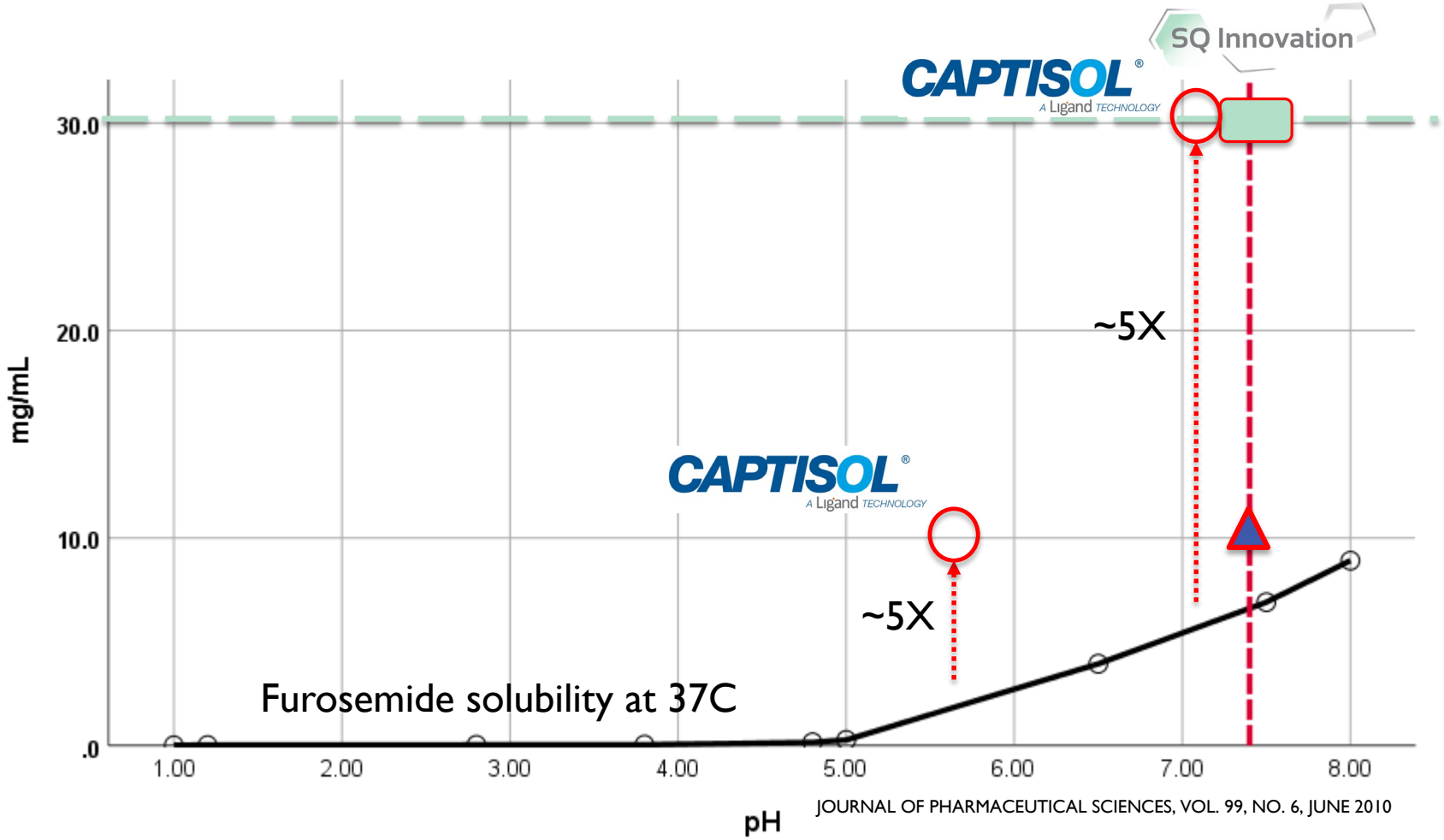
Requirements for Solubility Enhancements

