Safety First, Quality Always

ADAPTING THE SEPARATION PARAMETERS TO ADDRESS AN UNEXPECTED IMPURITY IN A VALIDATED PROCESS

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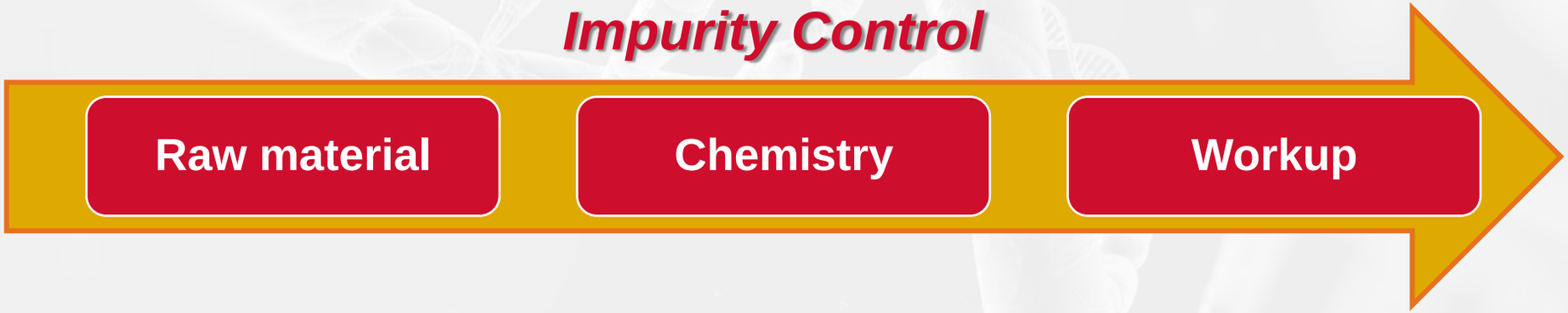
Impurity Control is Critical in API Manufacturing

- The main challenge of API manufacturing is centered around Impurities.
- Removal of the impurities can be done using various techniques:
  - Control of the raw material quality
  - Improvement of the chemistry
  - Removal post reaction: Crystallization, Extraction, Chromatography…



The fate of **Key Impurities** in the synthetic route should be evaluated and addressed

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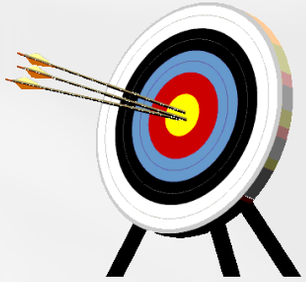
Do We Have More Arrow in the Quiver?

- Continuous Chromatography has been in use for over 20 years in the manufacturing of Active Pharmaceuticals Ingredients (API)
- Because of its BINARY nature, It is well accepted as an efficient/competitive technique to achieve chiral purity.
- Can a “binary” chromatographic technique solve more **Complex problems**

What is the fate of the impurities in the SMB process?



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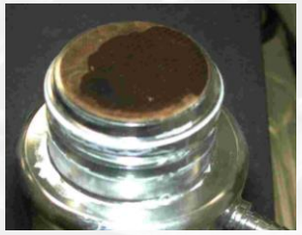
Handling Impurities Depending on Their Nature

Strongly retained impurities

- Strongly retained Impurities eventually reduce the loadability of the column by occupying the adsorption sites. Resulting in a loss of performance.
- The Stationary Phase acts as an expensive “filter” – Not ideal…



Easy fix:
Pretreatment
of the feed
(guard column)

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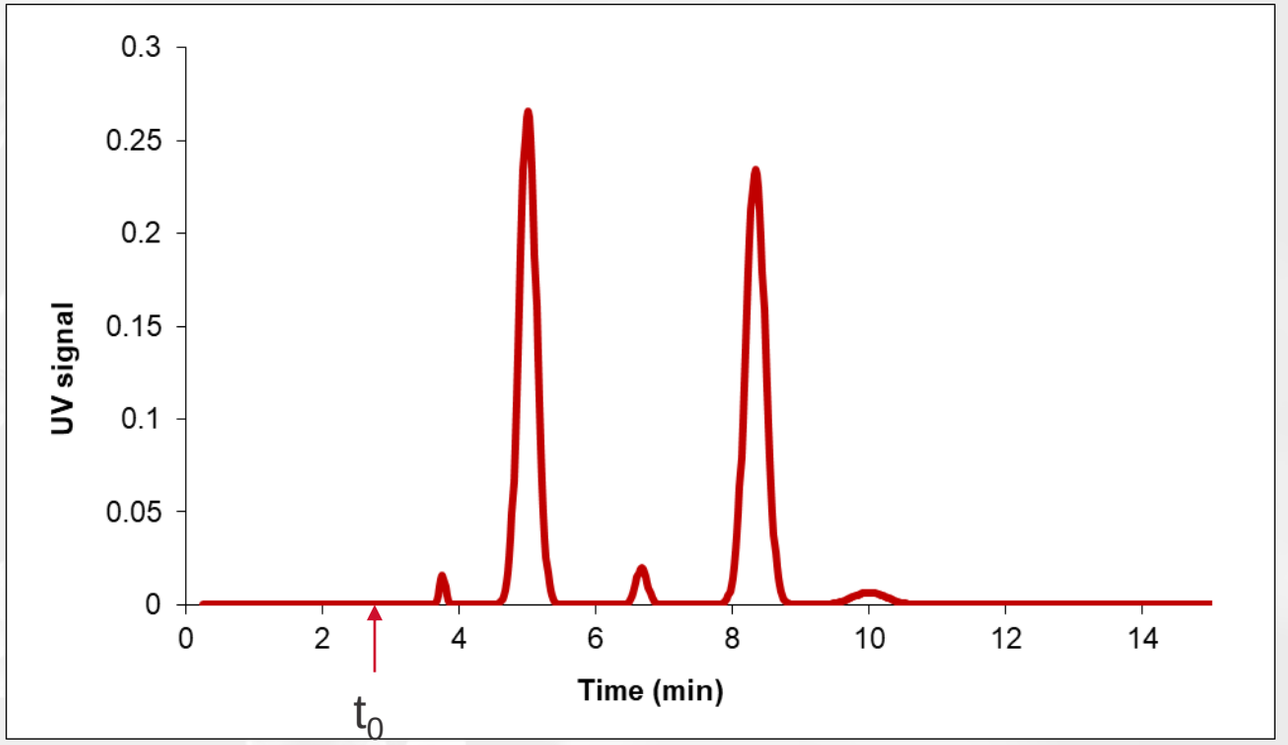
Handling Impurities Depending on Their Nature

