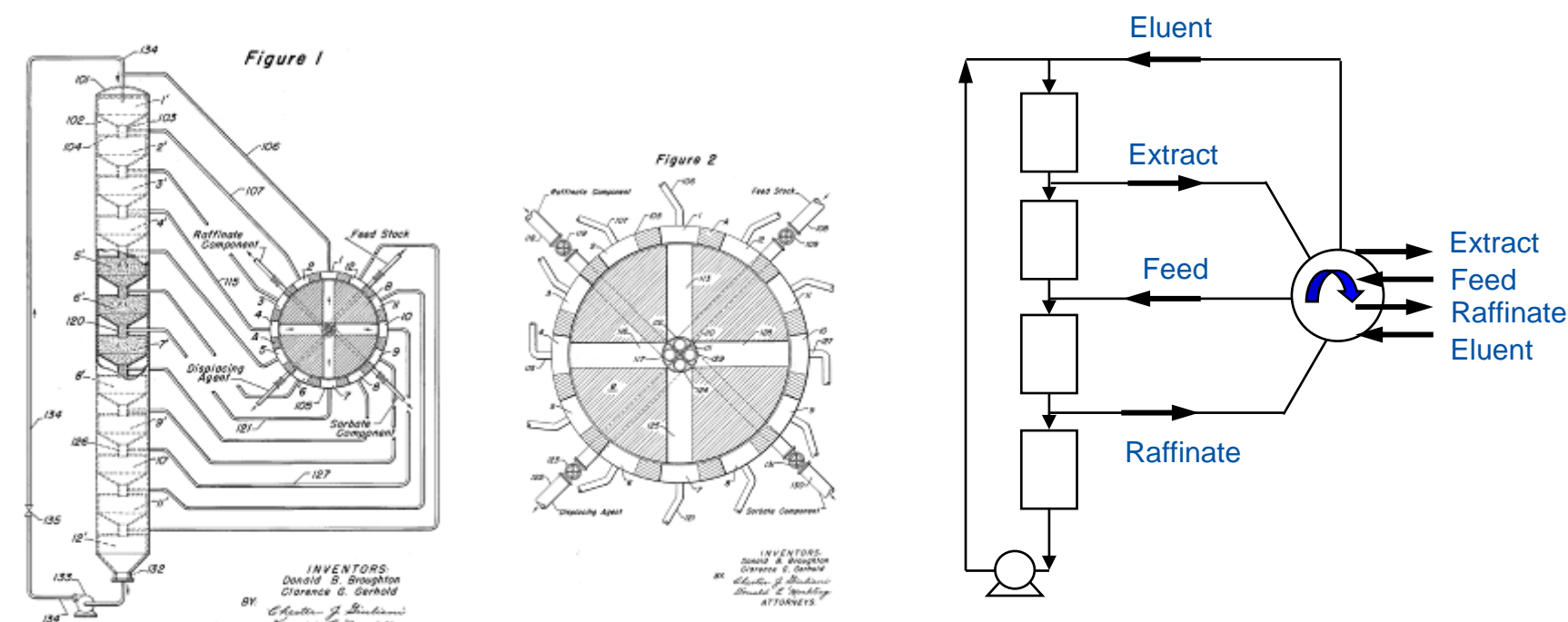


Continuous Chromatography for the Purification of APIs

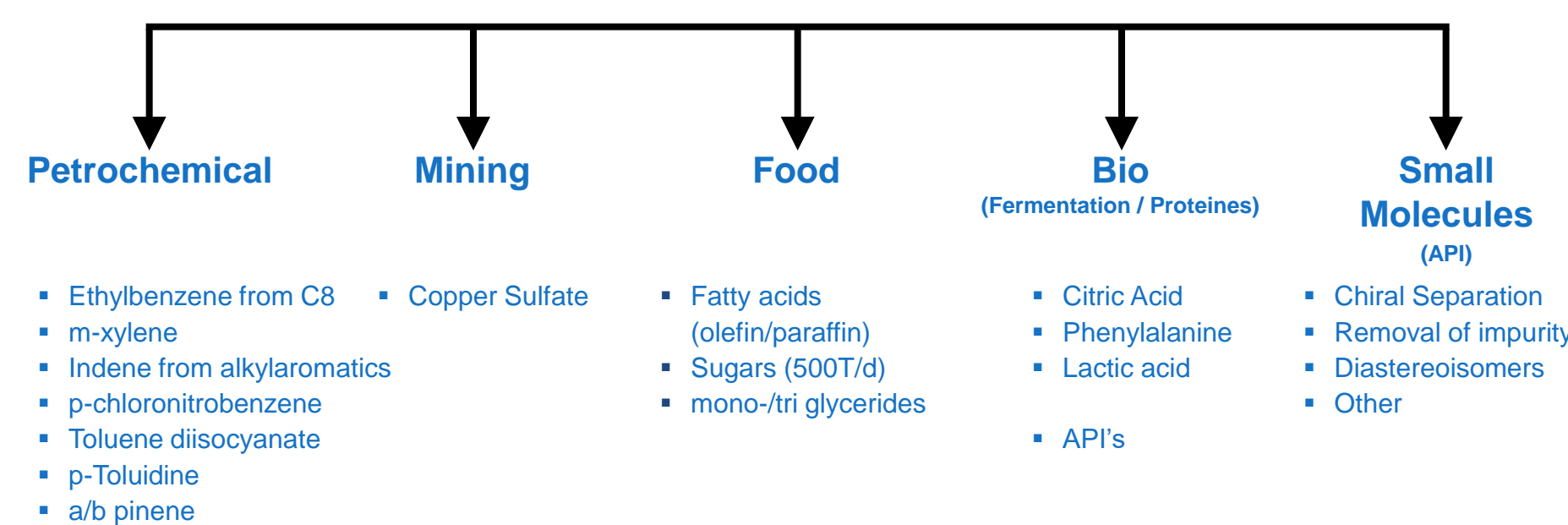
Chromatography – A Powerful Purification Tool

