

Sol Pompe Disease Argentina

Keeping the Patient's and Caregiver's Experience in Mind

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Evolution of Biologics Over the Last Decade

**Biologics represent a dominant share
of total pharmaceutical sales**

Worldwide biotech sales grew from \$36B to \$163B

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Number of biotech acquisitions by Big Pharma increased 5X from 15 to 75

Today's Reality Informs Strategy

Entire Healthcare Ecosystem is Under Pressure

Big Pharma - Patent Cliffs, Pipeline Challenges

- “Do It Alone” approach is no longer working
- Reliance on M&A, partnerships, globally distributed operations
- Downsizing of fixed infrastructure, outsourcing
- Shifting operations to tax advantaged jurisdictions (“tax-inversions”)

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Virtual Biotechnology Companies Now Operating

As much as ~ \$1.8B of VC funding
(1/3 total in US)

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Crowd-Funding for Early Stage Discovery

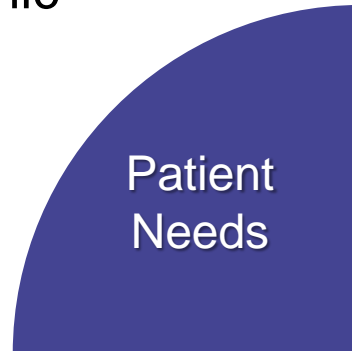
Equity based approach from non-
accredited investors still not
implemented by SEC; Donation
based approaches operative



Today's Reality Informs Strategy

Entire Healthcare Ecosystem is Under Pressure

- Acute to chronic
- Personalized
- Generics

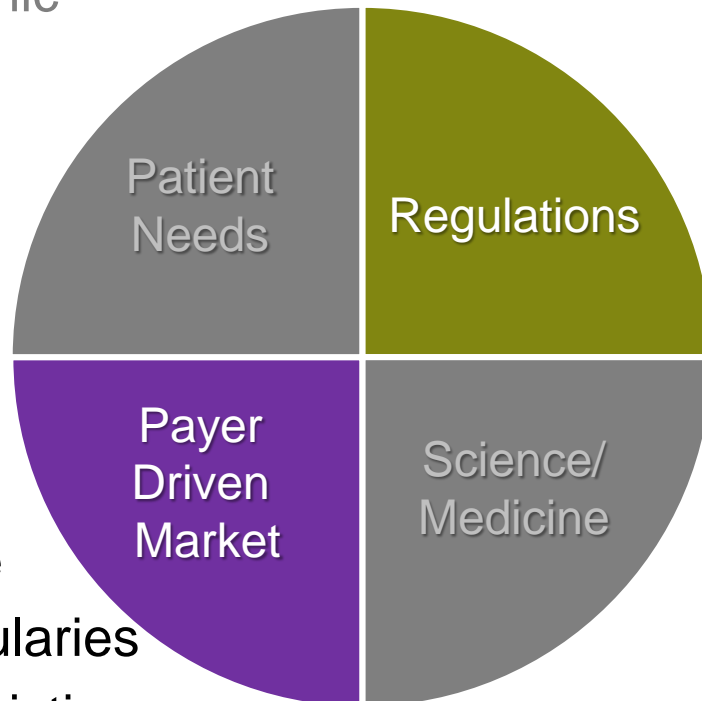


- Low predictability
- Focused on few targets
- Low success rates
- Low overall efficiency

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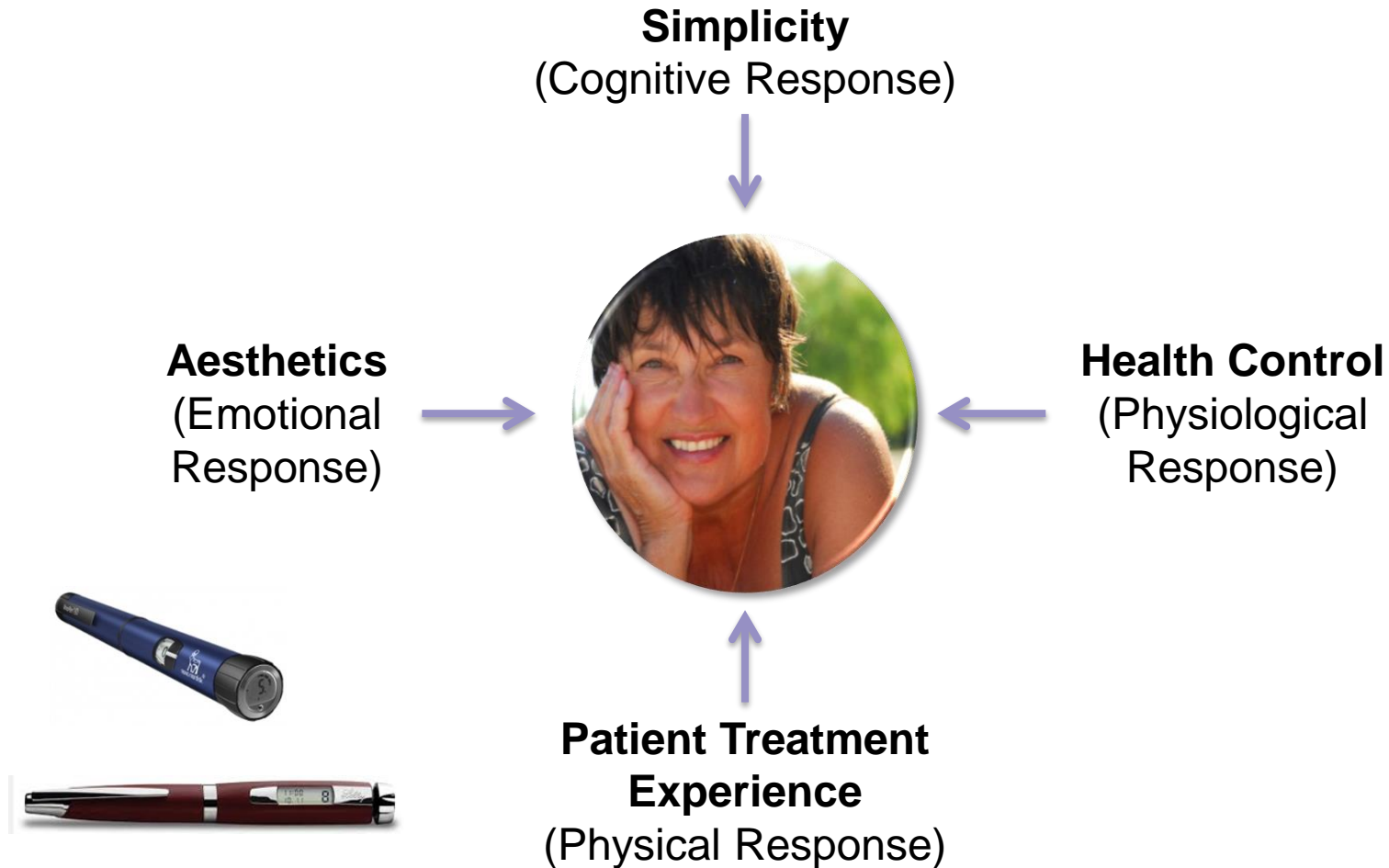
- Differential medical value
- Rise of Formularies
- Payment restrictions
- Price controls

