

# Continuous Improvement of Prothrombinex-VF Manufacture

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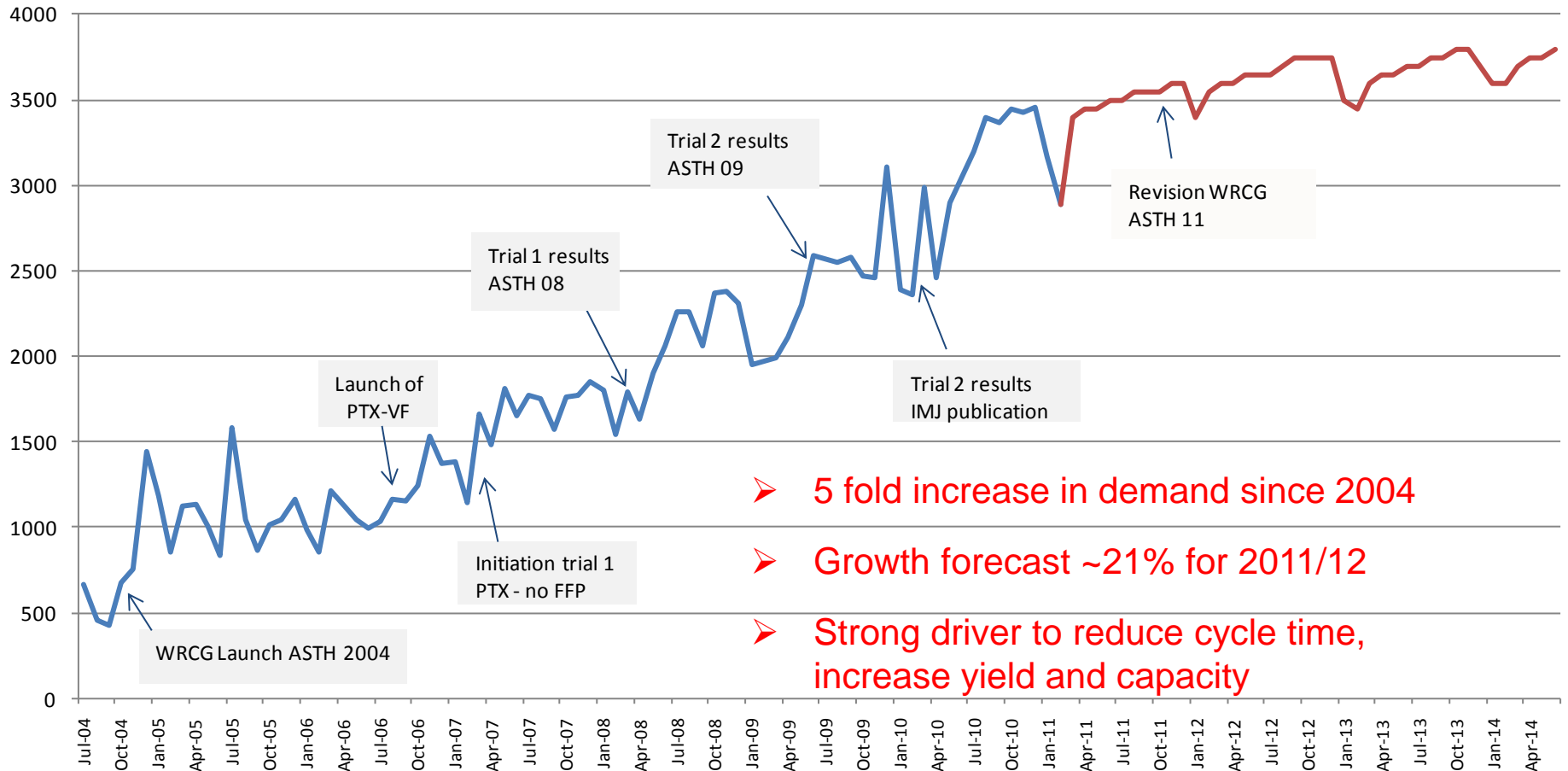
**CSL Biotherapies**