The Original Process: The SORBEX Process

A design strongly inspired by distillation/extraction columns



A Technology Used in Multiple Industries



Chromatography is used by chemists...

- Chromatography is widely used for
 - Analytical
 - Allows to evaluate the impurity profile of a compound
 - Identification: Combined with other techniques (LC-MS)
 - Production
 - Purification of sugars (ion exchange – multi tons)
 - Purification of Active Pharmaceutical Ingredients (API)
 - Purification
 - Chiral separation
 - Purification of biologics (Insulin)



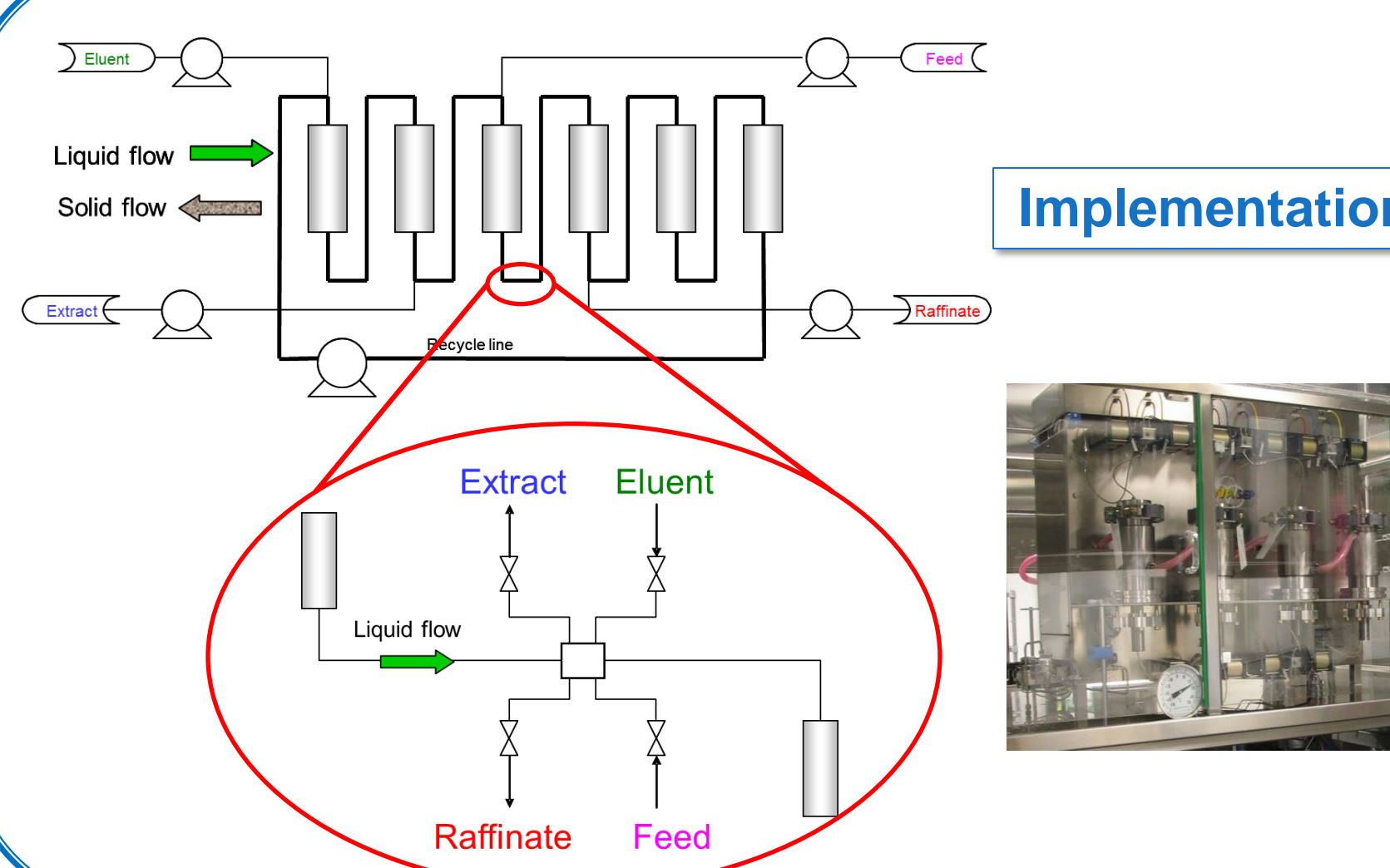
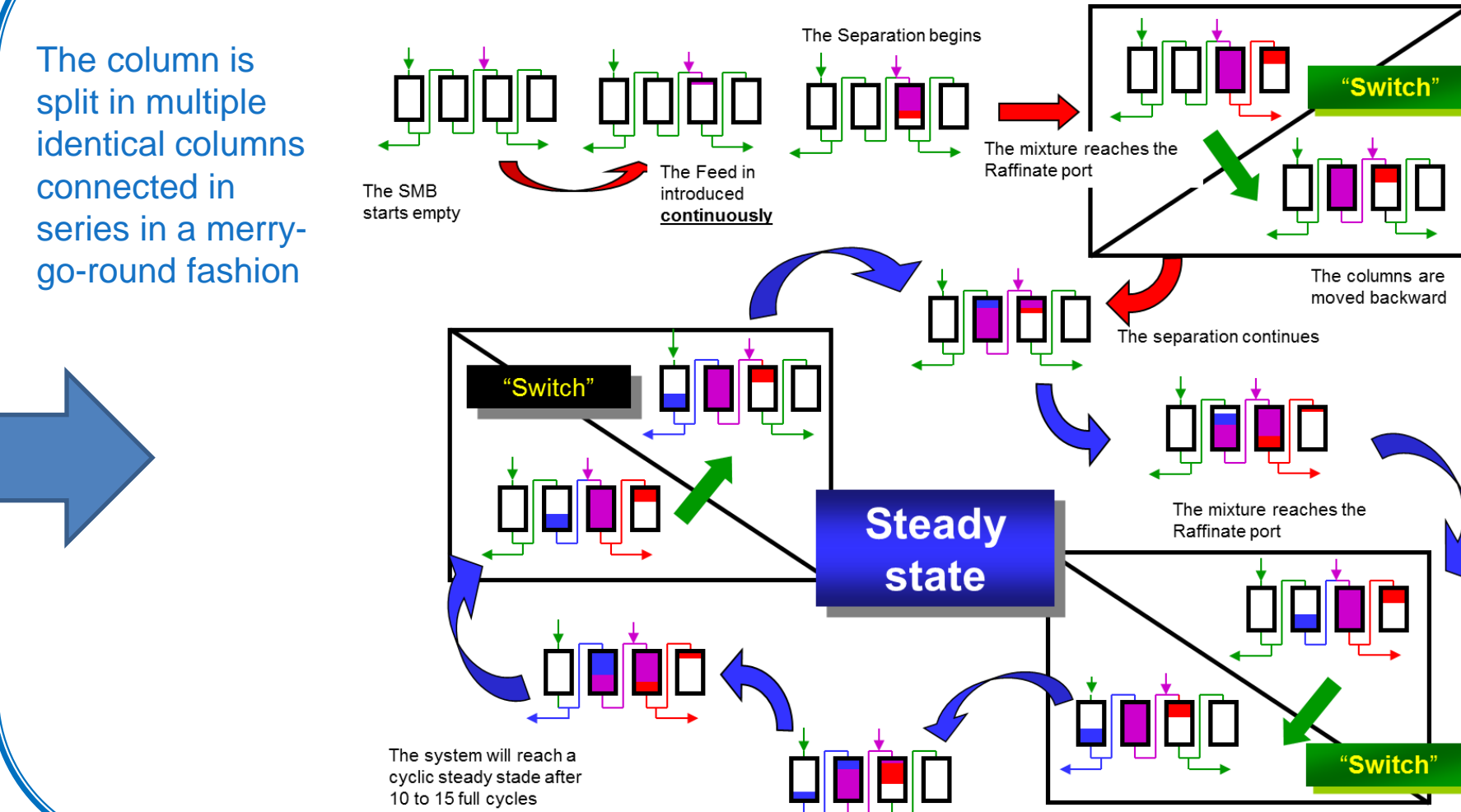
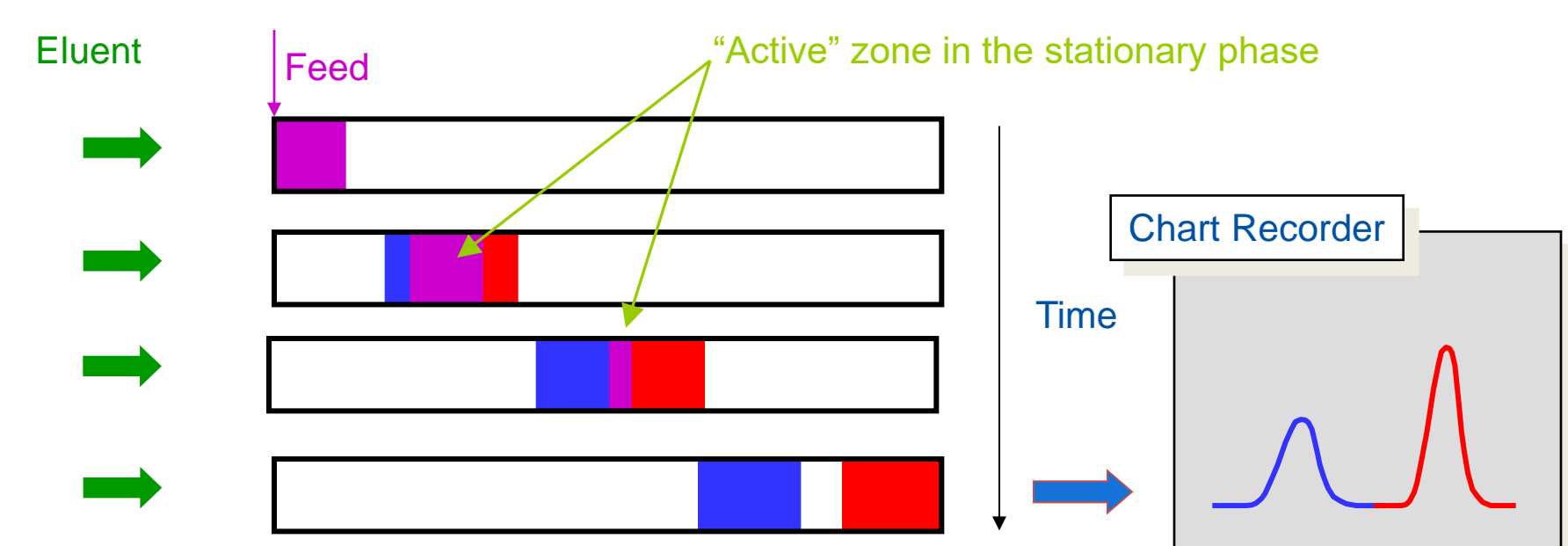
...on a routine basis