- Increasing burden
- Higher safety margins
- Post-marketing requirements
- Longer R&D cycles

- Low predictability
- Focused on few targets
- Low success rates
- Low overall efficiency

Consider What a Patient Experiences

Inform Competitive Advantage and Product Acceptance



Consider What a Patient Experiences

Drug Access is Not a Given

USA – Disseminated Approach

- Numerous Payors with different Formularies, cost sharing, tiering
- High subscriber turnover
- 2-3 year benefit horizon; need to be competitive
- If drug is high cost/clinical, no reimbursement or higher price tier
- Increasing patient out of pocket payments

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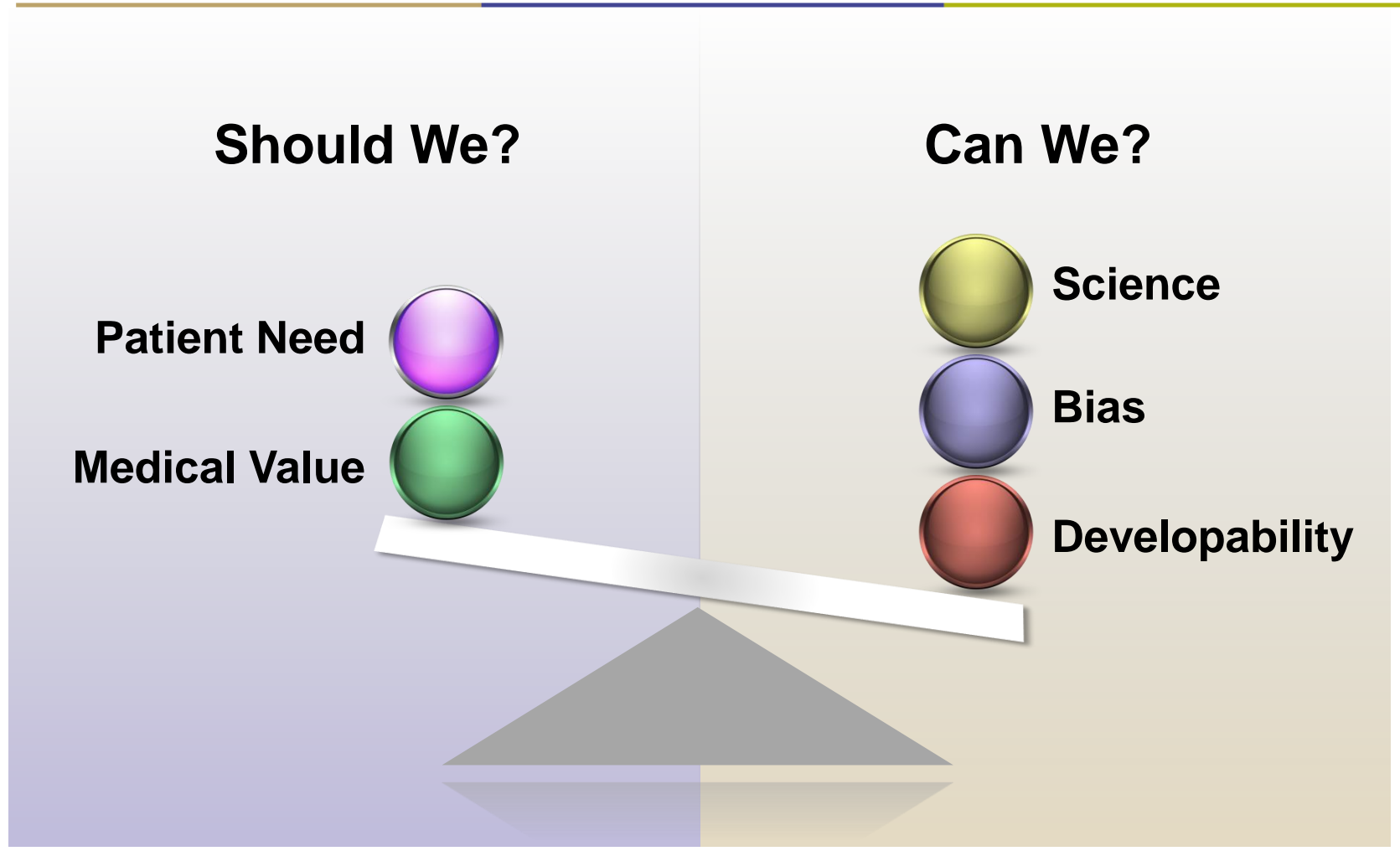
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EU – Centralized Approach

- Managed at the National Level
- Formulary decisions based on cost effectiveness, medical value, workforce productivity, etc.
- Long term benefit horizon
- If Health Authority decides drug is not cost effective, no reimbursement