# Prothrombinex-VF (PTX)

- A Prothrombin complex concentrate (PCC)
- Mixture of Clotting Factors II, VII, IX and X
- Developed for treatment of congenital deficiencies
- More commonly used to reverse the clinical effects of Warfarin (Warfarin reversal)



# PTX Performance and Forecasts



# History of PTX

- PTX process based on initial PCC developed by the SNBTA

Vox Sang. 24: 441–456 (1973)

## **A Therapeutic Concentrate of Coagulation Factors II, IX and X from Citrated, Factor VIII-Depleted Plasma**

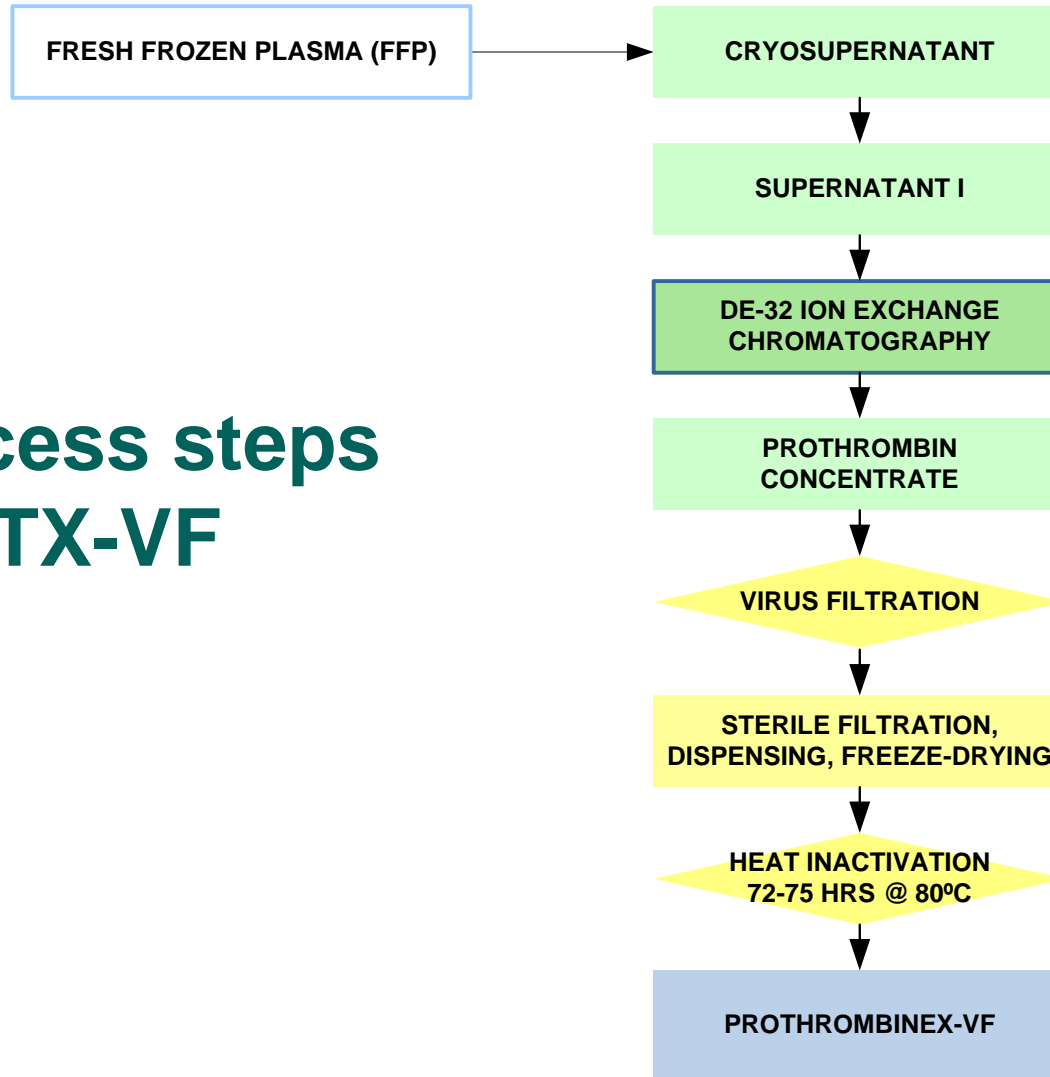
**SARAH M. MIDDLETON, IDA H. BENNETT and J. K. SMITH**