- Adsorption on a solid media followed by elution with a solvent
- Mild conditions
 - Ambient temperature
 - Non-reactive system
 - Scale up is linear
- Separation methods can be developed in **few weeks**
- Preparative batch chromatography is a **powerful technique**
 - High purity >99%
 - High recovery >95%

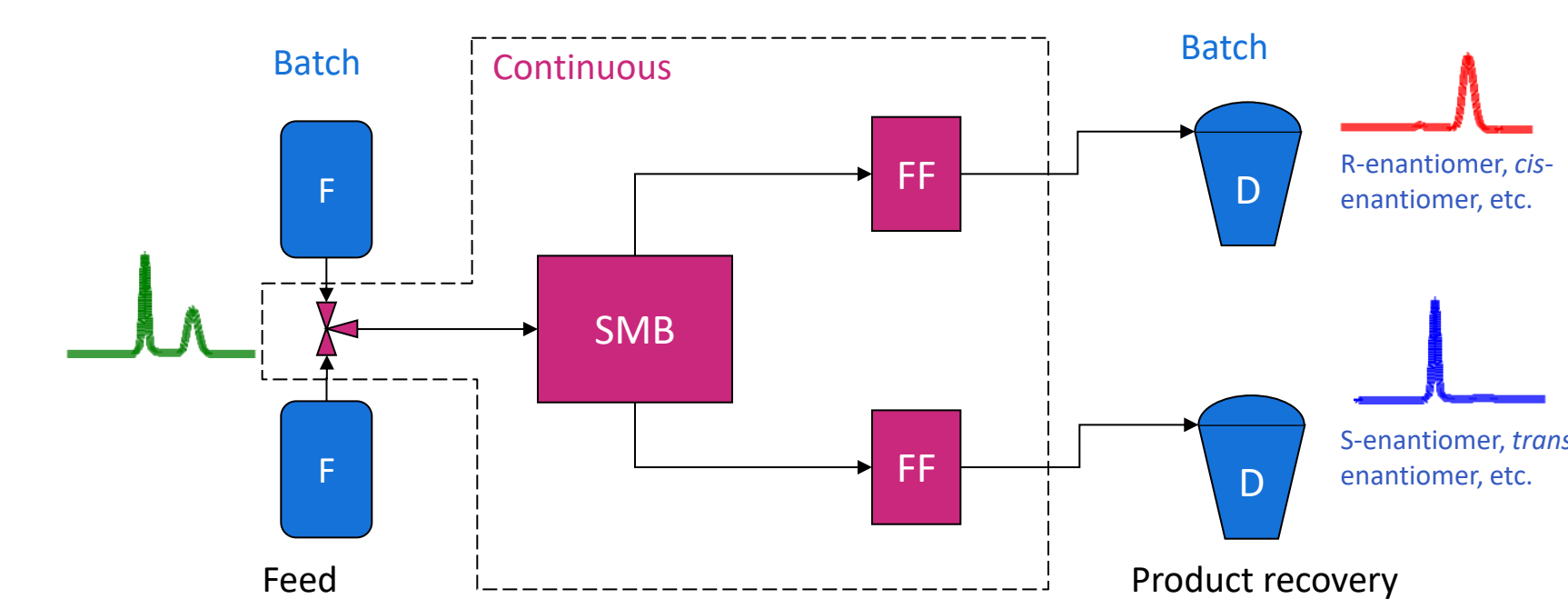
Continuous Chromatography Principle – Pushing the Limit of Batch Chromatography