- Non-toxic
- Previously used in FDA approved products

Our Solution

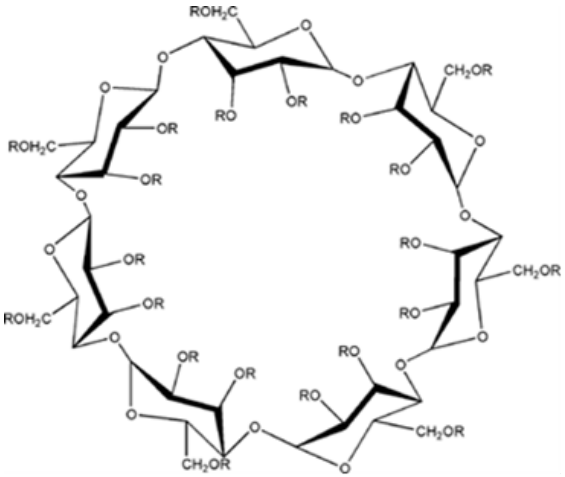
- Captisol gave us approximately a 5X increase in solubility



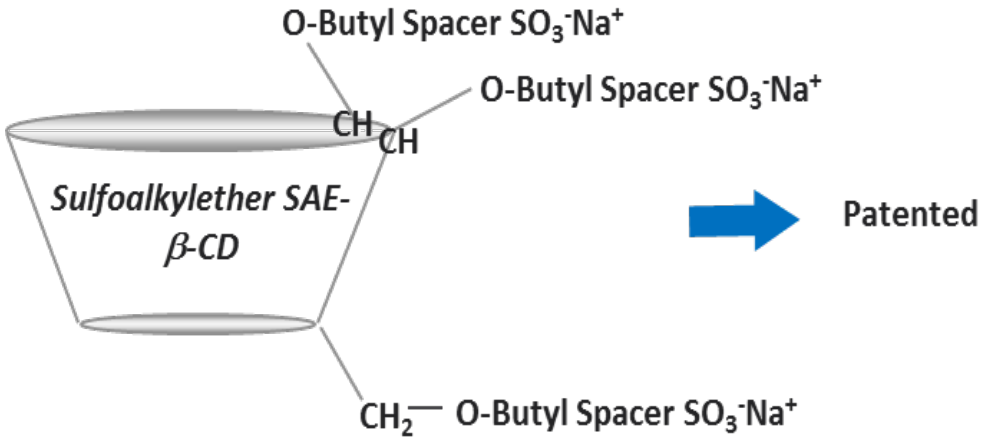
JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 99, NO. 6, JUNE 2010

What is Captisol?

- Captisol
  - A patent protected modified cyclodextrin,
  - Optimized for solubility, stability and bioavailability
  - Excellent safety record



R = H_{21-n} or $(CH_2CH_2CH_2CH_2SO_3^- Na^+)_n$
where n = 6.2 – 6.9



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Approved in Diverse Therapeutic Areas

CAPTISOL® A Ligand TECHNOLOGY

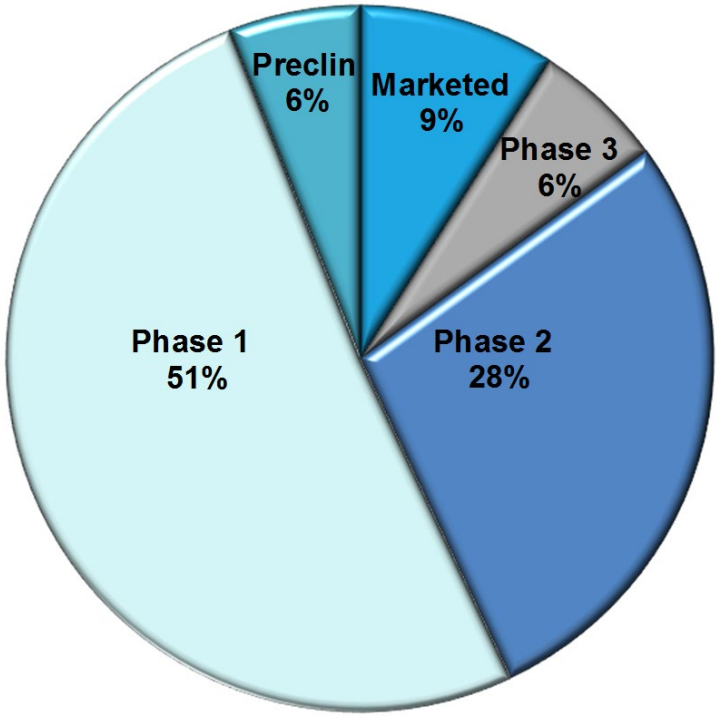
- Captisol® has enabled the development of 11 approved drugs
- Drugs produced by Amgen, Merck, Pfizer, Baxter, BMS, Lundbeck, Melinta and Sage

