A NEW APPROACH TO CONFIRMING ORGANIC VOLATILE IMPURITY TESTING IN PHARMACEUTICAL PRODUCTS.

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Application: Residual Solvents

- Pharmaceutical Formulations
- Guidelines for Testing
  - International Conference on Harmonization
  - European Pharmacopoeia
- Compound Lists Vary
  - Over 60 compounds of regulatory interest
  - Classes based on toxicities
  - Resolution of large lists on a single stationary phase can be extremely difficult

The Three Approaches:

- Existing Phases Evaluated
- Modeling for a New Stationary Phase
- Stop-Flow GC Technology
  - Using Existing RT Data
  - Applying RT Data for Stop-Flow

Existing Phases Evaluated

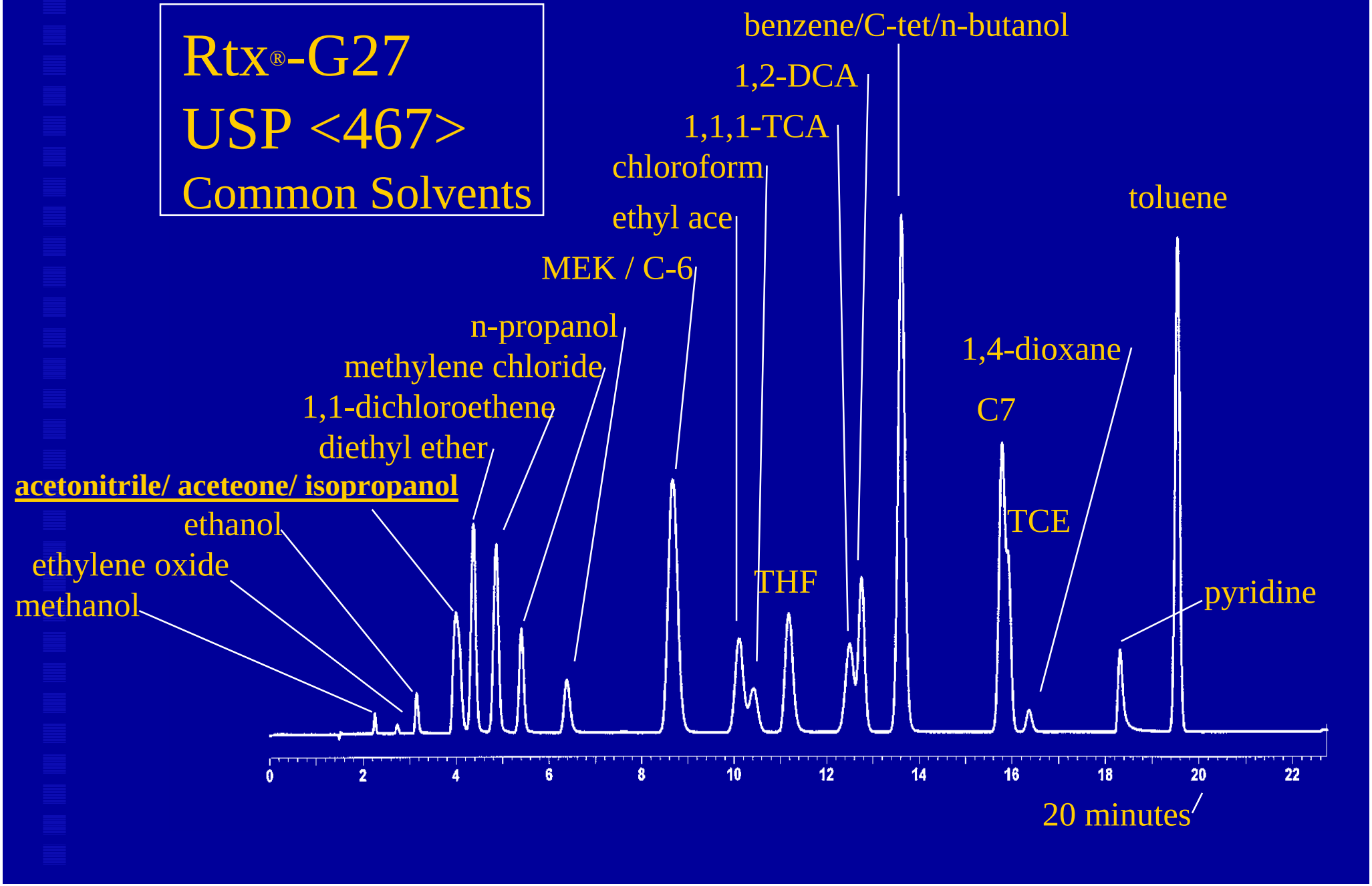
- Change in selectivity
- Low bleed
- Critical resolution
- FID or MS detection

- Column Design.