From a Batch Process...

A sample (binary mixture) is injected at the inlet of a column and is eluted by a solvent (mobile phase). At the other side of the column a detector allows to monitor the separation.



...to a Continuous Process



Process Development – Rapid Evaluation of the Separation and Scalability Reduce Time to Market

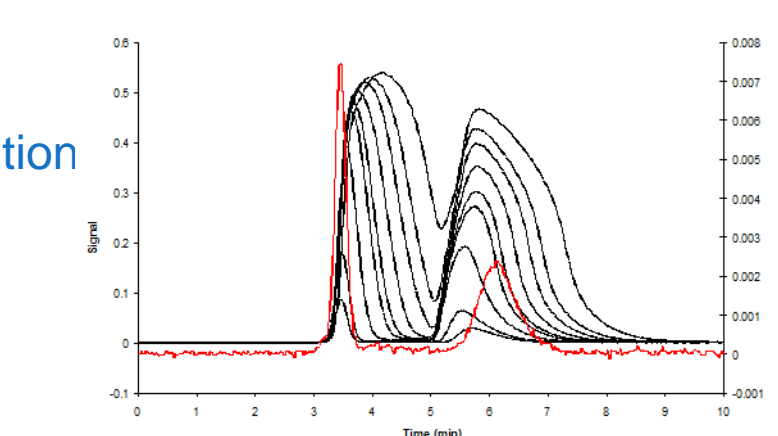
It Starts with a Screening...

- Feed characterization
 - Evaluation of solvent compatibility based on molecule functionality
 - Evaluation of solubility
 - Analysis : 1H and 13C NMR, HPLC, DSC, TGA, KF
- Selection of Mobile phases for screening
- Screening on commercial Phases
 - Coated phases
 - Chiralpak AD, AS, AY, AZ / Chiralcel OD, OJ, OZ, OX
 - Lux Amylose-1, Amylose-2, Cellulose-3, Cellulose-4
 - Immobilized phases
 - Chiralpak IA, IB, IC, ID, IE, IF, IG
 - Whelk O1, Whelk O2, ULMO, DACH DNB
 - Kromasil DMB, TBB



Further Development is Required...

- Loading studies
 - Selection of best separation condition
 - Evaluation of production rate
- Stability study
 - Evolution of retention over time
- Product recovery evaluation
 - Evaporation to dryness
 - Crystallization
 - Solvent exchange



About 2-3 weeks

Followed by a Demonstration Run...