**Scottish National Blood Transfusion Association, Protein Fractionation Centre, Royal  
Infirmary, Edinburgh**

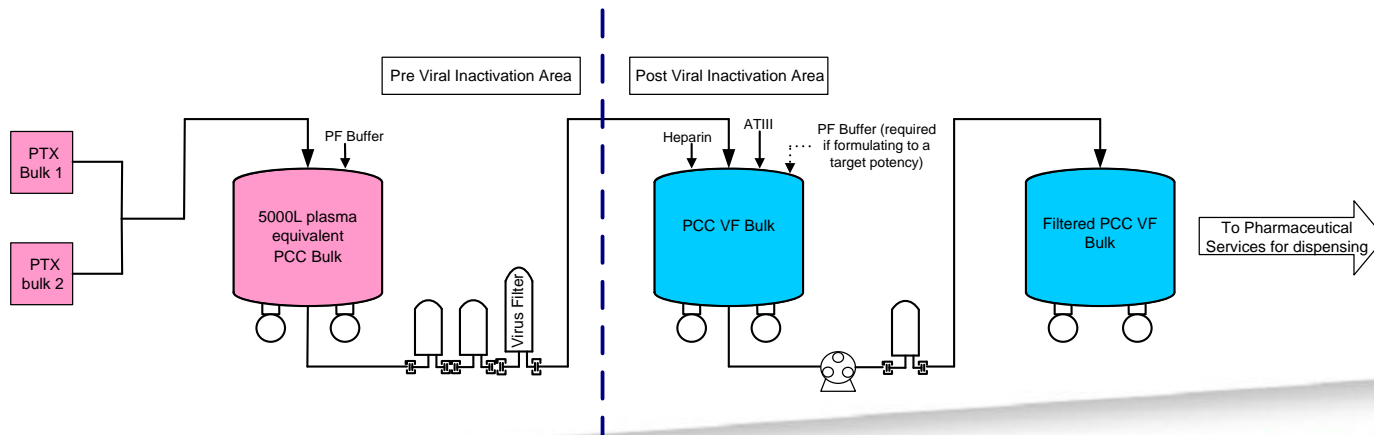
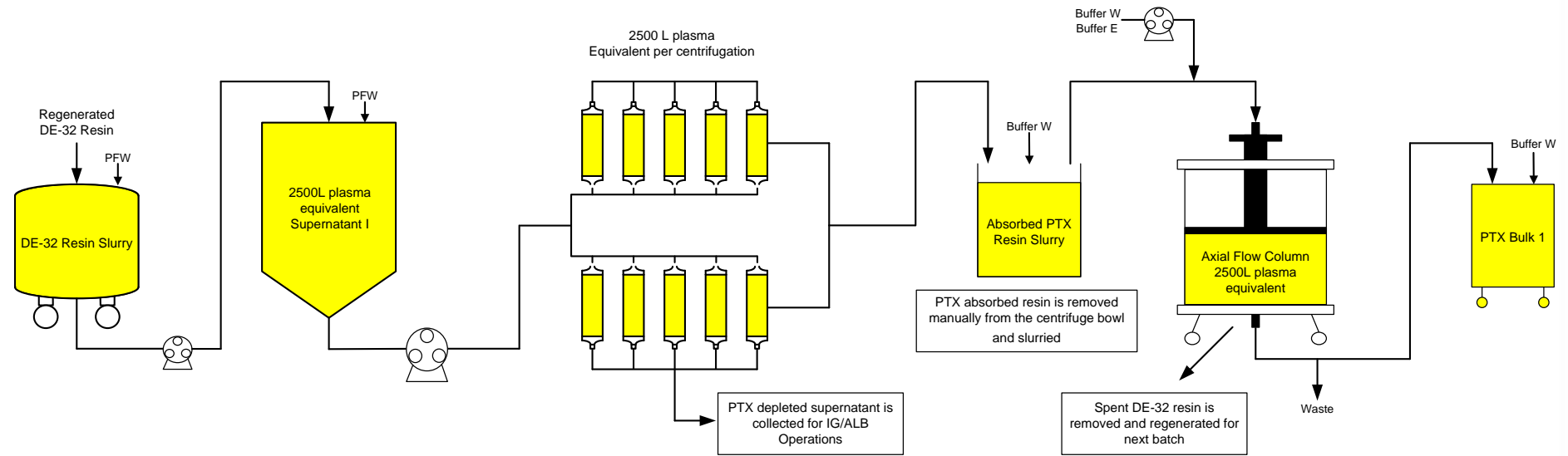
# History of PTX at CSL