GC Analysis of OVI by USP <467>

- Method I: G27 30m x 0.53mm x 5.0 df
  - Direct Aqueous
- Method IV: G43 30m x 0.53mm x 3.0 df
  - Static Headspace
- Method V: G43 30m x 0.53mm x 3.0 df
  - Direct Aqueous
- Method VI: choice of 9 columns, depending on monograph

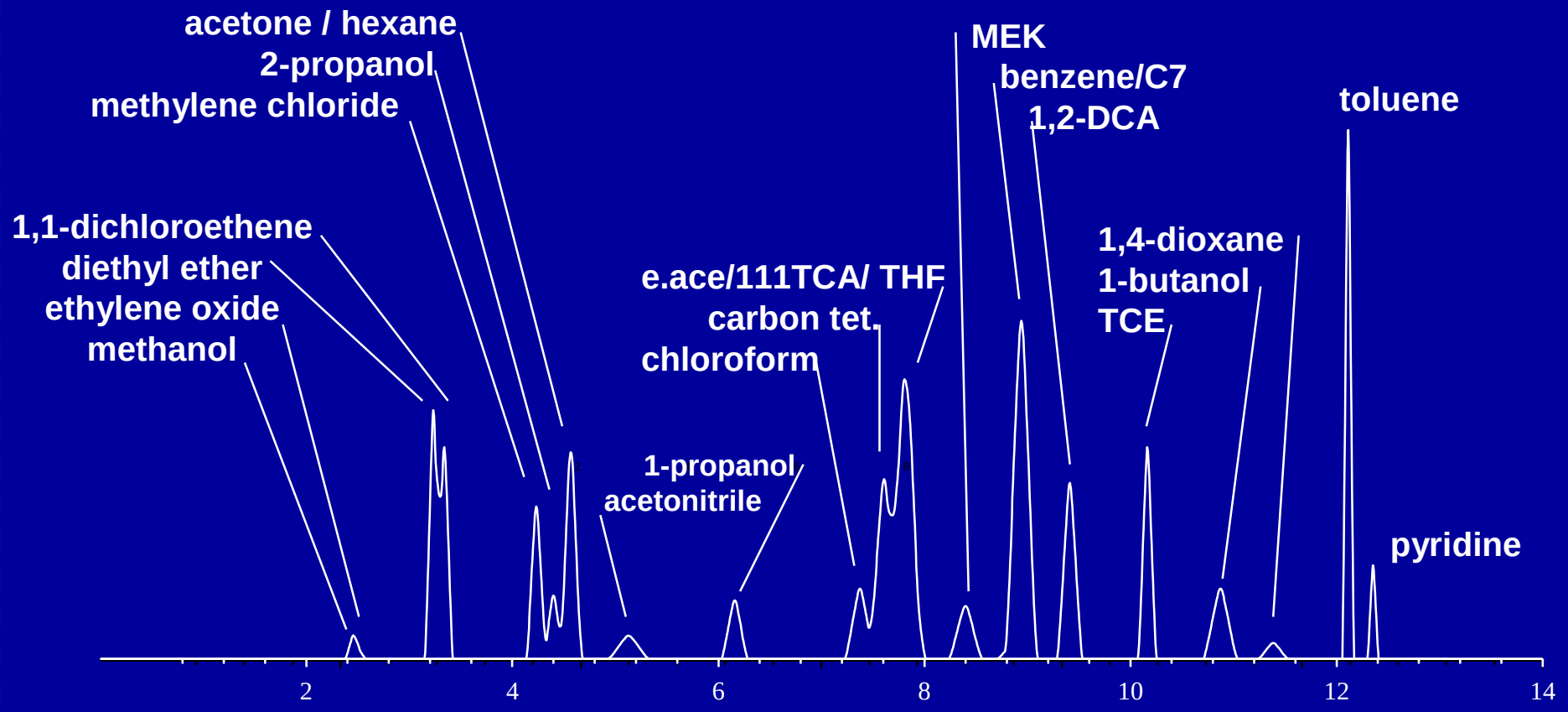
Rtx®-G27
USP <467>
Common Solvents



The Rtx-G27 Unresolved

- acetonitrile (II),acetone (III), IPA (III)
- MEK (III), C6 (II)
- benzene (I), carbon tet. (I), n-butanol (III)
- C7 (III), TCE (II)

