

2014 BIO World Congress on Industrial Biotechnology

Track 7: Research Presentations

Session 2: **Successfully Scaling Up Industrial Fermentations of Chemicals and Fuels**

Date/Time: May 13, 10:30 am – noon

Moderator Jeff Lievense	Genomatica	EVP, Process Technology
Panelists Chuck Kraft Marcel Lubben Mike Hess John Evans	Amyris Reverdia Novozymes POET	VP, Global Manufacturing & Process Development President Sr Manager, Process Innovation VP, Science & Technology

Successfully Scaling Up Industrial Fermentations of Chemicals and Fuels

Program

Introduction – Lievense (15 min)

Speakers & topic

1,4-Butanediol: A Case Study in Rapid Commercialization

Panelist Remarks – All (40 min)

Kraft, Launching a Business with New Products, Process, Plant, Geography

Lubben, Successfully Scaling Up Industrial Fermentation of Biosuccinimide™

Hess, Top Lessons Learned in Delivering Innovation to our Customers

Evans, From Bench to Commercial: the POET Experience

Panel Discussion, Audience Q&A

30 minutes

Diverse, Experienced Industrial Biotech Panel

Product, process innovation

Global manufacturing

Business models

Panelist/ Function	Company	Company Profile	Product/ Microbe	Plant Locations/ Feedstock
Jeff Lievens/ R&D, Eng	Genomatica	Chemical process licensing, 1 st drop-in replacement	1,4-butanediol/ E. coli	International/ Various
Chuck Kraft/ Eng, Operations	Amyris	Chemicals & fuels, 1 st to build/own/operate, 1 plant	Terpenes/ Yeast	Brazil/ Sucrose (integrated)
Marcel Lubben/ Business	Reverdia	DSM/ Roquette JV, 1 st bio- chemical building block	Succinic acid/ Yeast	Italy/ Corn (integrated)
Mike Hess/ Eng, Operations	Novozymes	Leading industrial enzymes, bioinnovation, >12 plants	Enzymes, microbes/ Various	International/ Various
John Evans/ R&D	POET	Leading bio-refiner, corn dry milling, cellulosic, 27 plants	Ethanol, feed, oil/ Yeast	U.S./ Corn (integrated)

Scale-up Success Factors – it's in the details



1985 Yugo GV

Not this.....



2014 Honda Fit

This!! Strive for perfection by:
process development
plant design
construction
utilities
operation
maintenance

Scale-up Ingredients for Success – no short-cuts

Markets,
Customers



Product,
process



Design,
Construction



Operations



- Enterprise vision, goals, scope, team, priorities
- Customers, product, quality definition
- Safety culture as a priority
- Skilled, dedicated project management
- Formal risk analysis and mitigations

- Integrated, robust, validated process & product
- Regulatory approvals
- Validated local raw materials
- Waste disposal (co-product)

- Plant design based on validated process
- Qualified detailed engineering
- Construction quality, cost, schedule
- 100.0% reliable utilities, SOPs, and automation

- Thorough commissioning and start-up (aseptic)
- Trained production team
- Preventative maintenance
- On-site R&D support

Scale-up Risk Factors – where it can go wrong

Learning the Hard Way

Minor (few months disruption)

Automation and human errors

Part-time project manager

SOPs written during start-up

Serious (>6 mo, large losses)

Project manager new to ferment'n

Unreliable utilities, deficient PM

Mothballed plant, deficient SOPs

Silo mentality

Fatal (> 1 yr, plant closed)

Flawed utilities, no maintenance

Inadequate aseptic design

Compressed schedule, rushed
commissioning, unreliable utilities

Recipe for Failure

Demand seriously lags production

Product quality is not robust (cost pressure)

Safety is an after-thought

Process not robust and/or representative at
small scale

Regulatory is an after-thought

Raw material surprises

Heavy process waste loads

Parallel plant design and process development

Inexperienced, disconnected design team

Poor construction project management

Unreliable utilities

Short-cuts in commissioning and start-up

Inexperienced production team

Contamination by foreign microbes

No on-site R&D support



Genomatica

BIO World Congress: Successfully
Scaling Up Industrial Fermentations of
Chemicals and Fuels