Impurities with limited retention

- The order of elution is important
- The impurity level in the final product can:
  - Double from the feed content (coeluting)
  - Be reduced drastically to non detect
  - Be distributed between the two SMB outlets.

- A simple Mass Balance problem!



$$Feed_{Imp} = Raffinate_{Imp} + Extract_{imp}$$

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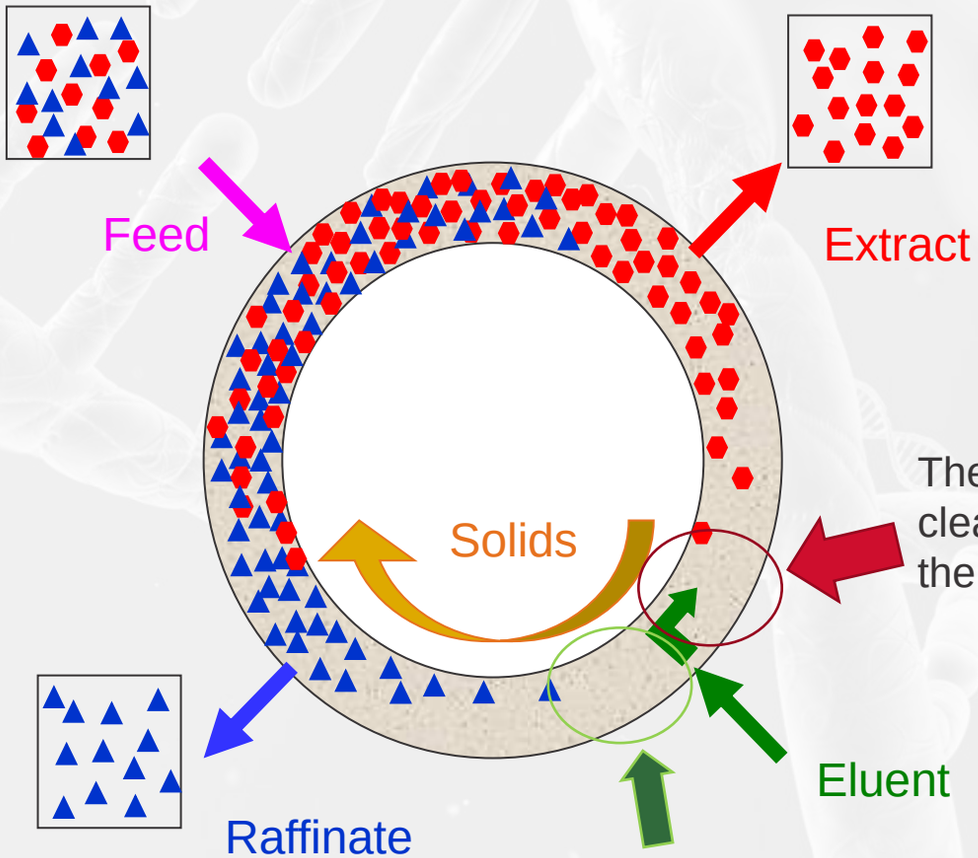
The SMB Process is a “Closed” Loop

- The SMB process “recycle” the media to create an “infinite” column

- The SMB process “recycle” also the eluent internally to minimize the solvent consumption