Rtx®-VGC
USP <467> Common Solvents

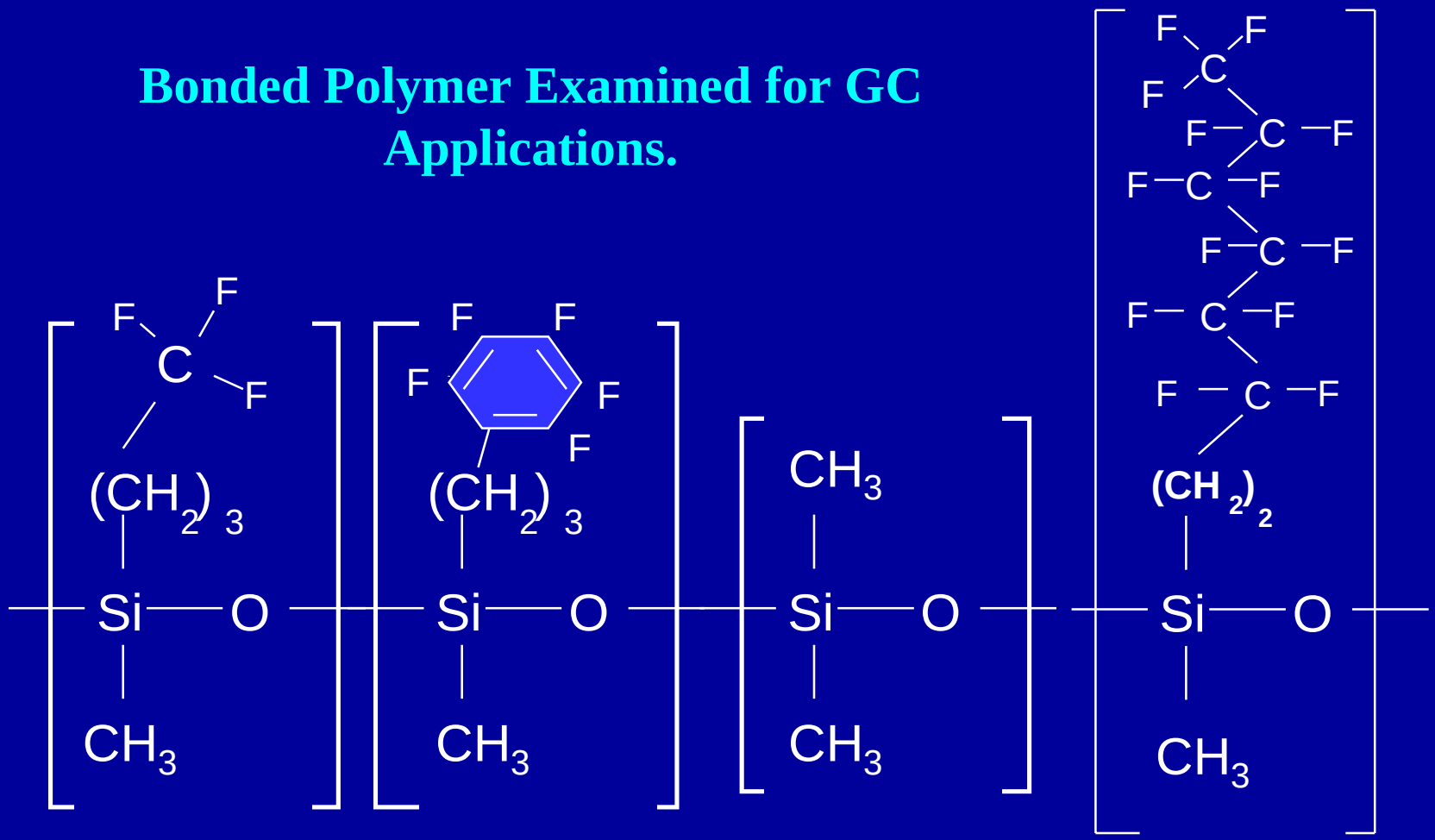


The Rtx-VGC Unresolved