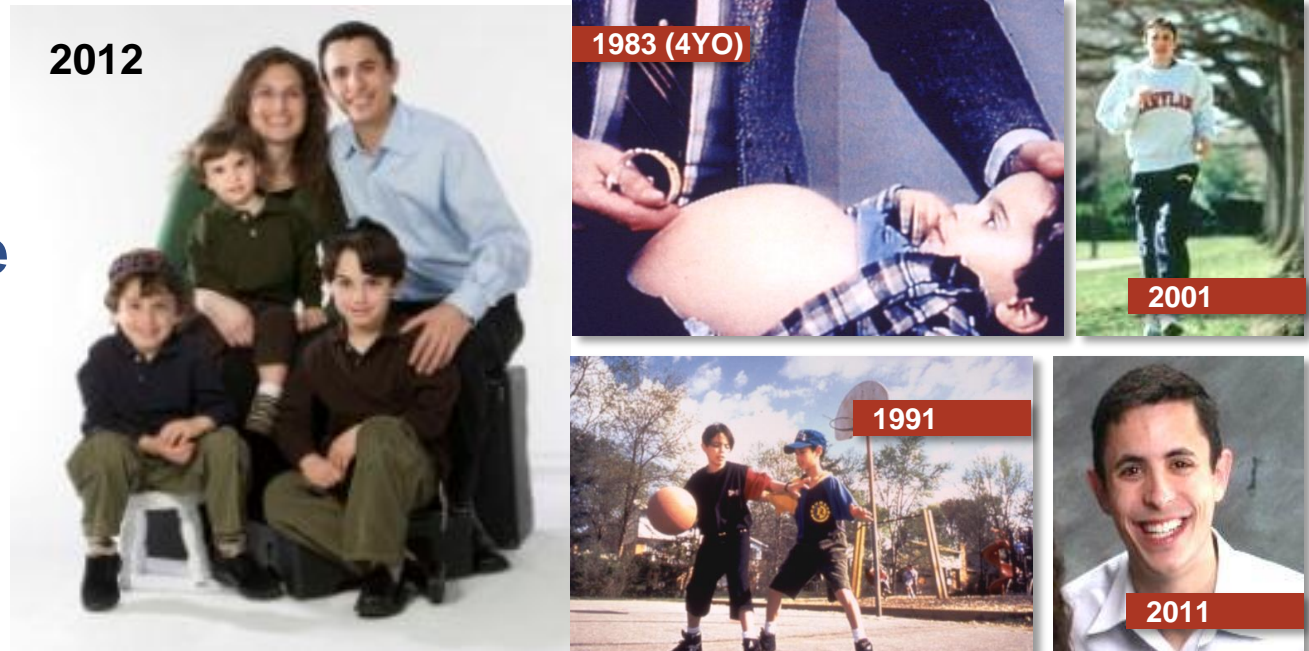
So What's a Solution?

Need to Capture More Value from the R&D Process



How to Capture More R&D Value? Lessons from Genetic Disease Therapies

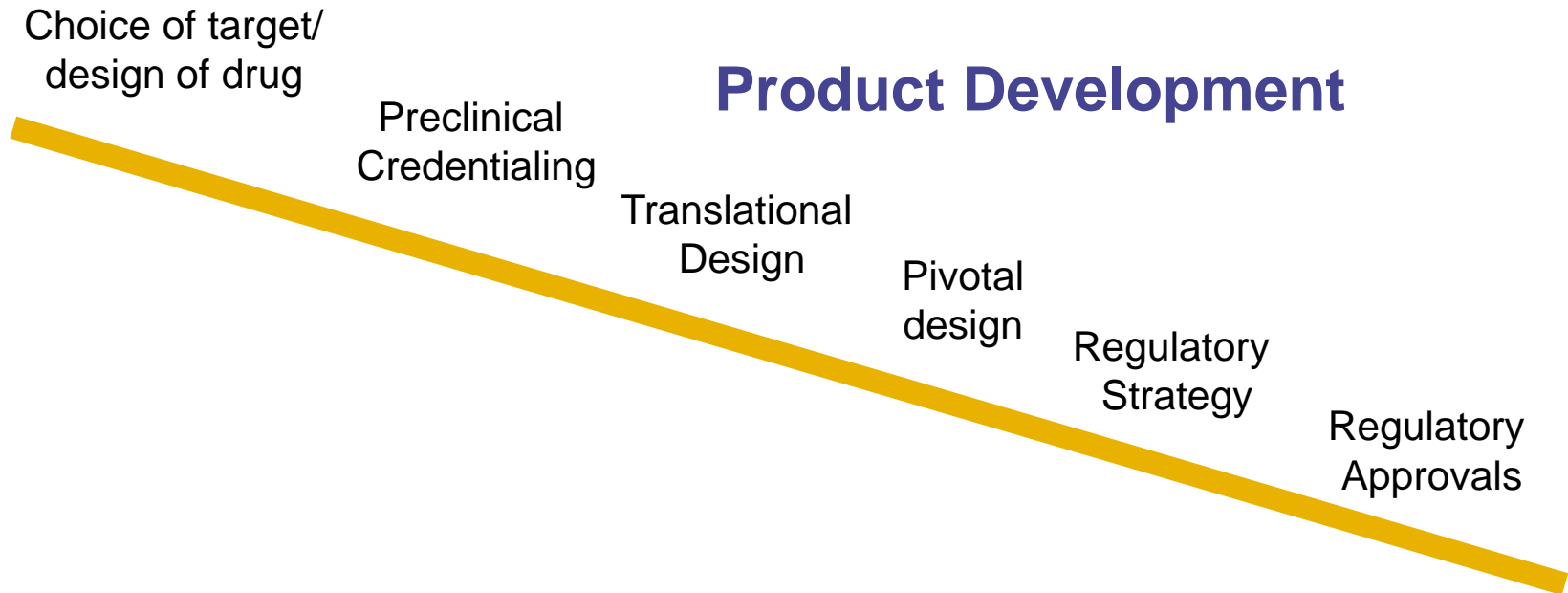
“I believe people like us with rare diseases can live normal lives.”