The packing needs to be clean before moving pass the eluent point

The eluent needs to be clean also before moving pass the eluent point

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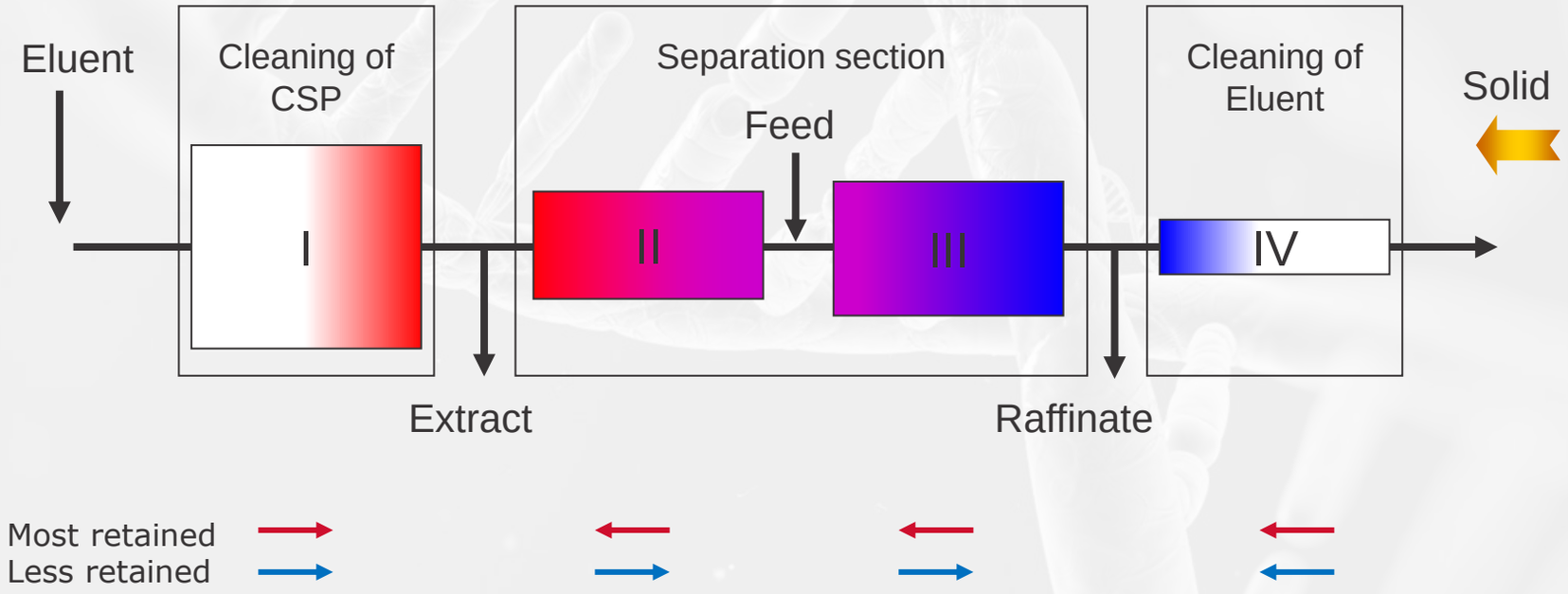
The SMB Principle Relies on Elution Time

SMB is characterized by 4 different flow rates to allow a continuous separation of a binary mixture by playing with the difference between residence times and column switching (period).



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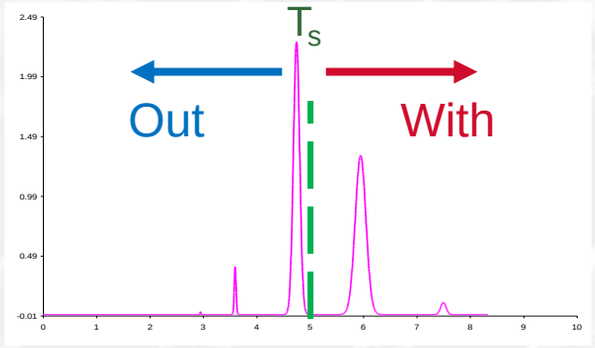
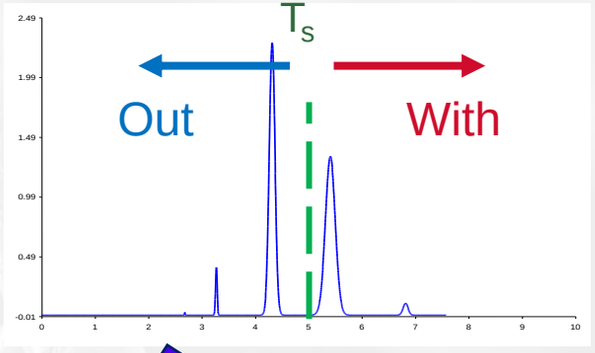
The Elution in Each Zone is Relative to the Switch Time