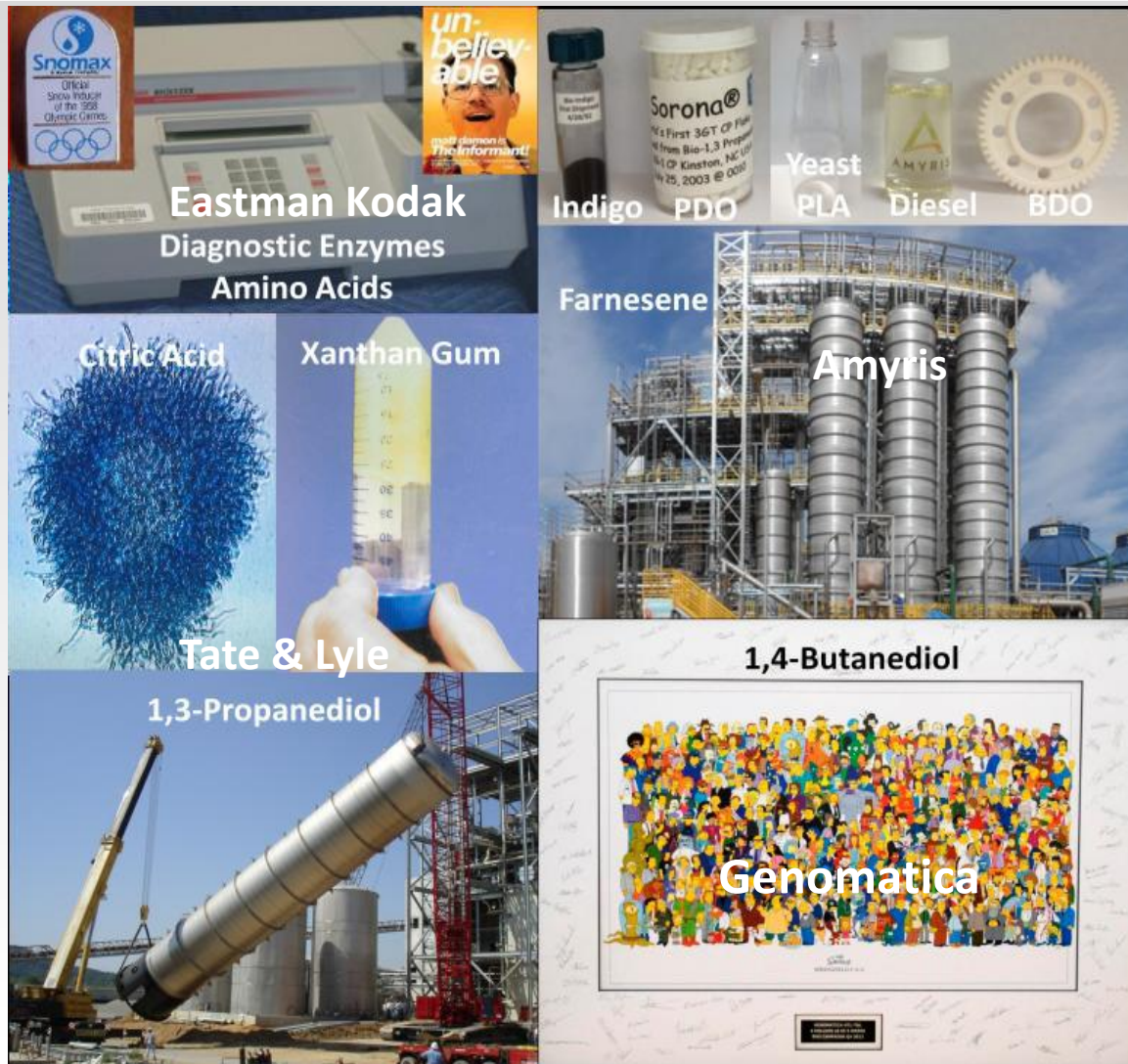
1,4-Butanediol: A Case Study in
Rapid Commercialization

Jeff Lievense

May 13, 2014

Jeff Lievens, EVP Process Technology, Genomatica

Industrial biotechnology (32 yr): milestones, bumps & bruises



1982-Present

18 genera (10 GM)

30 products (12)

lysine, tryptophan, methionine,
citric, xanthan, astaxanthin,
indigo, low pH lactic acid,
13PDO, farnesene, 14BDO

6 feedstocks

6 pilot plants

14 mfg plants

4 continents

500m³ fermentors

(bubbled, stirred)

Many unit operations

Developer of bio-based process technology for the chemical industry:
drop-in chemicals by fermentation of sugars, biomass, C1s