- Extensive history: Millions of Patients in 60+ Countries have been treated with Captisol containing products since 2001

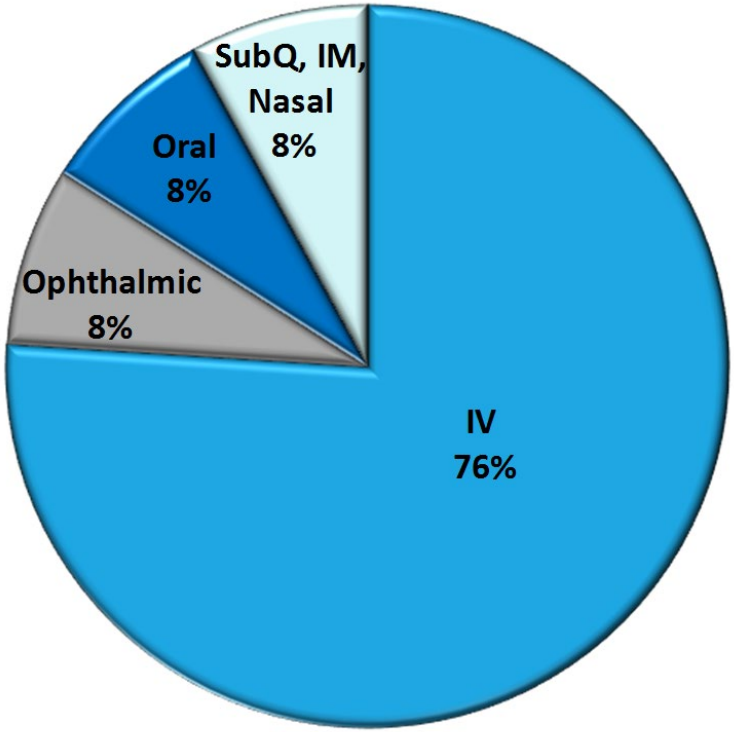
Delivery of Captisol-enabled® Pipeline

CAPTISOL® A Ligand TECHNOLOGY

Stage of Development

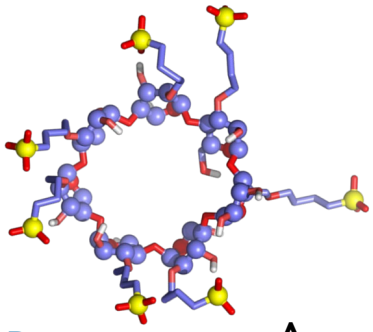


Routes of Administration



Captisol History

CAPTISOL® A Ligand TECHNOLOGY



Approved in Diverse Therapeutic Areas

US Drug Master File

Portugal cGMP Manufacturing Site

Canada Drug Master File

Captisol USP-NF Monograph

Ligand acquires CyDex

Subterranean US Distribution Established

Ireland cGMP Manufacturing Site (additional site)

Japan Drug Master File

China Drug Master File

Ireland Commercial Distribution Established

Cumulative cGM Production

2000 2002 2004 2006 2008 2010 2012 2014 2016 2018

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Summary

- The subcutaneous space is open for business.
  - It offers many advantages over IV, but requires a suitable infusion/injection device
  - There are no approved drugs in primary containers of 5mL or greater
  - For poorly soluble compounds beta-cyclodextrins offer an attractive option to enable subcutaneous delivery
    - The proprietary Captisol offers a number of attractive benefits:
      - Proven FDA inspected supply chain
      - Robust tox/information package
      - Additional IP

CAPTISOL® A Ligand TECHNOLOGY

Thank You

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Our Challenge