If disease mechanism is well understood –
drug development risk is reduced and
if there is an outstanding medical need, then
the probability of creating a transformative medicine is higher

Earliest Choices are Critical

'Value Lever' Concept to Drug Development

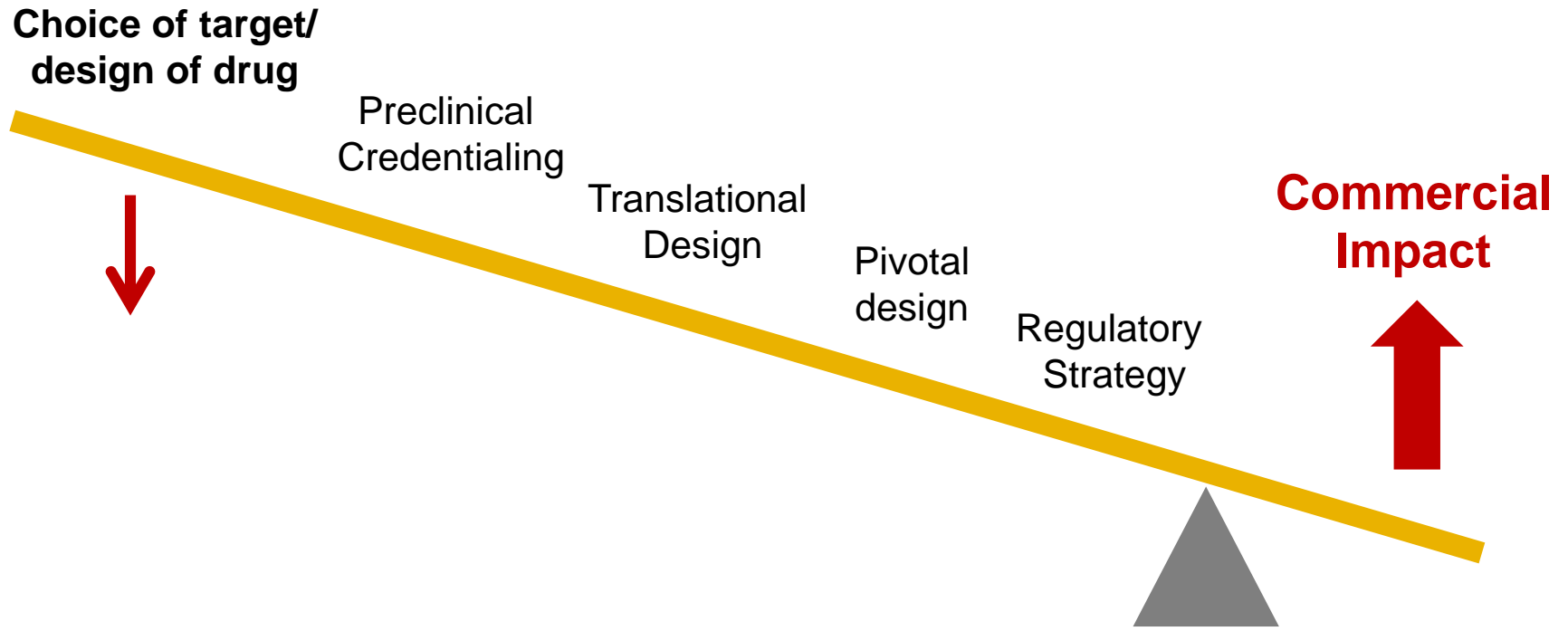


Earliest Choices are Critical

'Value Lever' Concept to Drug Development

Success at each step is critical, but earliest choices have the most influence on commercial impact

Product Design



Earliest Choices are Critical

'Value Lever' Concept to Drug Development

- **World class drug development can't compensate for poor early choices**
- **Making the drug is one thing, but how well understood is the disease or credentialed the target?**
- **Everyone has a stake in this knowledge.**

Trends Impacting Biologics Development ?

Better characterized patient populations

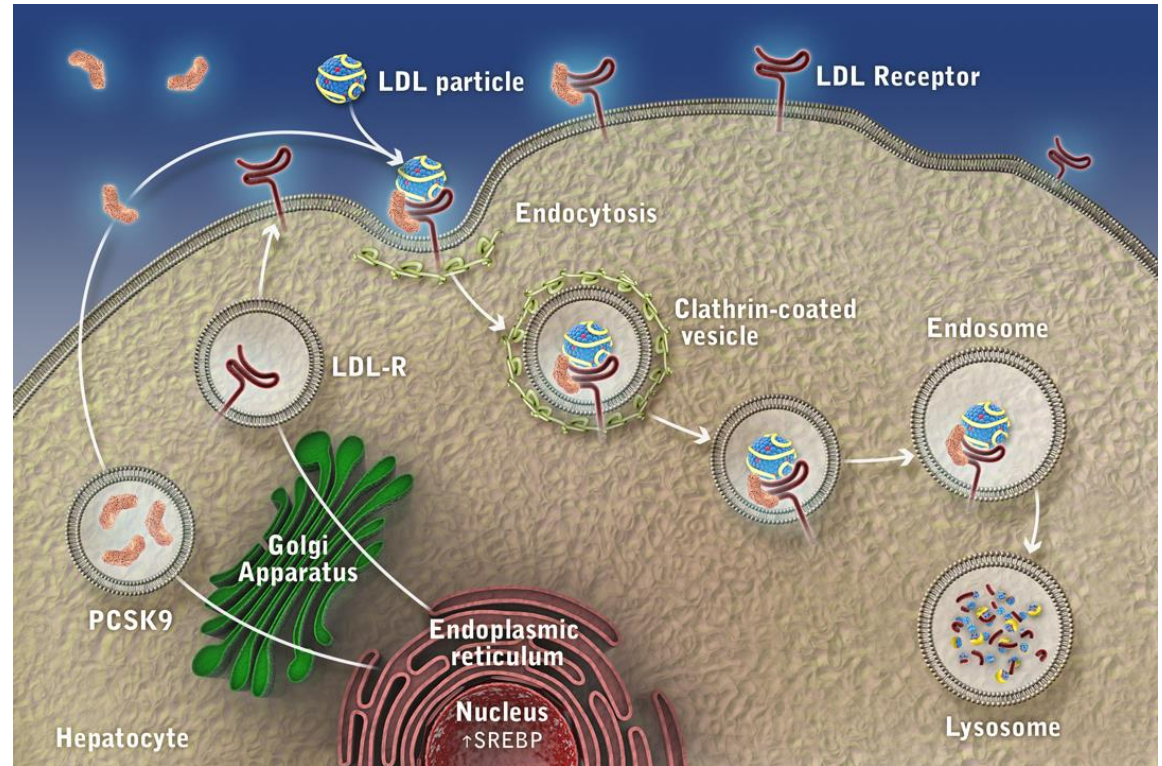
Impact on CMC and manufacturing strategies