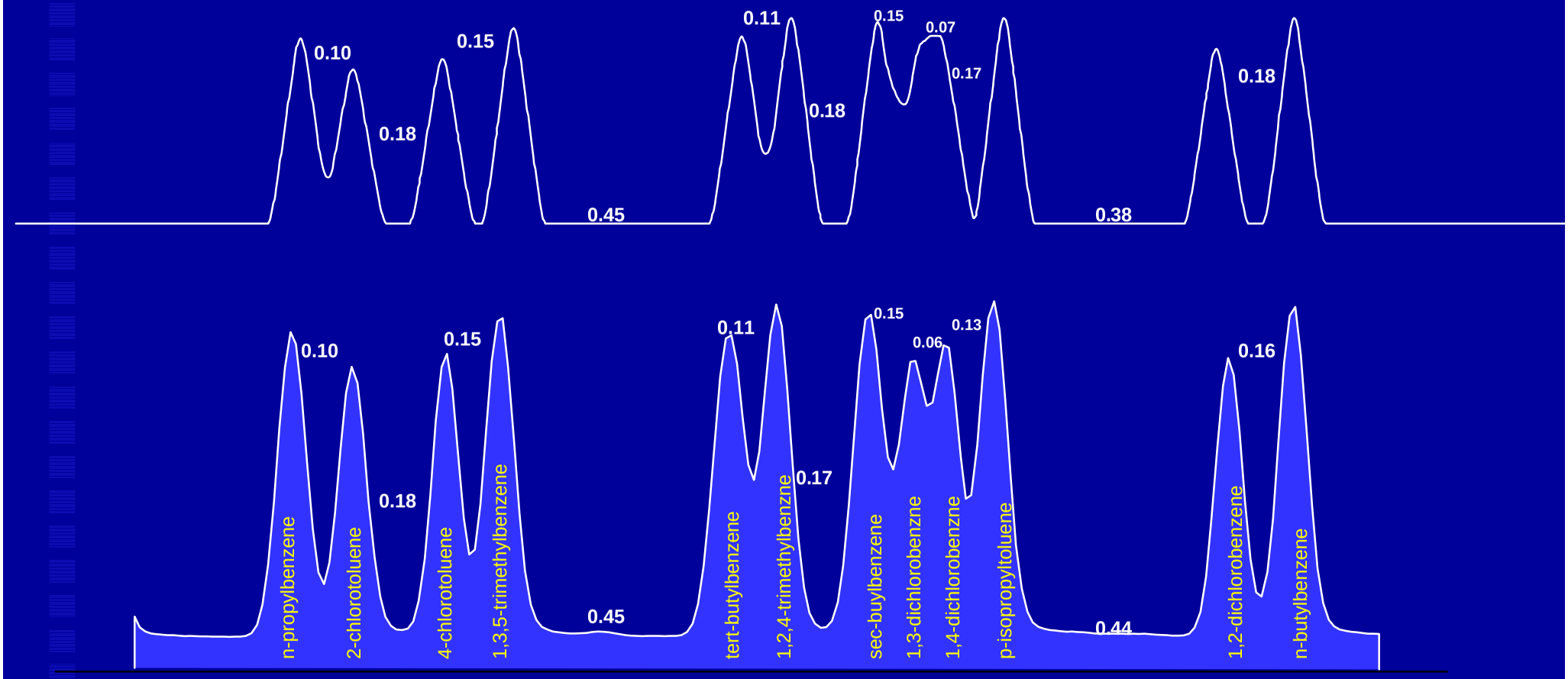
- acetone (III), C6 (II)
- E.ace (III),111TCA (I), THF (III)
- benzene (I), C7 (III)