1,4-Butanediol

Commercial, 2012

5 mil lb in 5 weeks

Licensed by BASF, Novamont

Validated by Lanxess, DSM,
Toray, Far Eastern, BASF, more



Butadiene

Lab scale, 2011

Versalis JV, 2013

Braskem JDA, 2013

> \$100 million in
industry support

Distinctive technology platform

~500 patents/applications for 20+ industrial chemicals

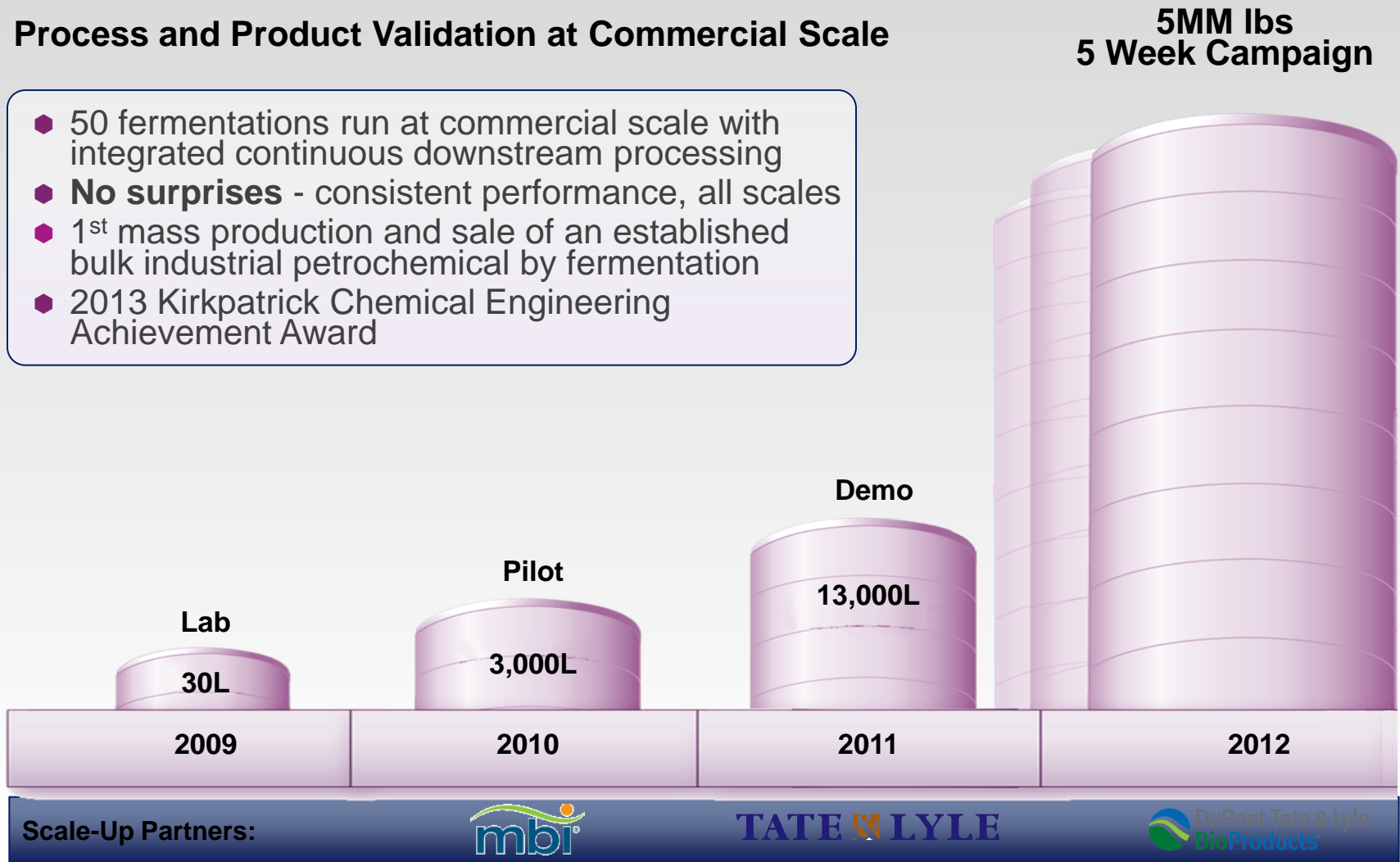
Leadership in biotechnology, chemical engineering and innovation



1,4-Butanediol: 5 years from concept to commercial production

Process and Product Validation at Commercial Scale

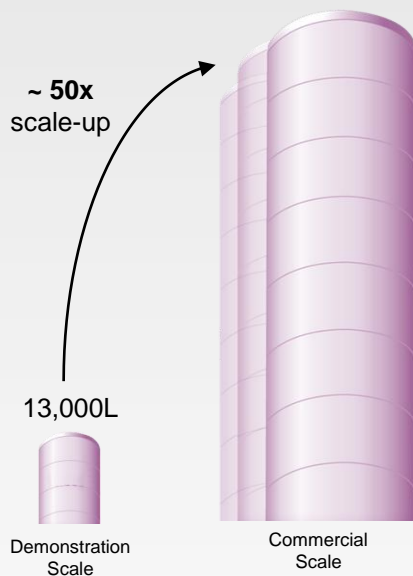
- ◆ 50 fermentations run at commercial scale with integrated continuous downstream processing
- ◆ **No surprises** - consistent performance, all scales
- ◆ 1st mass production and sale of an established bulk industrial petrochemical by fermentation
- ◆ 2013 Kirkpatrick Chemical Engineering Achievement Award