- 1977 – Prothrombinex first manufactured at Parkville
- 1984 – Addition of a 60°C dry heat treatment step
- 1991 – Name changed to Prothrombinex–HT upon adoption of 80°C dry heat step and formulation with ATIII in addition to Heparin
- 2006 – Name changed to Prothrombinex-VF upon addition of a virus filtration step

# Process steps of PTX-VF



# PTX-VF process flow chart



# Areas for improvement – 1. Collection of resin via centrifugation



- 10 x Sharples centrifuges
- Cumbersome, time consuming cleaning
- High level of maintenance
- Used for both DE32 and Cryoprecipitate separations
- Incomplete recovery of PTX-bound resin



# Areas for improvement – 2. Manual Resin Packing



- Manual handling



- Column packing and unpacking

# Areas for improvement – 3. Chromatography



- Fully manual process
  - Low tech
- Poor process consistency
  - Packing
  - Washing
  - Elution

# Areas for improvement – 4. Resin regeneration



- Double handling of resin
  - Packed in axial flow column for chromatography
  - Transfer into radial flow columns for regeneration

# Process Development Goals

- Minimise manual handling
- Increase process automation
- Increase PTX-VF process scale to 5T throughout
- Minimal MoM changes for maximum efficiency gains (yield and time)
- Maintain product characteristics

# Process Changes – Sharples Centrifuge Replacement



FRESH FROZEN PLASMA (FFP)

