

ACN Recovery in Biosynthetic Human Insulin Manufacturing

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Background

Biosynthetic Human Insulin (BHI)

- Active Pharmaceutical Ingredient (API) in one of Lilly's insulin products
- Life-saving medicine for diabetics
- Identical to human insulin produced by our bodies
- Biotech product: protein, MW 5800
- Subject to alteration by even trace impurities in raw materials
- Reversed Phase chromatography: 'post-API'

Acetonitrile (ACN)

- Organic solvent
- BHI: Reversed Phase Chromatography
- Normal bp = 82 °C
- Azeotrope with water: 88% ACN (v/v)
bp = 77 °C

Before:

\$1.1MM/yr to purchase ACN
\$ to incinerate after use
Idle distillation equipment

Recovery (pro):

Environmental benefit
Put idle capital assets to work
\$ savings

Recovery (con):

Never recovered solvent 'post-API'
in a biologic product
Trace impurities: ?
Negative BHI quality impact?

Major Steps to ACN Recovery (1)

- Waste characterization:
- Identify all volatile components
 - Will they separate from ACN/water azeotrope?
 - Will *their* azeotropes “ “ “ “ “
- Analytical:
- GC, ABS methods for lot release at Tippe
 - % ACN potency, A_{230} , A_{280} , % total foreign solvents, color
- Process development:
- Distillation: lab-scale proof-of-concept
foaming? pH adjustment? L/D ratio?
 - Aspen process simulator: COL 19-3 at Tippe work?
different packing? pressure drop?
- Pilot recovery:
-
- Major milestone
- Proof of concept: achieve near-azeotropic ACN
 - Study fouling/foaming at-scale
 - Produce 60,000 L RecACN for BHI Plant Trial

Major Steps to ACN Recovery (2)

- Evaluate BHI impact:
(Eng'g and T/S labs)
- affects of 12% water
 - affect of any (unseen) ACN impurities
 - confirm suitability for use in BHI RP models
 - set specifications for RecACN
- Capital project:
- New: waste ACN holding tank
 - Modify tanks: RecACN (88%)
NewACN (100%)
- BHI plant trial:
- proof-at-scale, generate data for FDA

Major milestone

Waste Characterization

0.1 g/L protein load: decomposes in reboiler (100 °C) → NH_3
: add H_2SO_4 to feed → traps NH_3 as $(\text{NH}_4)_2\text{SO}_4$

Volatile components:

- acetic acid
- propanenitrile
- 2-methoxyethanol
- morpholine
- pyridine
- 4-acetylmorpholine
- No low-boiling components present that will “follow” ACN
- No components form H_2O -azeotrope that will “follow” ACN
- Waste composition provided “recipe” for pseudo-waste used in lab distillation studies

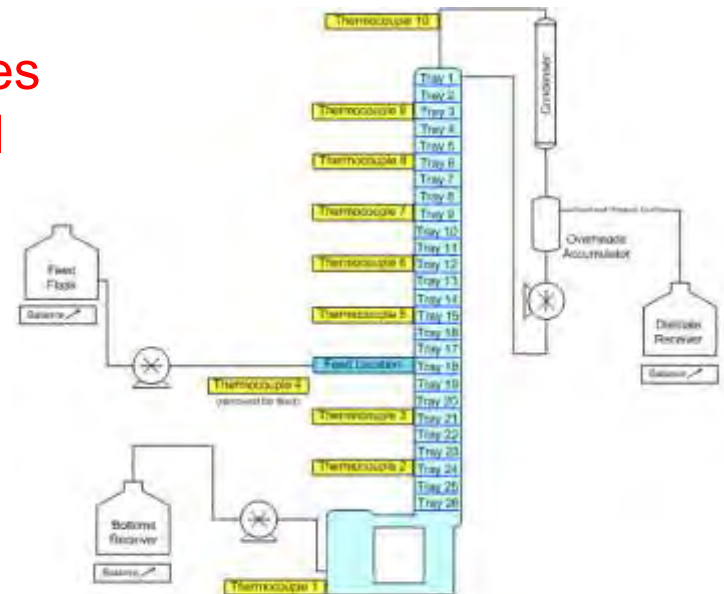
*Results: recovery to the azeotrope
can be accomplished in 1 column*

Distillation Process Development (lab)

- 5X-recycle of plant waste
- feed location
- reflux (L/D) ratio
- Aspen modeling of COL19-3
- fouling? cleaning agent?
- foaming? antifoam effective?
- acid flow rate? → control NH_3
- ~ 88% ACN in distillate?