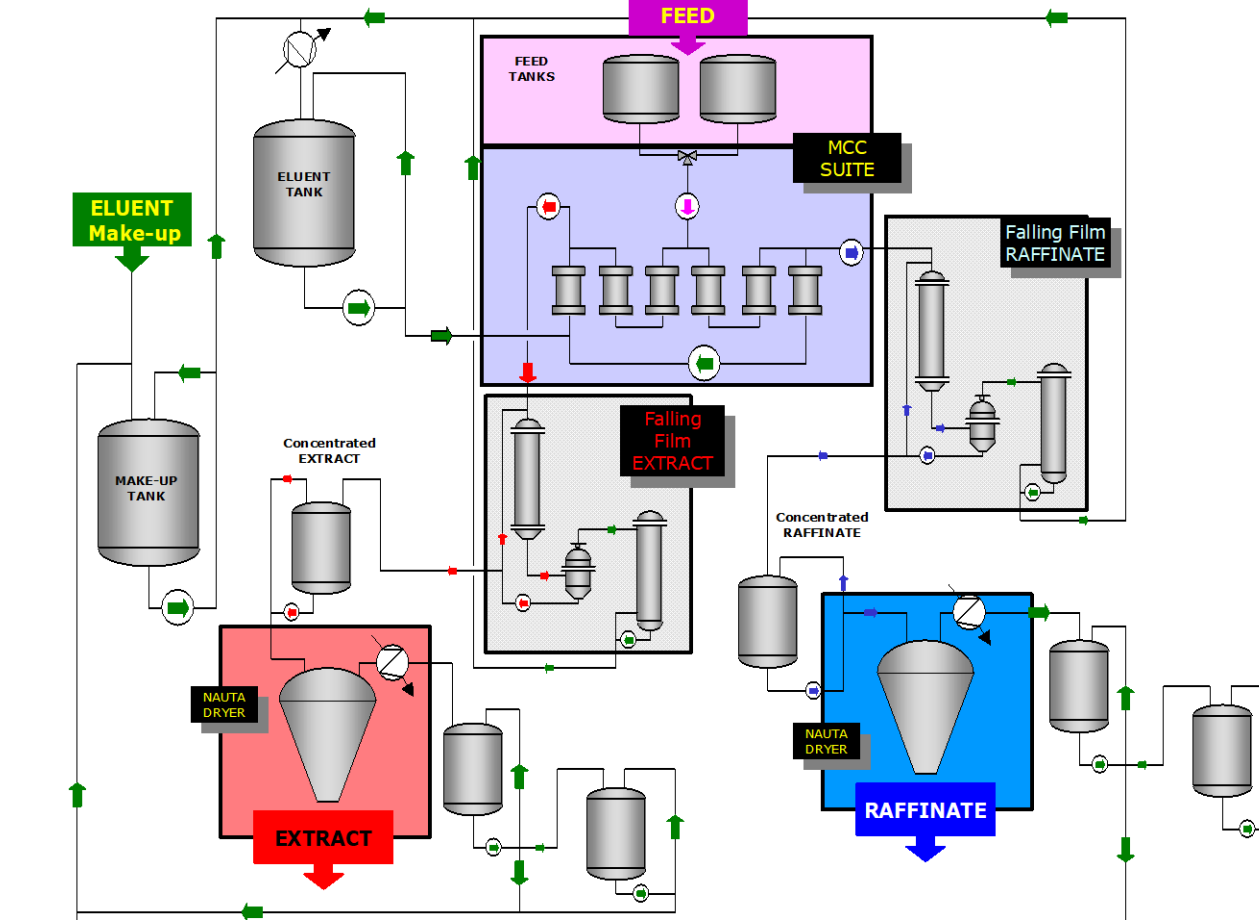
- Separation on a bench-top unit
 - 4.6 or 10 mm in diameter
 - Process 10 to 50 g /d
 - Requires small amount of feed
 - Requires small amount of solvent
 - Achieve high purity and high recovery
 - Both enantiomers available for testing



About 2 weeks for parameters optimization

Another few weeks can be used for product manufacturing (100 g)