CRYOSUPERNATANT

SUPERNATANT I

DE-32 ION EXCHANGE  
CHROMATOGRAPHY



Westfalia  
separator

Filter  
Press



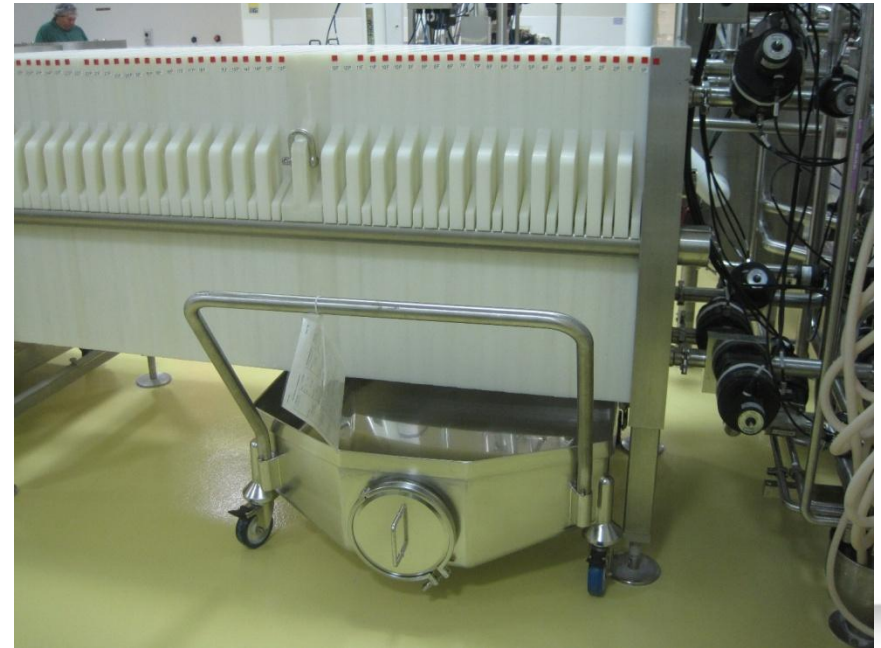
# Filter press collection of resin

- Recent transition of upstream depth filtrations to filter press operations
- Schedule currently allows different operations on the same press

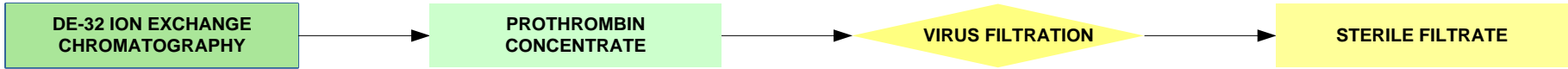
Full filter area for Delipidation  
(paste discarded)



Partial filter area for 5T PTX operation  
(DE32 resin collected)

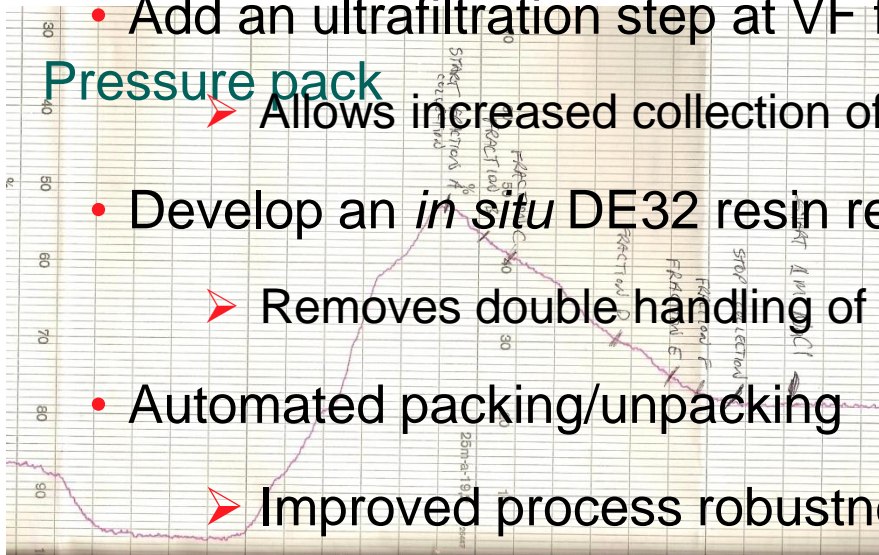


# Strategies to improve DE32 chromatography



- Improve packing of DE32 resin
  - Shift from pressure to vacuum packing (short term option)