When the switch time occurs, everything left of the switch time is

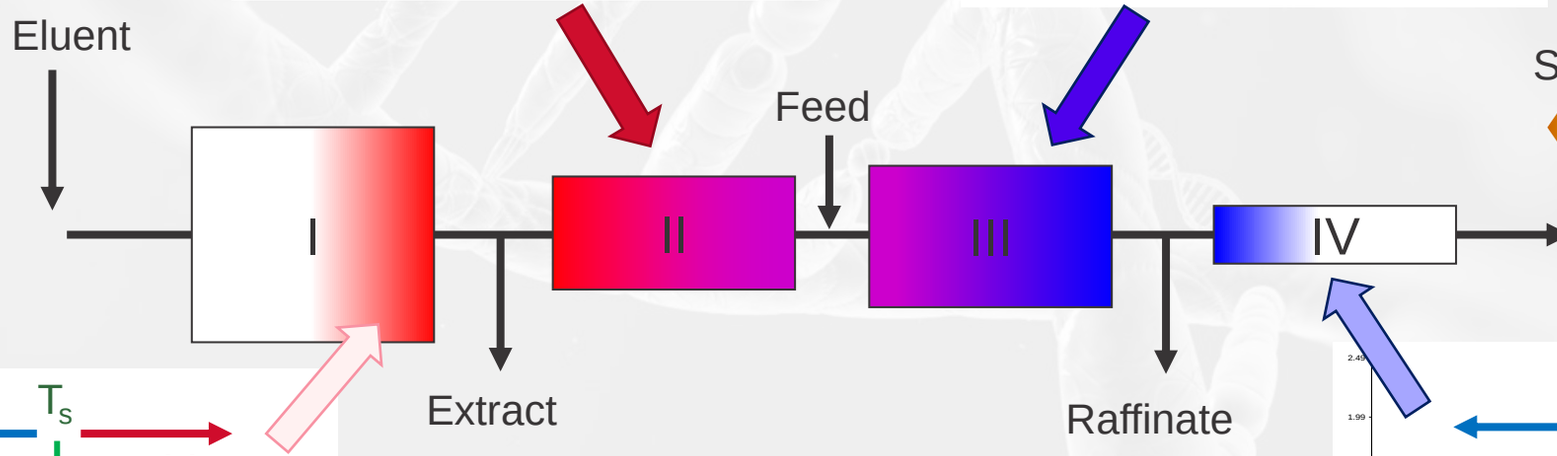
Out of the column

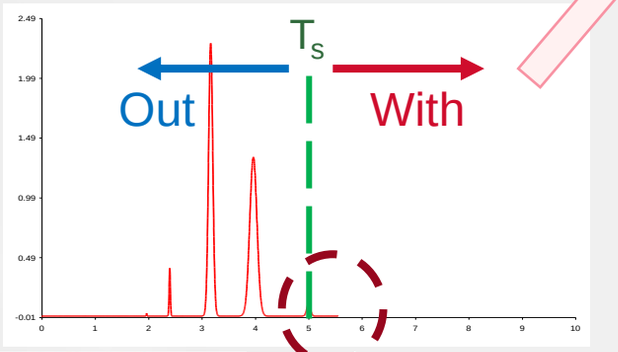


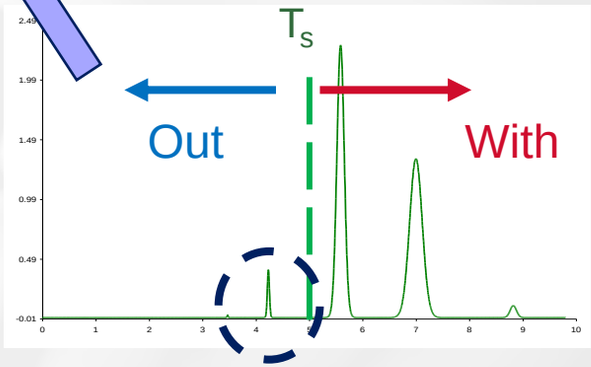


Everything to the right is moved upstream

with the column







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Strategies to remove the Impurities with the SMB

- Multiple Cases to consider leading to either a partial reduction or a complete removal of the impurity.

Case	Product stream	Impurity	Comment
1	Extract	Fast eluting	Full removal (lower zone IV + Raf increased)
2	Extract	Last eluting	Partial removal
3	Extract	In between	Partial to complete removal with lower throughput
4	Raffinate	Fast eluting	Partial removal
5	Raffinate	Last eluting	Full removal (Increase zone I, Ex increased)
6	Raffinate	In between	Partial removal

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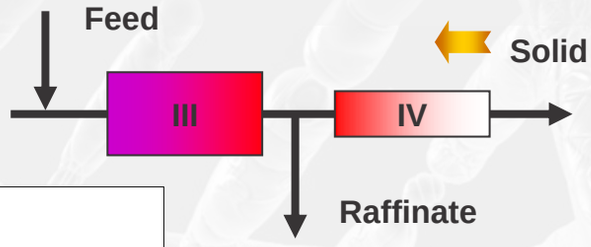
Cas #1: Fast Eluting Impurity and Product in the Extract Stream

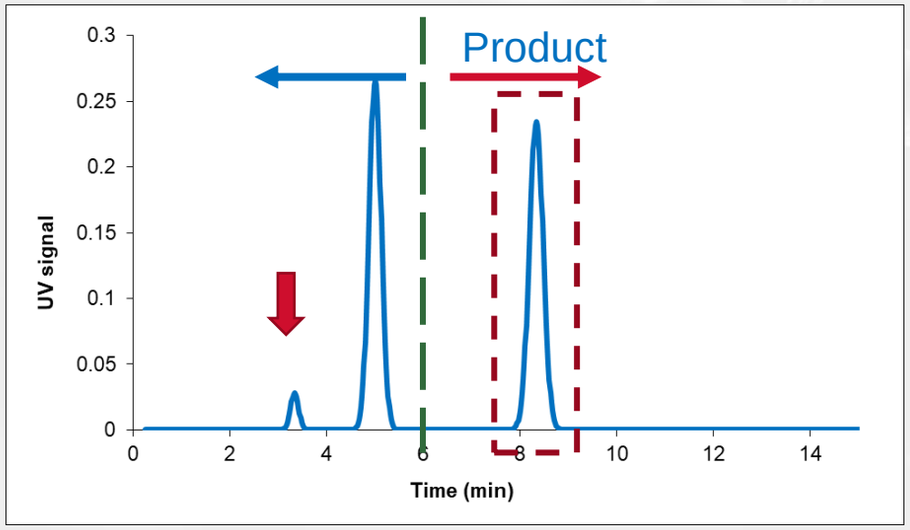
The “volume” of solvent comprised between t_0 and the switch time, is leaving the column and is recycled at the inlet of zone I

- The “fast” eluting impurity exit Zone IV with the recycled eluent,
- It moves rapidly through zone I
- And pollutes the Extract stream