Before Implementation at Large Scale

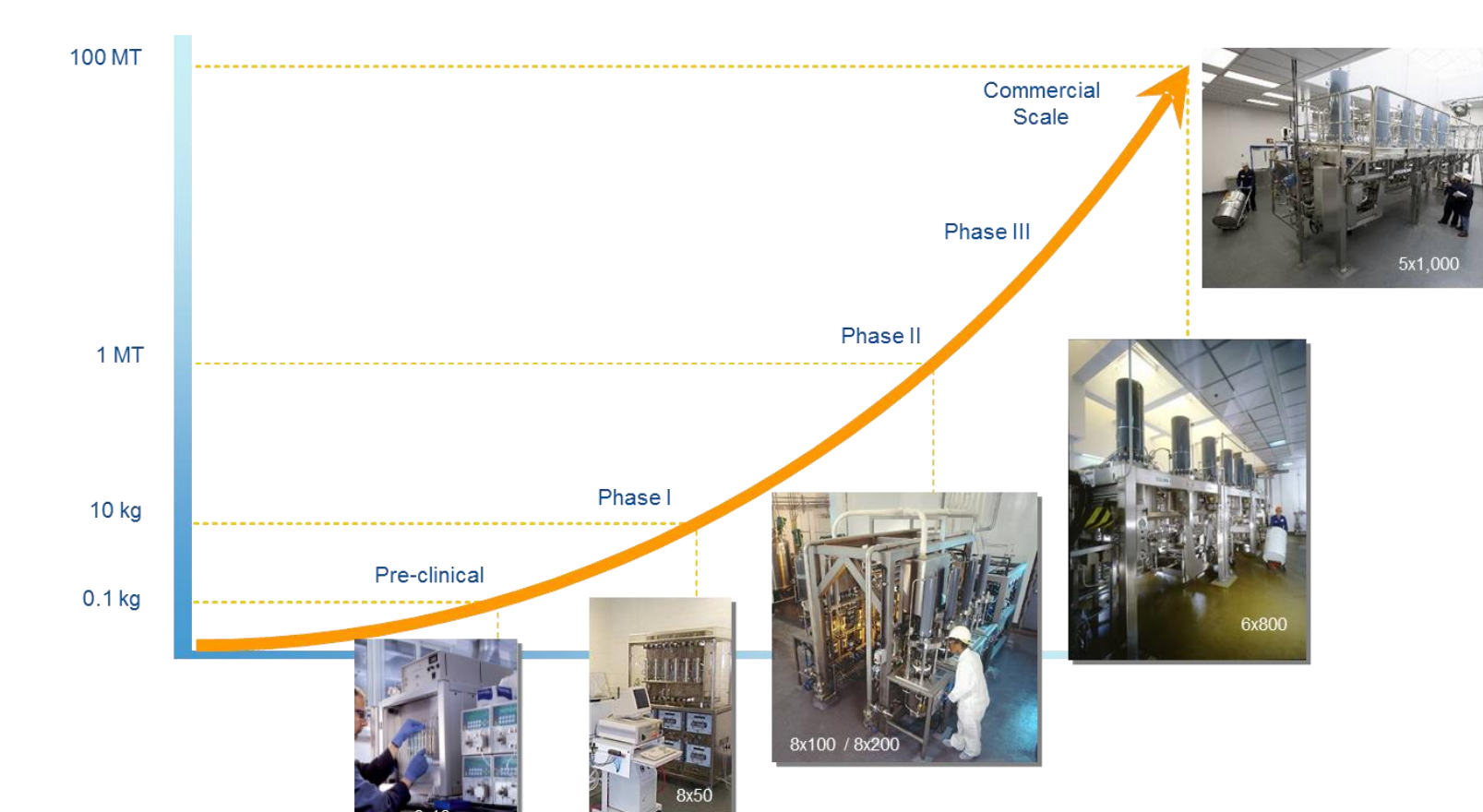


A Technology with Benefits – Lowered Production Costs

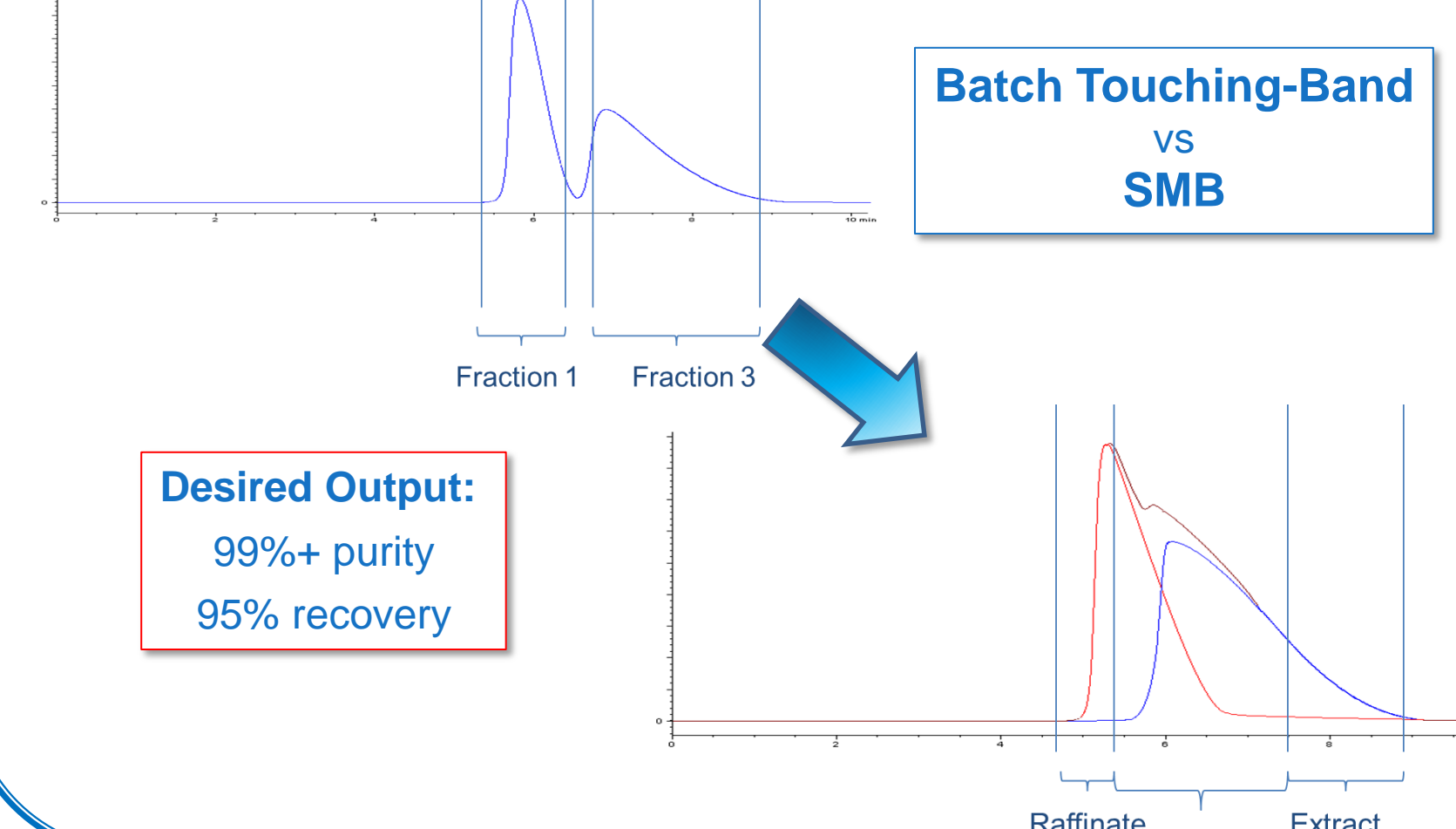
A Truly Scalable Process...