Experimental Fluorinated Phase

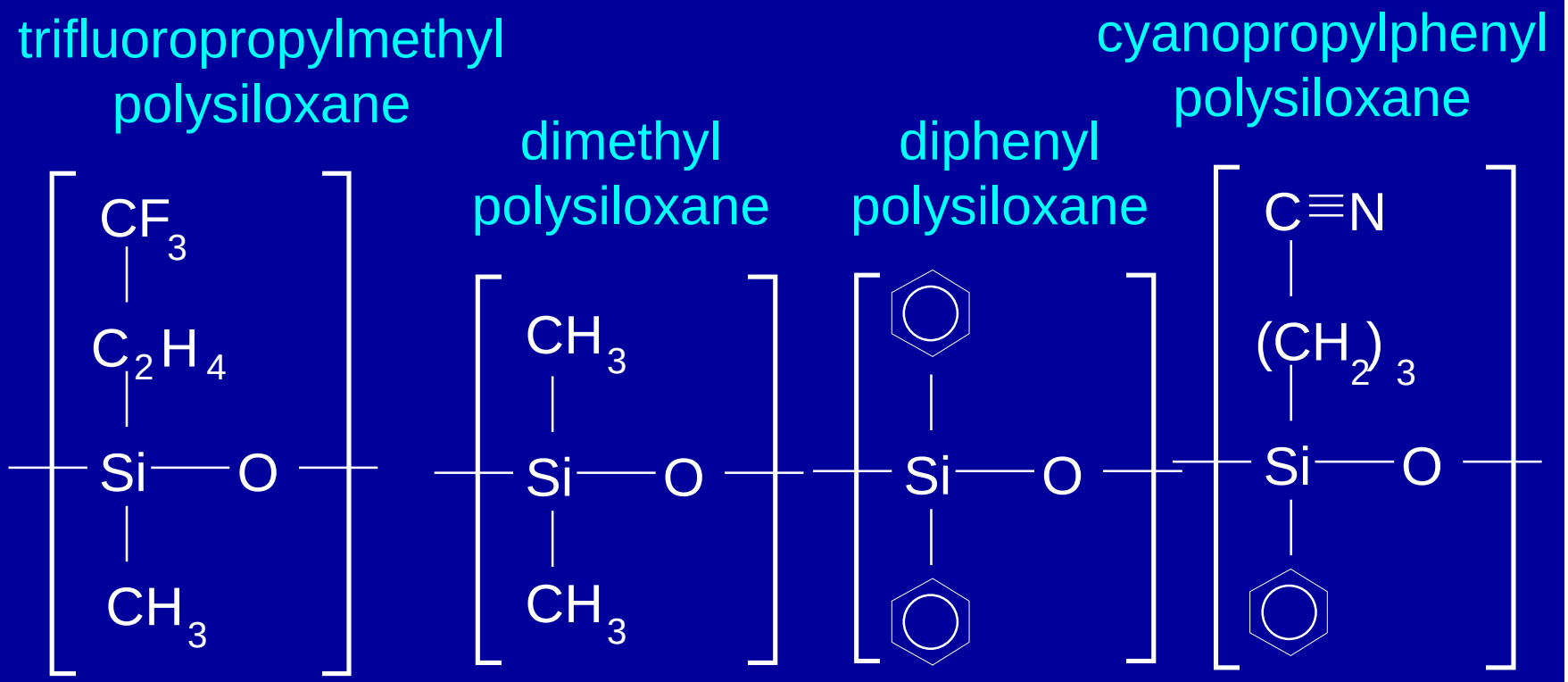
Bonded Polymer Examined for GC Applications.