Zone III flow rate

T_s

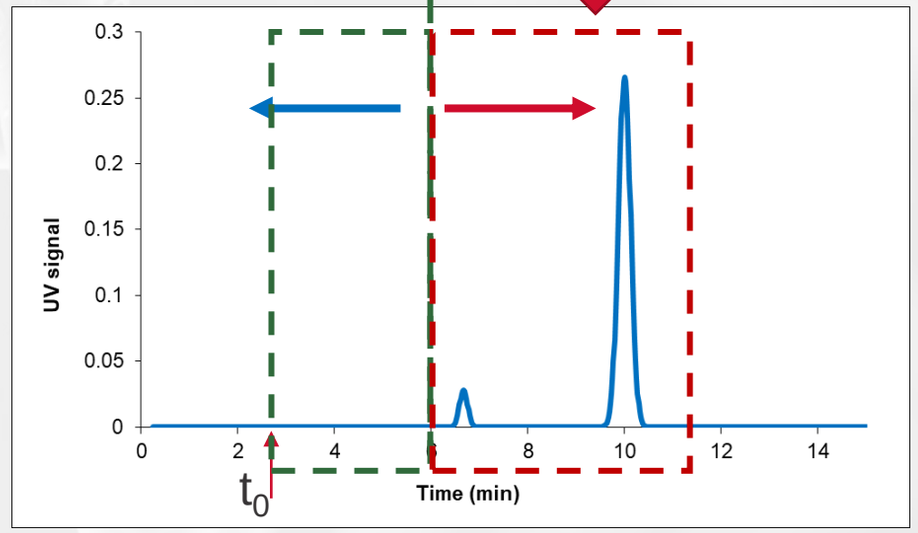


Composition of the “Recycled” stream (Zone IV outlet)

T_s

Composition of the Raffinate stream

Zone IV flow rate



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Cas #1: Fast Eluting Impurity and Product in the Extract Stream

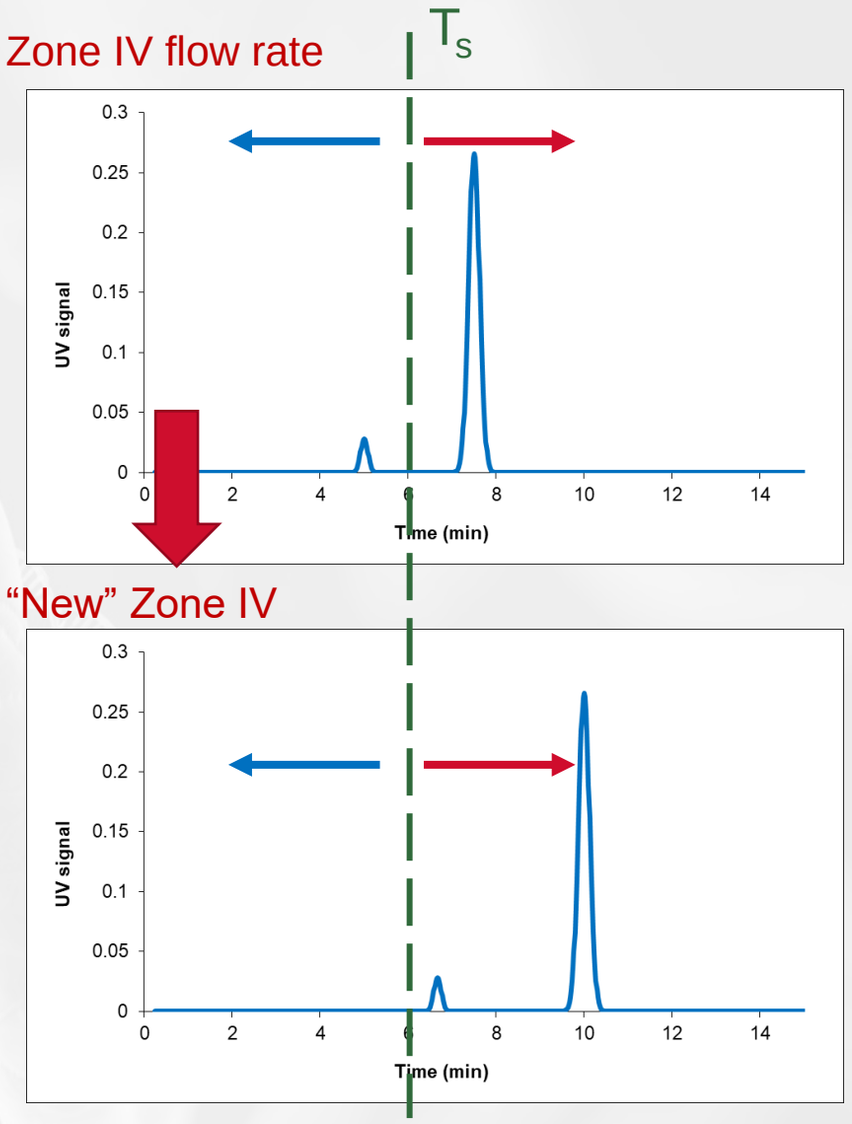
By reducing the zone IV flow rate, the impurity is retained longer than the switch time and therefore carried back into zone III to be eventually removed in the Raffinate stream.

Consequences

- ⬇ Lower internal eluent recycling
- ⬇ More eluent make up to use
- ⬇ More diluted Raffinate
- ⬇ Added stress to the evaporation downstream