Better Characterized Patient Populations

The Drug Development Process Can Be More Efficient

Proprotein Convertase Subtilisin/Kexin Type 9

PCSK9 Prevents Re-cycling of LDL-R, Leading to Elevated LDL-C Levels



Toxic Gain of Function (Hypercholesterolemia) – Abifadel *et al*, Paris

Beneficial Loss of Function (Low LDL-C levels) – Zhao *et al*, Dallas

Better Characterized Patient Populations

The Drug Development Process Can Be More Efficient

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia.
Nat Genet. 2003



Molecular Characterization of Loss of Function Mutations in PCSK9 and Identification of a Compound Heterozygote.
Amer J Clin Genet. 2006



PCSK9 discovery

Human CV Risk Reduction

First subject treated with PCSK9 mAb (SAR236553)

Proof of Principle in animals

PCSK9-targeted mAb preclinical

Three Phase 2 studies

2nd Gen mAbs

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2012

Seidah NG. *Proc Natl Acad Sci USA* 2003;100:928-33. Abifadel M. *Nat Genet* 2003;34:154-6. Maxwell KN. *Proc Natl Acad Sci USA* 2004;101:7100-5. Rashid S. *Proc Natl Acad Sci USA* 2005;102:5374-79. Cohen JC. *N Engl J Med* 2006;354:1264-72. Zhao Z. *Am J Hum Genet* 2006;79:514-23. Hooper AJ. *Atherosclerosis* 2007;193:445-8. Chan JC. *Proc Natl Acad Sci USA* 2009;106:9820-5. Stein et al. *N Engl J Med* 2012;366:1108-18.

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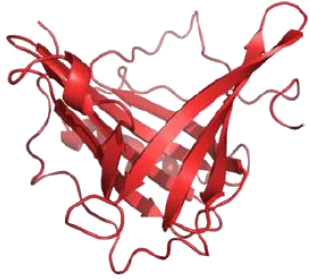
Impact on CMC and manufacturing strategies

New combinations & formats, in addition to mAbs, Fc fusions & fragments

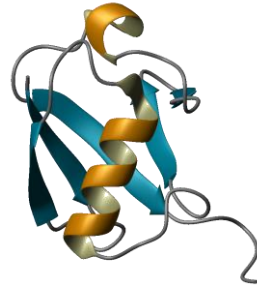
ADCs, protein scaffolds, bispecifics

New Combinations & Formats

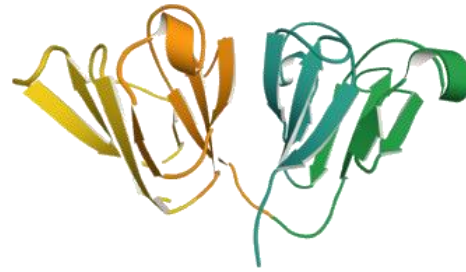
Engineered biomolecules appearing on the horizon



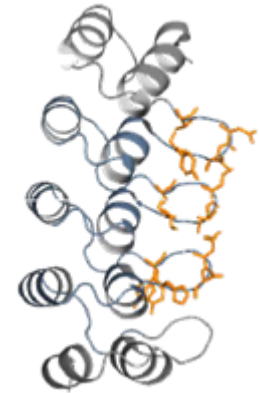
Anticalin



Ubiquitin



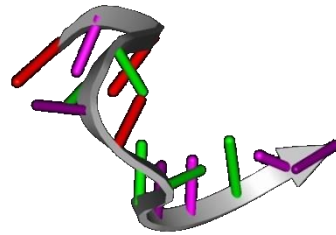
Crystallin



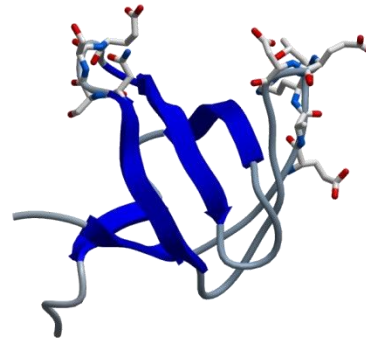
DARPin



Affibodies



Aptamers



Fynomers



Tetranectins

Characteristics of biologically engineered and e.g. microbial based expressed proteins:
small (10 - 30 kDa), high binding-affinity, high pH & temperature stability, short half-life time
Target: e.g. solid tumors, CNS-diseases,...

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Progressing gene therapy and cell based medicines

New challenges in manufacturing and regulatory approaches

Consider Spinal Muscular Atrophy (SMA)

- Orphan disease, high unmet need
- Leading genetic cause of death in children < 2 years of age
- ~ 1 of 6000 infants born affected
- ~ 1 of 40 carrier frequency
- Mutations in survival motor neuron 1 (SMN1) resulting in SMN deficiency
- Spinal cord motor neuron cell loss, skeletal muscle wasting, paralysis, respiratory defects, attenuated lifespan