Modeling for a New Bonded Phase

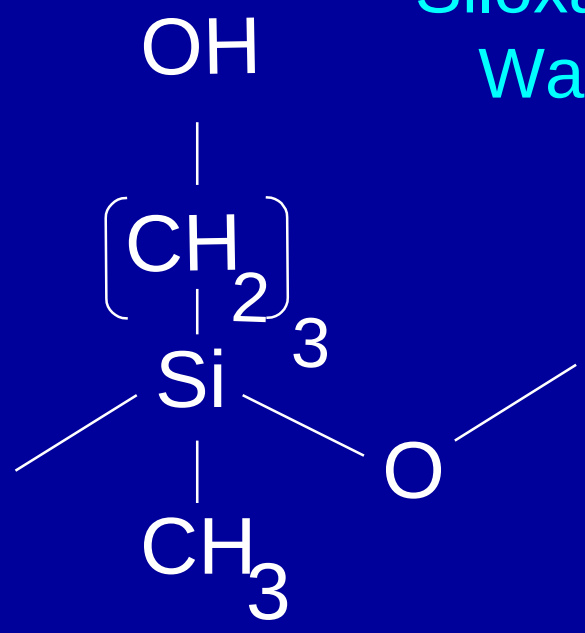


Stationary Phases Used for Modeling

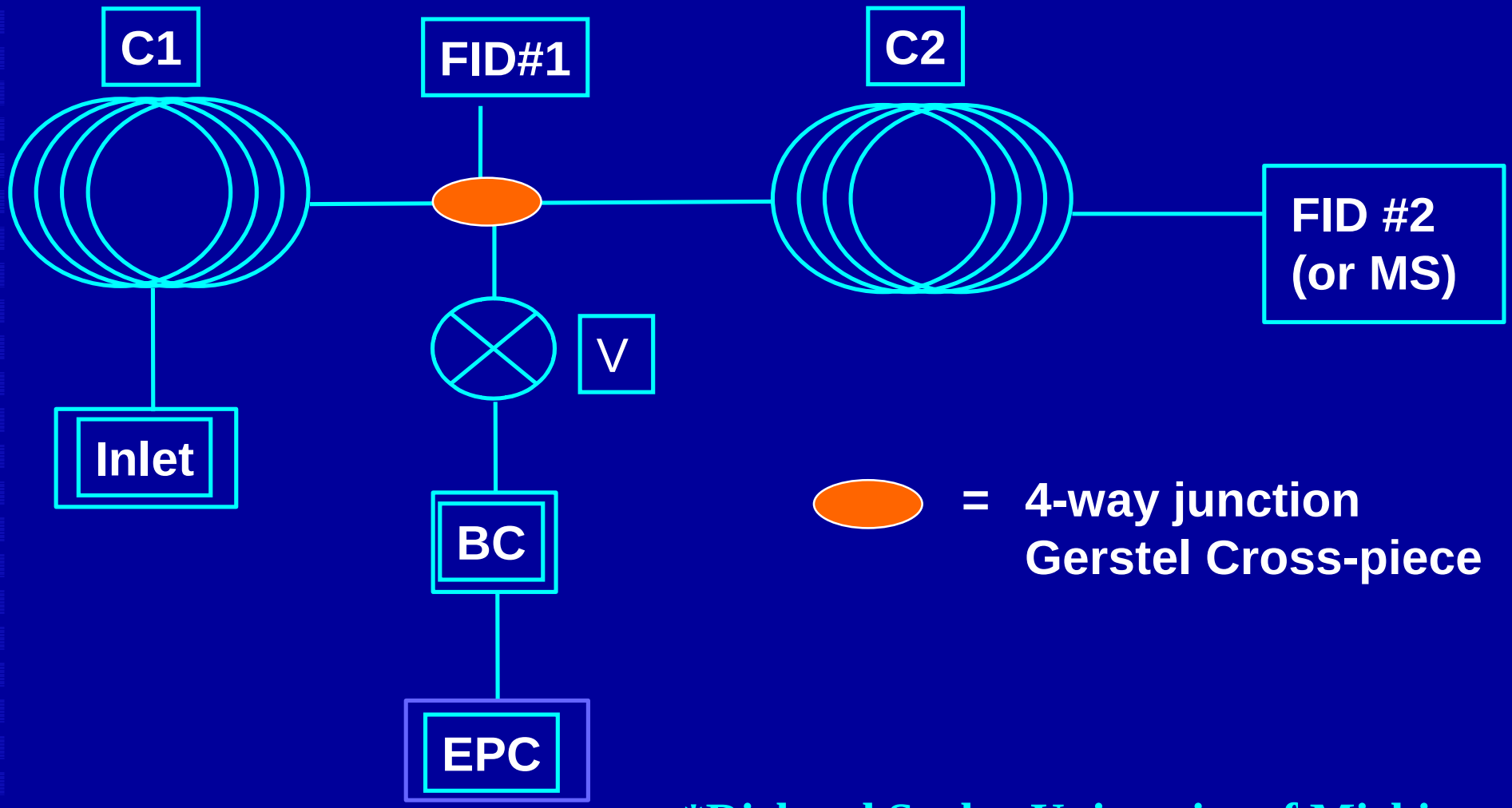


1-hydroxypropyl-methyl

Experimental
Siloxane-based
Wax Phase



Stop Flow GC System: Sacks, et. al.*



*Richard Sacks, University of Michigan