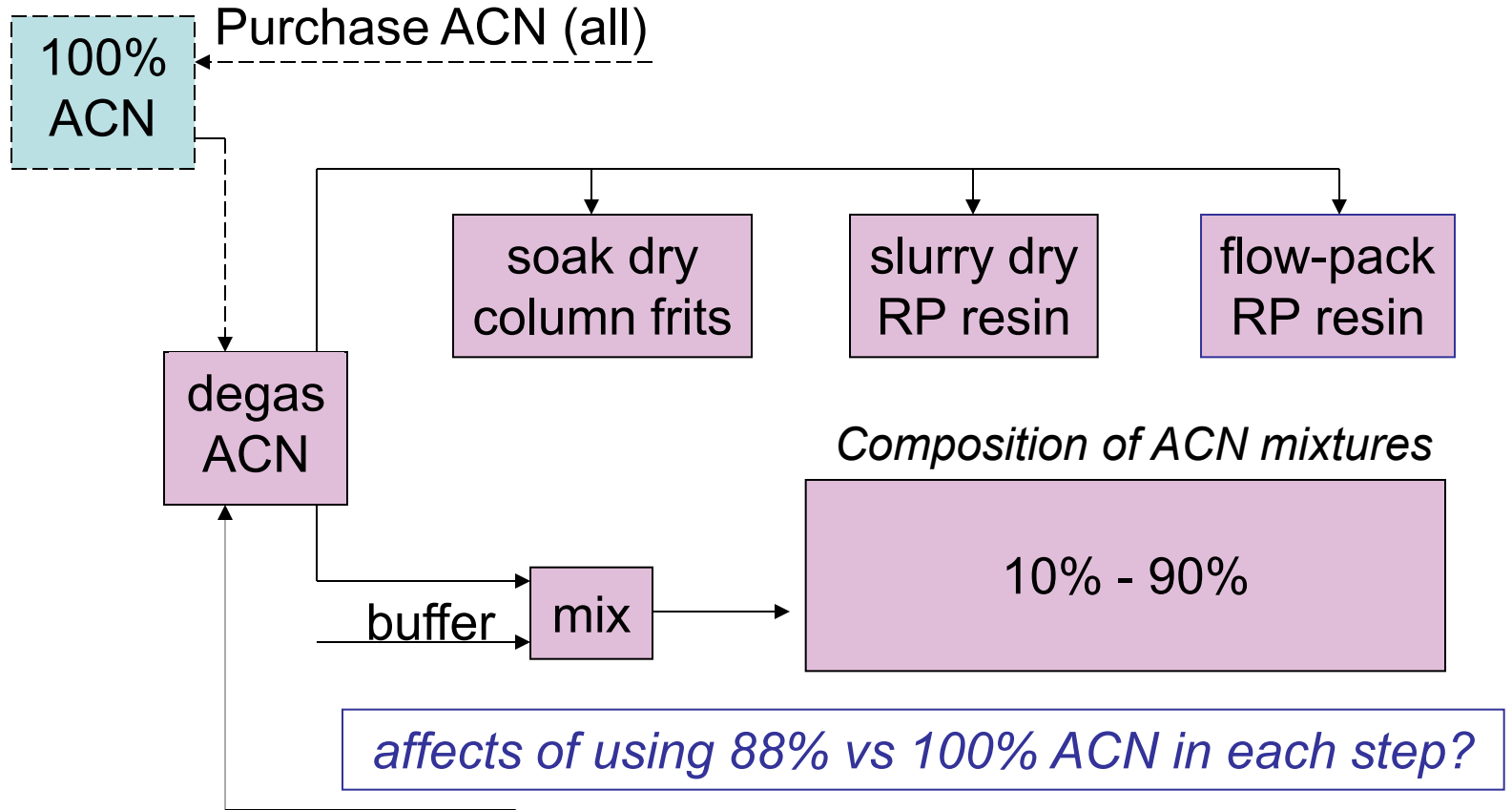
Results:

- no low-boilers concentrate after 5X recycles
- COL19-3 will be able to achieve 88% ACN
- $L/D > 6$ required
- antifoam will be needed
- fouling occurs; clean with NaOH
- feed pH < 5 controls NH_3 in ACN

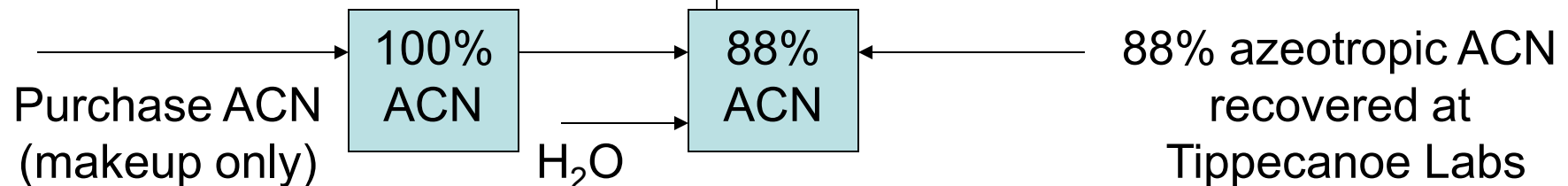


Uses of ACN in Reversed Phase

Original:



Current:



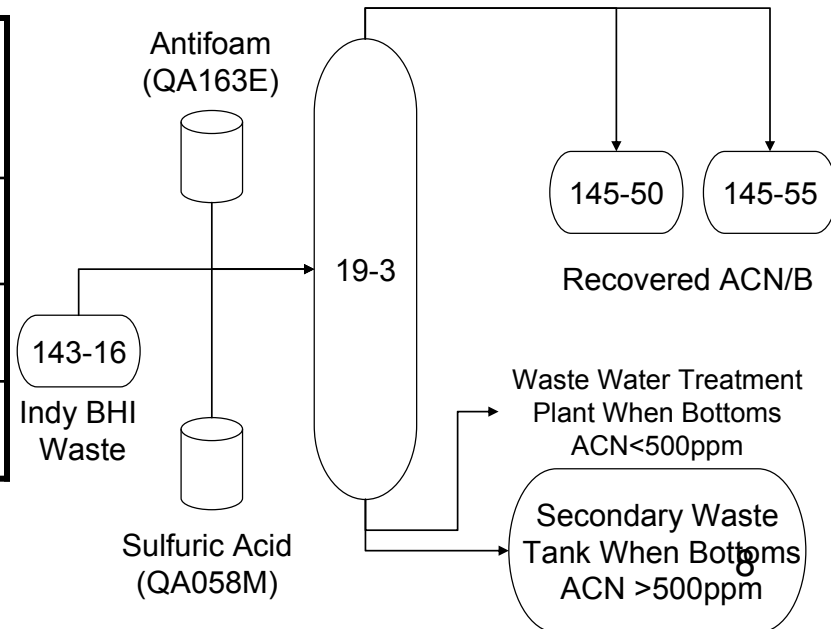
Pilot Recovery At-Scale (Tippe, COL19-3)

Critical Factors:

- Export waste from BHI (without contamination!)
- Import waste to Tippe (without contamination!)
- Process 330,000 L of waste ACN from BHI
- Prepare 60,000 L RecACN for BHI Plant Trial
- Operate COL19-3 as in normal recovery
- Import RecACN to BHI (without contamination!)
- QCL methods approved and in-place

Pilot Recovery Results:

<i>Lot No.</i>	<i>A₂₃₀</i>	<i>A₂₈₀</i>	<i>% ACN</i>	<i>% For. Solv.</i>
A21802	0.02	0.00	86.3	0.02
A21803	0.03	0.00	87.0	0.02
A21804	0.03	0.00	88.6	0.02



Affects of 88% ACN vs. 100% ACN (in lab)

RecACN

Suitability for use:

- Lab-recovered ACN
- Pilot-recovered ACN
- Results: BHI produced w/ RecACN **not different** from that made w/100% ACN

Dry resin slurry:

- 88% ACN → significant foaming (!)
→ poor resin incorporation (!)
- Solution: ↑ resin add'n time (15 → 75 min)
↑ agitation rate (115 → 175 RPM)
eliminate pneumatic resin transfer
reverse flow (downflow → upflow)
lower impeller position on shaft

Capital Requirements: \$2.1MM

BHI Tank Farm:

- Construct new 20,000 gal waste ACN tank
- Modify existing New ACN tank → RecACN
- Modify existing waste tank → New ACN
- Add controls to makeup 88% ACN
- Online density to measure ACN composition
- Automation/controls

14-month Project Schedule

Tippe:

- Re-commission COL19-3 & tanks (moth-balled)
- Add pH controls
- Add H₂SO₄ feed capability

Affects of 88% ACN vs. 100% ACN (in plant)