- Add an ultrafiltration step at VF filtrate



Pressure pack

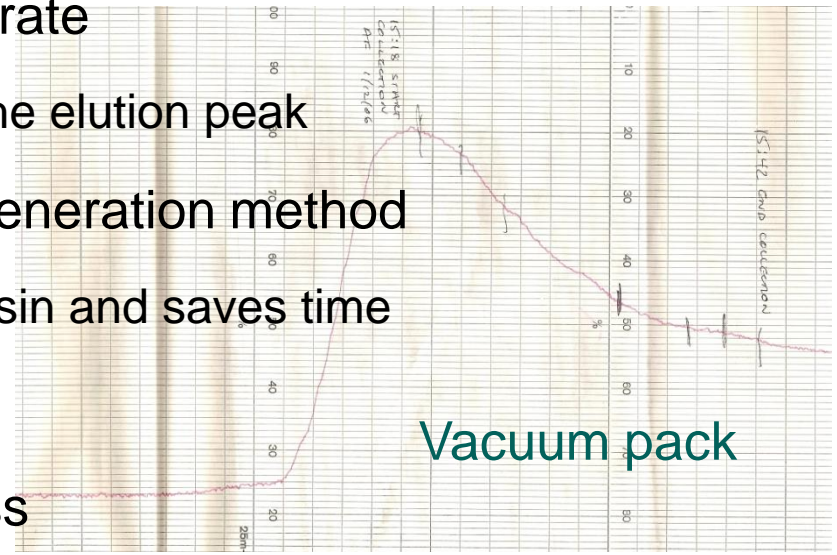
- Allows increased collection of the elution peak

- Develop an *in situ* DE32 resin regeneration method

- Removes double handling of resin and saves time

- Automated packing/unpacking

- Improved process robustness



Vacuum pack

- Size DE32 column to suit 5T process scale
- More even profile, with a steep ascending peak

# Automated chromatography – GE Healthcare AxiChrom™ 800 self packing/unpacking column and Manual chromatography AKTA Process™ work station



## Drawing the PTX-bound DE32 slurry into the AxiChrom™ column



## Controlled packing of the PTX-bound DE32 resin bed

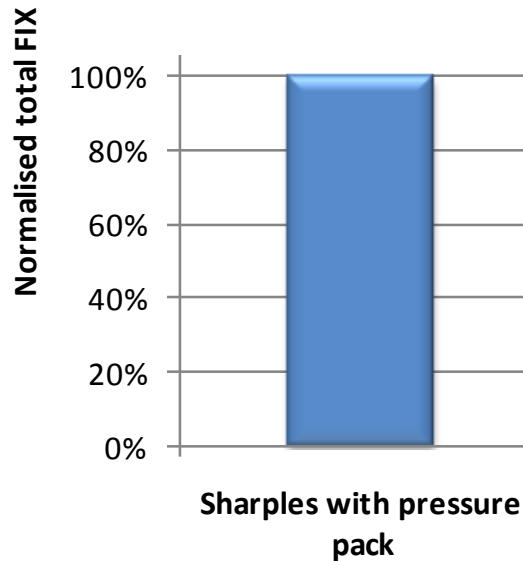


# Project support and validation

- R&D and Pilot scale data to support Cat III submissions to the Therapeutic Goods Administration (AUS regulatory body)
- IQ/OQ, HAZOP, FMEA
- Software development and validation
- Cleaning and process validation
  - To assess process consistency and confirm batch segregation
  - All process trials performed under validation protocols
  - Product characteristics assessed by extensive QC and R&D testing

# Impact of changes upon process yield

FIX/kg plasma present at PCC bulk



→ 25% increase in PTX-VF yield in the last year

# Summary

- The process changes outlined will make a significant impact upon the PTX-VF process
  - Increased capacity (2.5 → 5 T process stages)
  - Increased Automation
  - Reduced manual handling
  - Reduced maintenance
  - Increased yield (~ 50% overall)
  - Reduced PTX process time by 2 days

Integrated plant → Significantly improved efficiency

# Conclusions

- Continued development of established processes is a worthwhile endeavour
- Allows capture of technological advancements to assist with increasing automation and improving process robustness
- Can lead to increased process yields and operating efficiency gains

# Acknowledgements

- Sharples replacement project team
- Manufacturing staff @ Broadmeadows
- George Tsirbas
- John Lontos