Summary of Stop-Flow GC

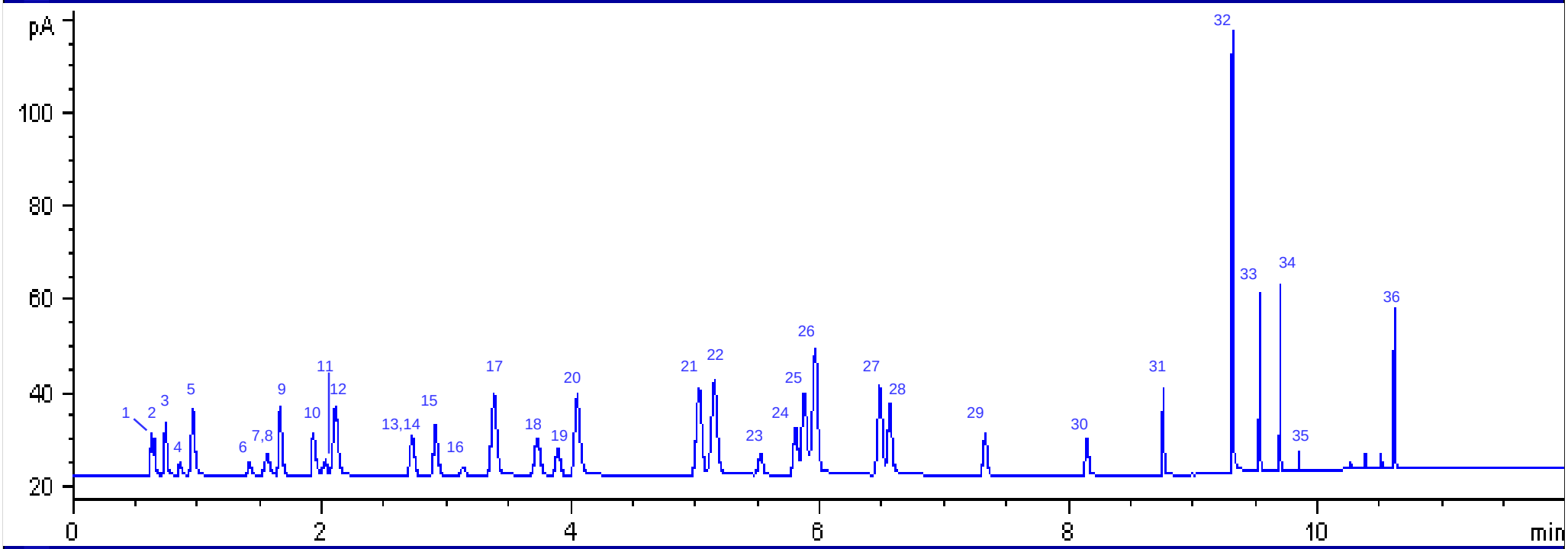
- Ability to “Tune” the Selectivity
- Flexibility
  - Standard dimension columns
  - Can vary the pulse sequences
- Significant Improvements in Analysis Times Possible
  - Fast oven programs, high flow rates