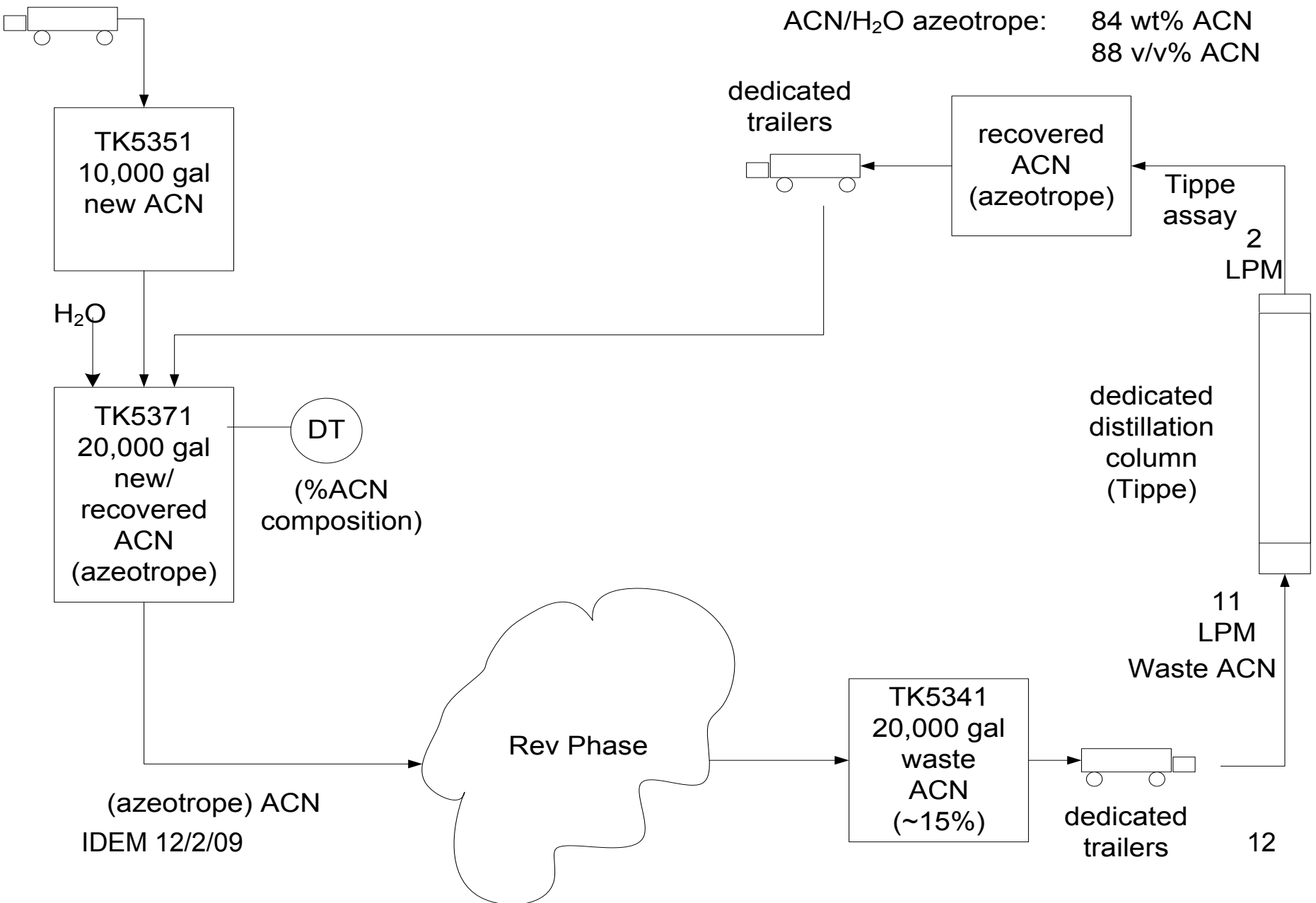
BHI Plant Trial:

- Once-through affect of RecACN
- Long-term affects of recycling obtained later
- 36 lots at Reversed Phase
- 10 lots at Insulin Crystals
- Collect data for FDA Submission

Results:

- All Reversed Phase lots met acceptance criteria
- All Crystal lots met acceptance criteria
- Process validation successful
- Dataset generated for FDA Submission

ACN Recovery Operation



BHI Manufacturing



Waste ACN: 15% in water
1 truck/day



BHI Tank Farm



IDEM 12/2/09

Lilly's Tippecanoe Laboratories
Lafayette, IN



1 truck
per
week

The ACN Recovery Team

- RecACN: a 24-month relay race
- > 60 people with significant contributions
- Completed 1st year operation: May, 2008
- Long-term recycling: no quality problems
- Governor's Environmental Excellence Award

Tippe: K. Beach, A. Schneider, D. Roadruck

MS&T: L. Thompson, P. Irwin, M. Deacon, M. Krivan

Eng'g: A. Charlton, B. Parker, G. Kinnett

Analytic: S. Kaerner

Opns: K. Gerbers, S. Carter, P. Carter

BHI's ACN Recovery Key Successes

ACN Purchase:	\$1.1MM/yr direct savings.
Recovery:	>99% of purchased ACN
Waste stream:	880,000 L/yr not incinerated
CO ₂ :	3.3x10 ⁶ lb/year not emitted
Quality:	insulin purity unaffected
Replication:	rapidly implemented ACN recovery for another insulin process

Comments, Questions?