1,4-Butanediol Commercial Scale Performance

Process robust, performed as planned, performance upside

Consistent Scale-up to Commercial



Average Fermentation Performance
(~50 runs at commercial scale vs. average demo scale)

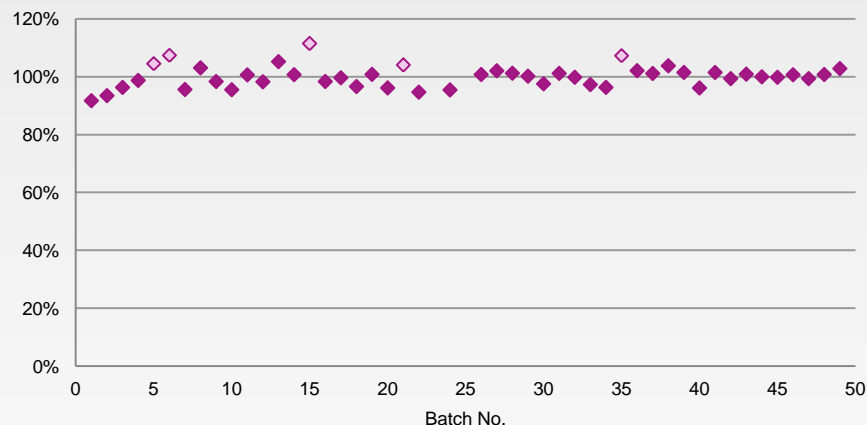
Campaign Strain

Titer	98%
Rate	104%
Yield	100%

Robust Performance at Commercial-Scale

◆ Fermentation Run ◇ Top 5 Fermentation Run

Percent Average Commercial-Scale Yield



- ◆ Fermentation performance at commercial-scale equivalent to demonstration-scale
- ◆ Low variability in fermentation performance indicates process robustness and predictability
- ◆ Top 5 commercial-scale fermentations indicate continuous improvement opportunity

Commercial Campaign: Why did it work?

Followed the recipe for success – no short-cuts



Well run plant

Project management

Piloting/tech transfer

Large-scale preparation

On-site technical support

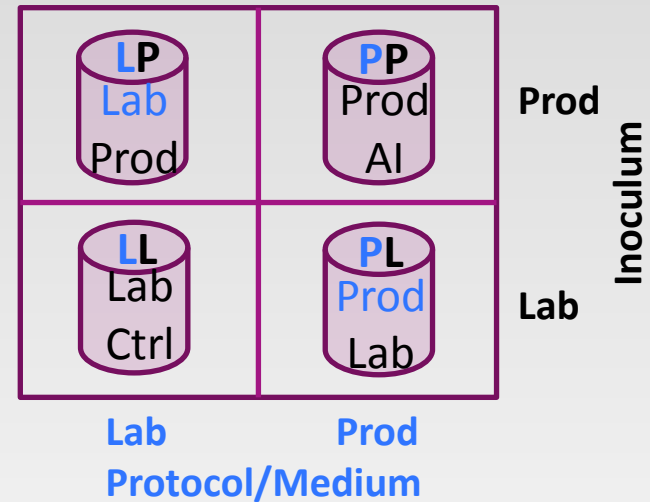
- ✓ Safety culture as a priority
- ✓ 100.0% reliable utilities, SOPs, and automation
- ✓ Trained, experienced production team
- ✓ Dedicated, detailed project management
- ✓ Formal risk analysis and mitigations
- ✓ Integrated, robust, validated process & product
- ✓ Regulatory approvals
- ✓ Validated local raw materials
- ✓ Waste disposal (co-product)
- ✓ Thorough commissioning and start-up (aseptic)
- ✓ On-site R&D support, including lab fermentors

Fermentation Scale-up Tool

Parallel lab fermentors, indispensable for validation and troubleshooting



2 x 2 lab fermentor study
quickly isolates root causes



L L	P L	L P	P P	F S	Failure
-	-	-	-	-	Lab-to-lab transfer
+	-	+	-	-	Production media prep
+	+	-	-	-	Production inoculum
+	+	+	+	-	Full-scale environment

Genomatica's Innovation Center, San Diego, CA