- ⬆ No change to the throughput
- ⬆ Complete removal of the impurity

$$Feed_{Imp} = Raffinate_{Imp} + Extract_{imp}$$



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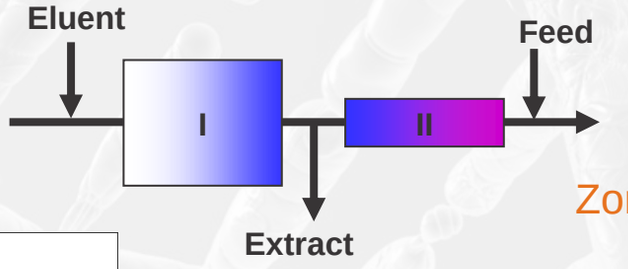
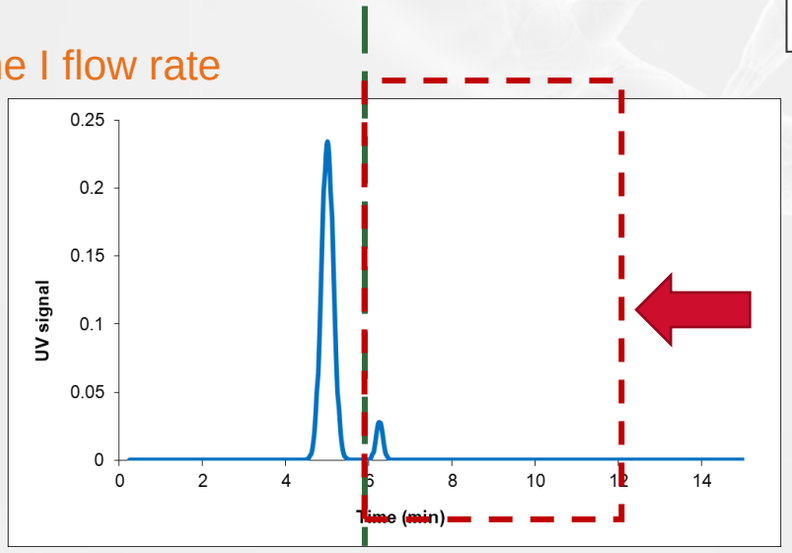
Case #2: Long Eluting Impurity and Product in the Extract Stream

- Adjustment of the zone I flow rate is required to “allow” the impurity to retain on the column.
  - The column is moved into zone IV where the flow is the lowest – increased retention
  - The impurity level in the SMB will eventually reach a steady state.



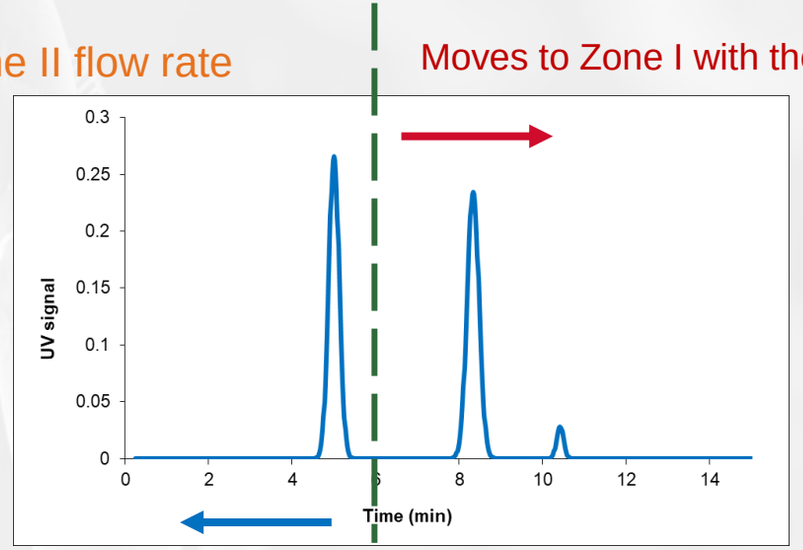
Zone I flow rate



Composition retained on the column moving to Zone IV

Zone II flow rate

Moves to Zone I with the column



Moves to Zone III with the eluent

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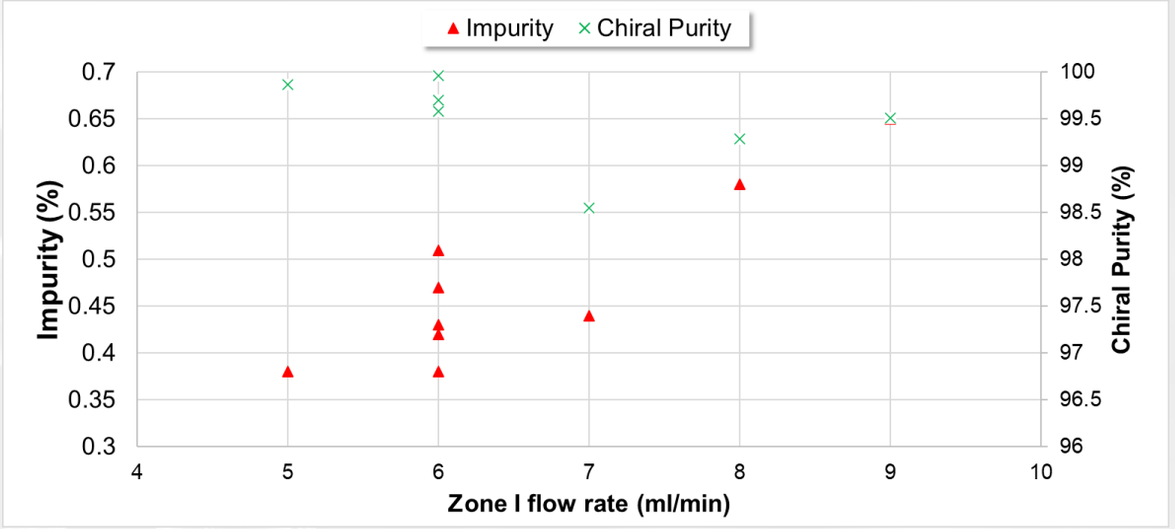
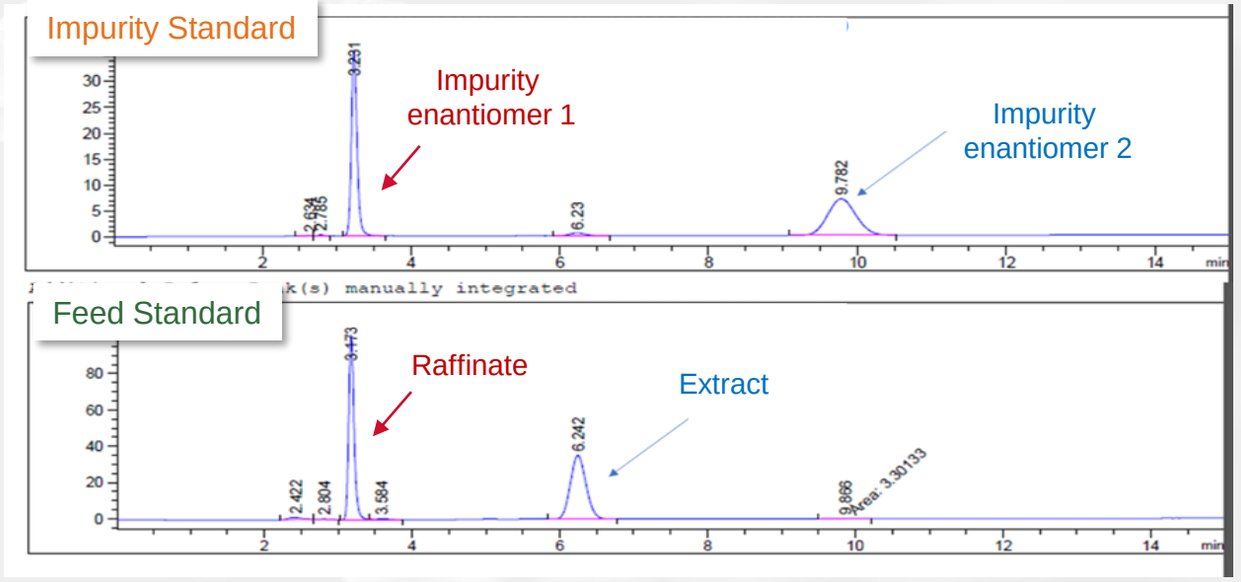
Case #2: Long Eluting Impurity and Product in the Extract Stream