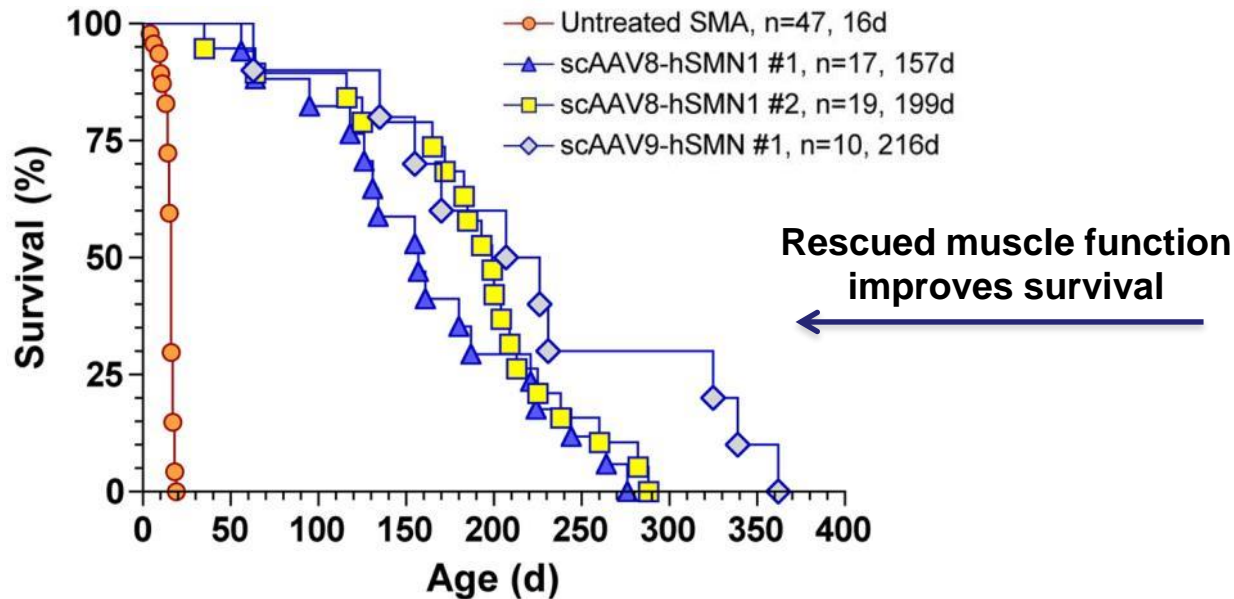
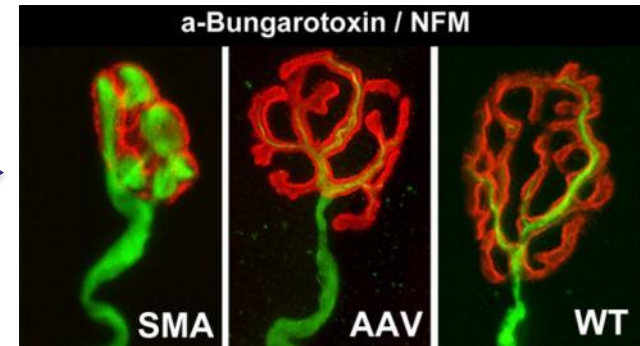
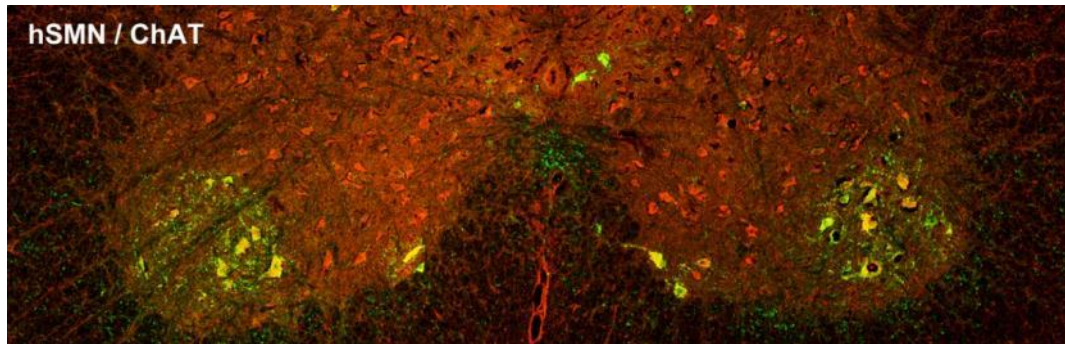


Be Agnostic With Respect to Platform

AAV GT Improves Function and Survival in Mice



Transduction of motor neurons corrects the neuromuscular junction (NMJ)



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Increased use of patient friendly devices and autoinjectors

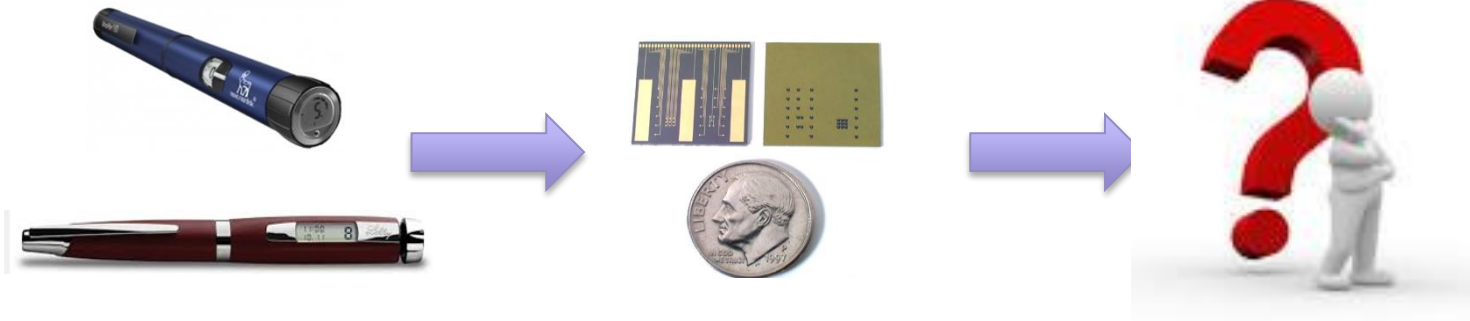
New devices adapted to high concentration biologics

Trends Impacting Biologics Development

Increased use of patient friendly devices



- Patients with chronic diseases are doing more to manage their conditions on a daily basis
- We must treat biologics- devices as fully integrated systems
- What will it take for biologics to be “needle-free”? Can we get there in 10 years?