	Discovery	Early Development	Full Development	Production
Amount	1mg - 50g	100g - 10kg	5 -100kg	Tons
Needed isomer	Both enantiomers	Both enantiomers	Active enantiomer	Active enantiomer
Time Frame	Days	Weeks	Months	Months to Years
Cost importance	Minor	Minor	Middle	Major
Scale-up feasibility	Minor importance	Middle importance	Major importance	Prerequisite

From Grams to Multi Tons...



A More Efficient Process...



... Resulting in Lower COGS!

SMB provides superior performance

- Load 1 to 5 X larger
- 1 to 5 X less solvent – **99.98% recycling at commercial scale!**
- No injection = **no dead time** => Continuous flow
- No need for full chromatographic resolution
- More separation options**

But!

- Isocratic only** – Watch for strongly retained impurities!
- Feed **MUST** be dissolved in the Eluent!
- Binary separation** – less flexibility than batch!

AFC Equipment – A Full Range of Sizes Available for All Phases of Development up to Commercial Scale

SMB 8x10 – Bench top unit (3 units)

- R&D (non GMP)
- Columns: 10-mm x 10-cm
- Pumps: Dual piston pumps
- Temperature controlled

Application

- Method Development and Optimization
- Proof of concept



SMB 8x50 – the “kilo” scale

- c-GMP facility
- Columns: 50-mm x 10 cm
- Pumps: Dual piston pumps
- Temperature controlled
- Product recovery:
 - Two 20-L evaporators (continuous)

Application

- Method Development and Optimization
- Production of clinical trial material
- Production rate 0.5 - 3 kg of enantiomer per day

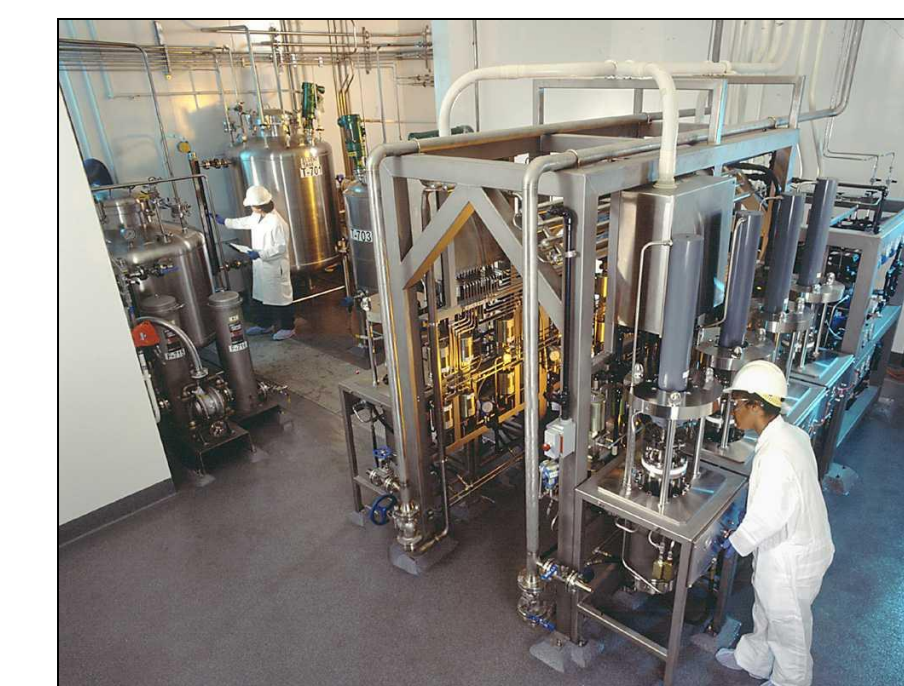


SMB 8x100/200 – The Pilot Scale

- c-GMP facility
- Columns:
 - 316L Stainless steel columns
 - 100 mm or 200 mm I
- Temperature controlled
- Product recovery:
 - Two falling film evaporators

Application

- Production of phase I, II material
- Production rate 8 - 50 kg of enantiomer per day



Commercial Scale units (2 units)



6x800

- 165 kg CSP
- 50 to 200 MTA Feed
- >95% on stream factor
- >99.98% solvent recycled



5x1000

- 215 kg CSP
- 75 to 300 MTA Feed
- >95% on stream factor
- >99.98% solvent recycled