- The demonstration is performed on the mini-SMB equipped with 8 column 10x100 mm

- Feed contains ~ 0.63% of a racemic impurity
  - Technically 2 impurities to consider (0.32% each)
  - ⇧ One enantiomer elutes with the undesired enantiomer – Full removal
  - ⇩ Other impurity is 0.6% in the extract if zone I flow is too high (impurity is pushed in the extract stream)
  - ⇩ Potentially 0.32% impurity expected if allowed to recirculate
  - ⇧ Same throughput – no reduction of feed rate





Case #2: Long Eluting Impurity and Product in the Extract Stream

- The removal of the impurity is **only partial**
- The level of the impurity in the product stream is similar to the level in the feed stream
- A 2nd pass of the extract stream will be required for a full removal
  - Impurity is recovered in the extract
  - Product is recovered in the raffinate stream
  - Same conditions, longer switch time.

$$Feed_{Imp} = Raffinate_{Imp} + Extract_{imp}$$

50/50 split

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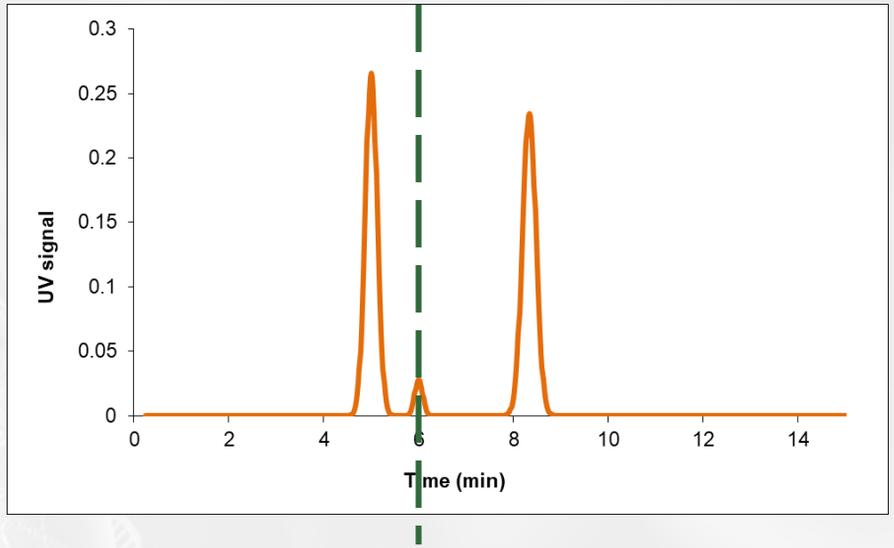
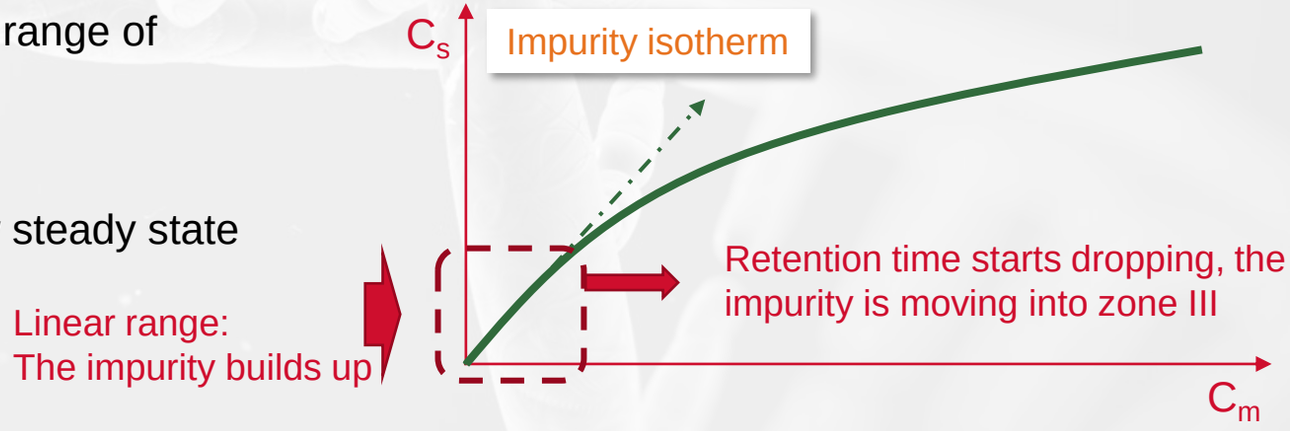
Case #3: The Impurity is Eluting in Between the Enantiomers