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Biosimilars including mAbs as well as bio-betters

Development and scale-up strategies and qbd impact on comparability

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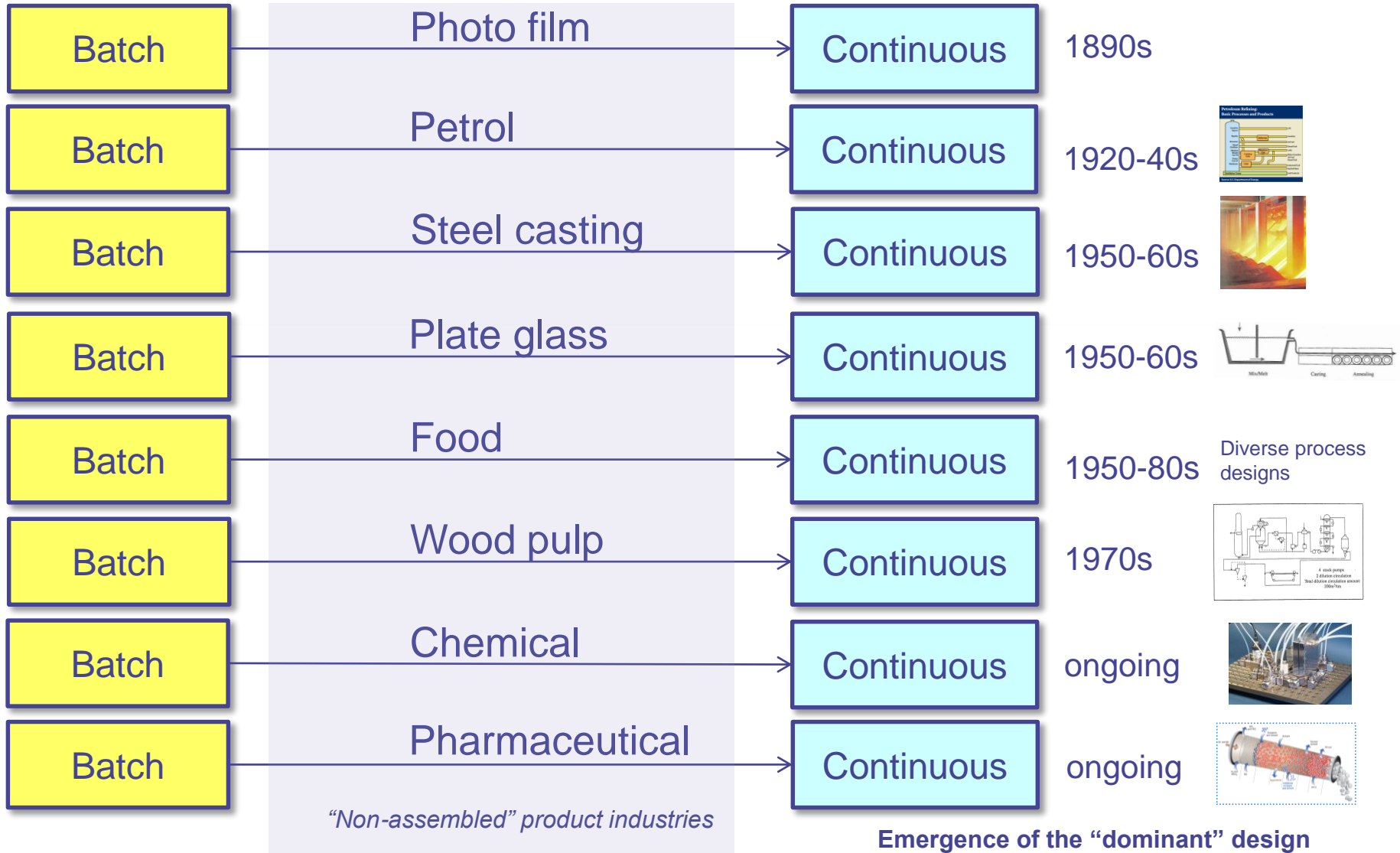
Development and scale-up strategies and qbd impact on comparability

Pilot & Production: massive use of disposables, higher USP & DSP productivities

Need flexible plant design & operation, new (disruptive) approaches

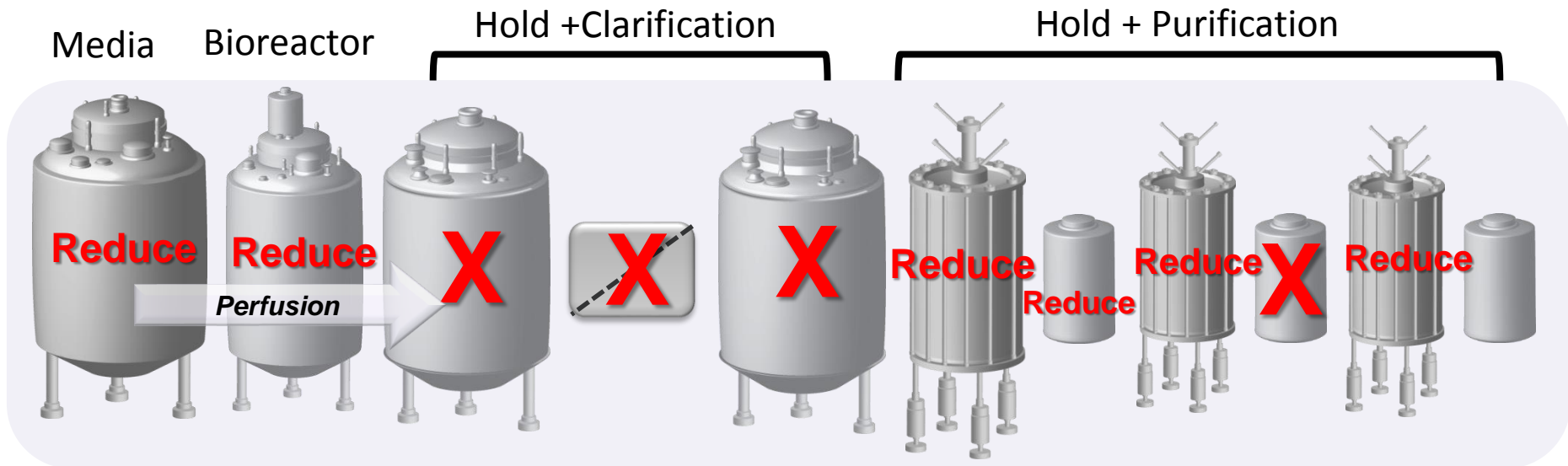
Consider The Evolution to Continuous Processing

Do we have open minds to disruptive innovation?