- The impurity elutes in between the enantiomers
- The impurity will split depending on the separation conditions
- The isotherm is important
  - Displacement
  - Tag-along effect
- Avoid the match of retention time and switch time
  - ⬇ Slow build up of the impurity until non-linear range of isotherm is reached
  - ⬇ Sudden drop in raffinate total purity
  - Mass balance on the impurity is key to show steady state





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Case #3: The Impurity is Eluting in Between the Enantiomers

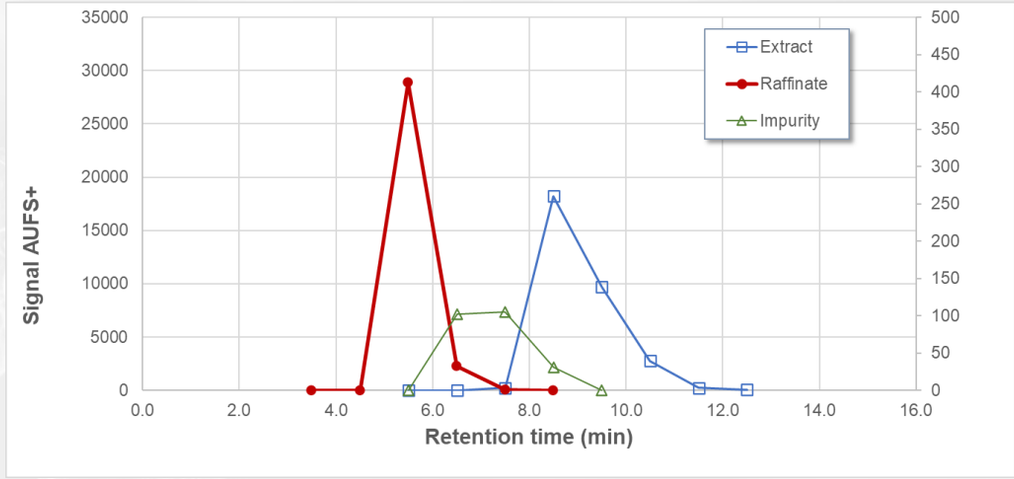
Strategies for removal are dependent on the desired product

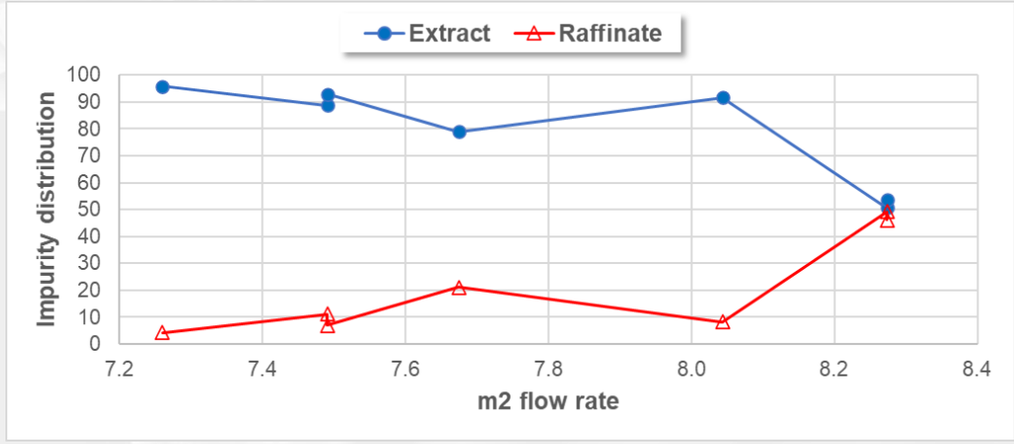
- **If product is the Extract**:
  - Increase switch time to push the impurity in the raffinate
  - ⬇ Limit the feed rate to avoid yield loss – Lower Productivity
- **If product is the Raffinate**:
  - Reduce the switch time to drive the impurity to the extract
  - ⬇ Limit the feed rate to avoid impurity overloading– Lower Productivity

Separation on the 8x10 SMB unit

Distribution of the impurity as a function of the zone II flow rate (m_2/m_3 plane)

- ✓ m_2 =7.2 the impurity is mostly in the extract stream (95% of the feed)
- ✓ m_2 = 8.3 the impurity is evenly split between extract and raffinate





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Conclusion

Impurities are always a challenge in API manufacturing

Technique for removing impurities could be expensive and yield consuming

SMB is a BINARY process that can provide some solutions to avoid added unit operations

Impurities MUST be handled preferably before the chiral separation

Consistency on quality of the feed stock is essential to the viability of the SMB unit operation as an economical process.

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Thank You

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