Integrated Continuous Bioprocessing

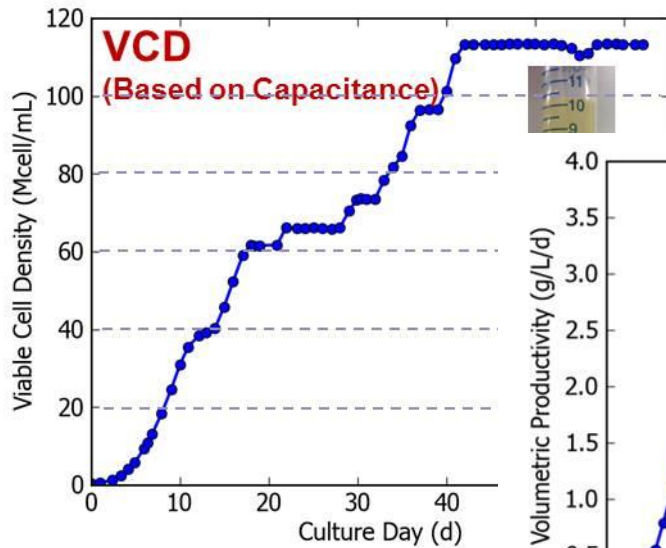
Turning Biotech SciFi into Manufacturing Reality?



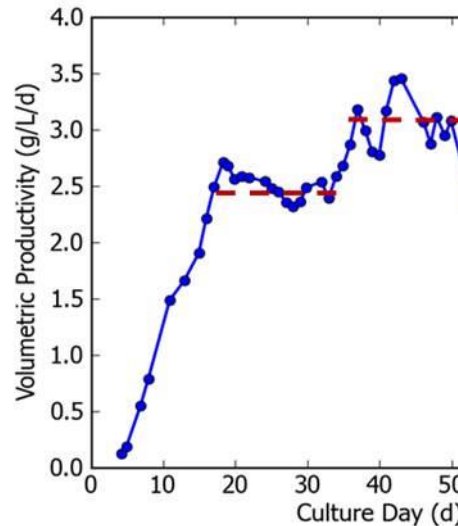
Enablers

- Steady-state high cell density and productivity
- Continuous purification (*PCC*)
- Robust cell separation
 - maintains favorable culture conditions,
 - ensures complete removal of cellular debris
 - allows the protein of interest to pass freely to downstream operations

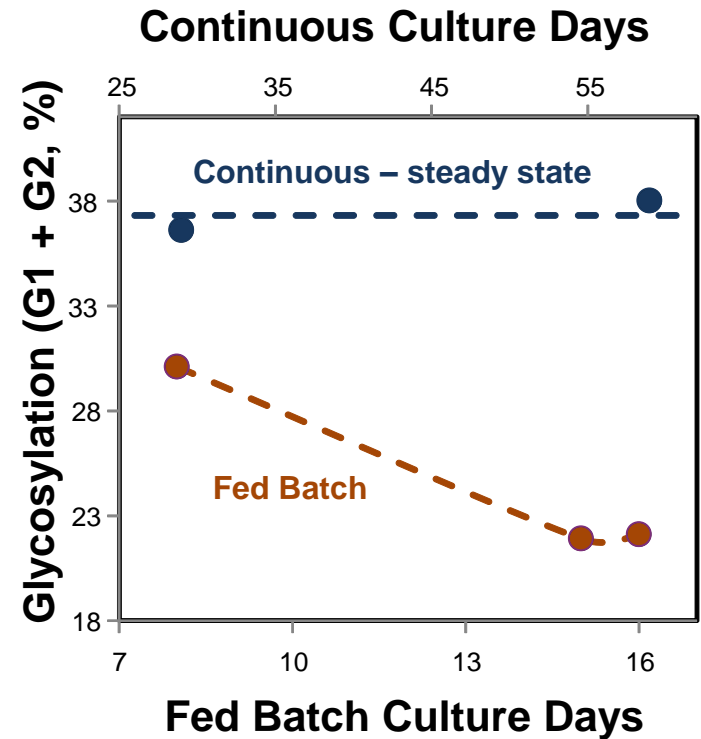
Does Steady State Process Operation Confer a Product Consistency and Quality Advantage?



84% viability for >30



Peak VPR of 3.5



Implications for Plant Design and Flexibility?

Continuous Process Scale Range Examples



Assumptions:

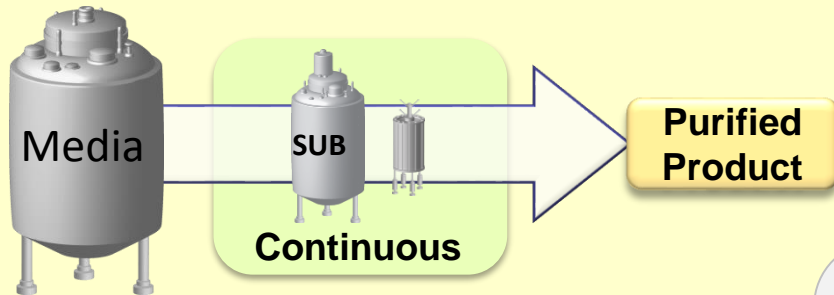
SPR = 20-40 pg/cell/day (stable), Cell Density = 50-150e6 cells/mL

DSP yield = 70%, Capacity utilization = 80%

Bioreactor size = Annual FDS throughput, e.g. 2 x 2,000 L = 4,000 kg

Implications for Plant Design and Flexibility? Flexible, Modular, Automated, Clonable, Mobile

Small footprint



**Universal platform
(mAbs & non-mAbs)**



<http://www.theengineer.co.uk/in-depth/analysis/prefab-pharma/1015238.article>



<http://www.autobild.de/bilder/man-sattelzug-studie-concept-s-iaa-nutzfahrzeuge-2012-3605655.html#bild1>

A Few Closing Remarks



Learn about the disease, the patients, and the caregivers

Be objectively assured that the molecular targets are well credentialed

Think about the products we seek to develop from the perspective of what a patient will experience

Don't be afraid of disruptive innovation; embrace it

A Few Closing Remarks



**Don't lose sight
that we are all
trying to change
someone's life**

Thanks to the Patients, Families and Caregivers