Class I & II Residual Solvents

Peak #	Compound	Peak #	Compound
1	2-methylpentane	19	1,2-dichloroethane (1,2-DCA)
2	hexane	20	2-hexanone (MBK)
3	methyl cyclopentane	21	p-xylene
4	1,1-dichloroethene (1,1-DCE)	22	m-xylene
5	methyl cyclohexane	23	nitromethane
6	*trans*-1,2-dichloroethene	24	2-methoxyethanol
7	carbon tetrachloride (CCl4)	25	pyridine
8	1,1,1-trichloroethane (1,1,1-TCA)	26	o-xylene
9	methanol	27	chlorobenzene
10	1,2-dimethoxyethane	28	2-ethoxyethanol
11	methylene chloride (CH2Cl2)	29	1,1,2-trichloroethane (1,1,2-TCA)
12	benzene	30	dimethyl formamide (DMF)
13	*cis*-1,2-dichloroethene	31	N,N-dimethylacetamide (DMA)
14	trichloroethene (TCE)	32	1,2,3,4-tetrahydronaphthalene (THN)
15	acetonitrile (MeCN)	33	ethylene glycol (EG)
16	chloroform	34	1-methyl-2-pyrrolidinone (1-MP)
17	toluene	35	formamide
18	1,4-dioxane	36	sulfolone

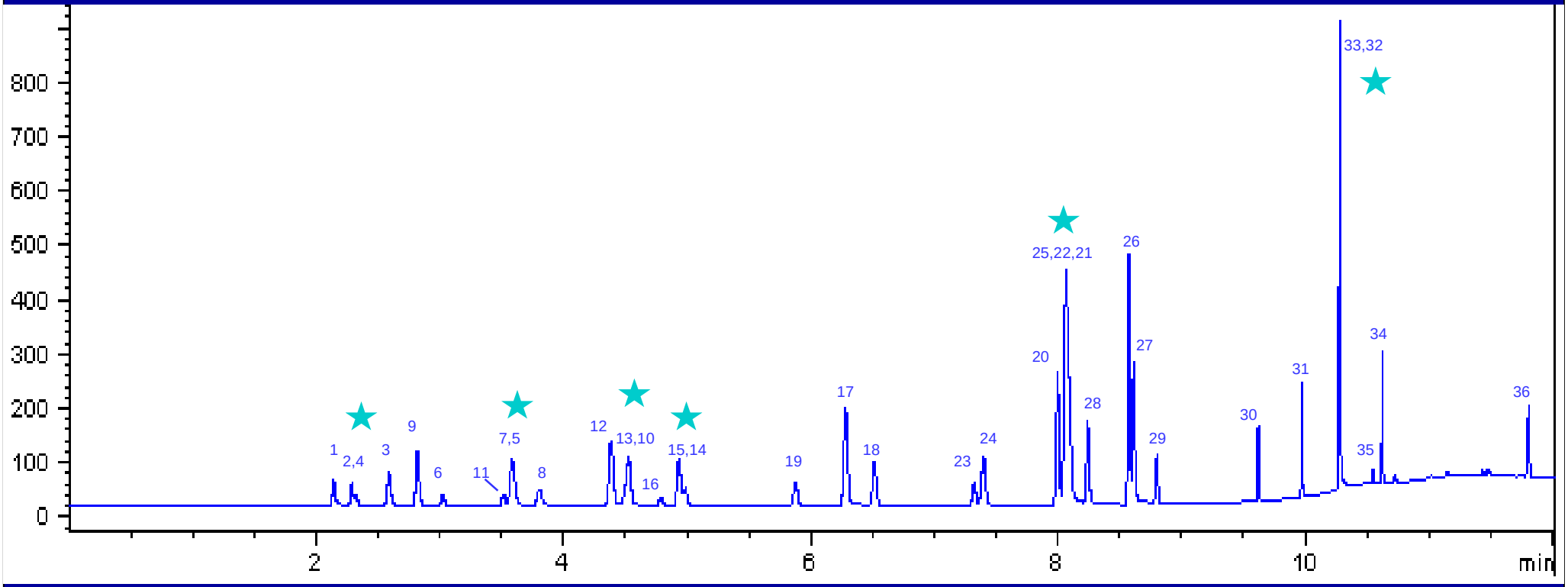
Fast Run Conditions: 1st FID

After Rtx-Stabilwax, 15m x 0.25mm x 0.5µm



Fast Run Conditions: 2nd FID

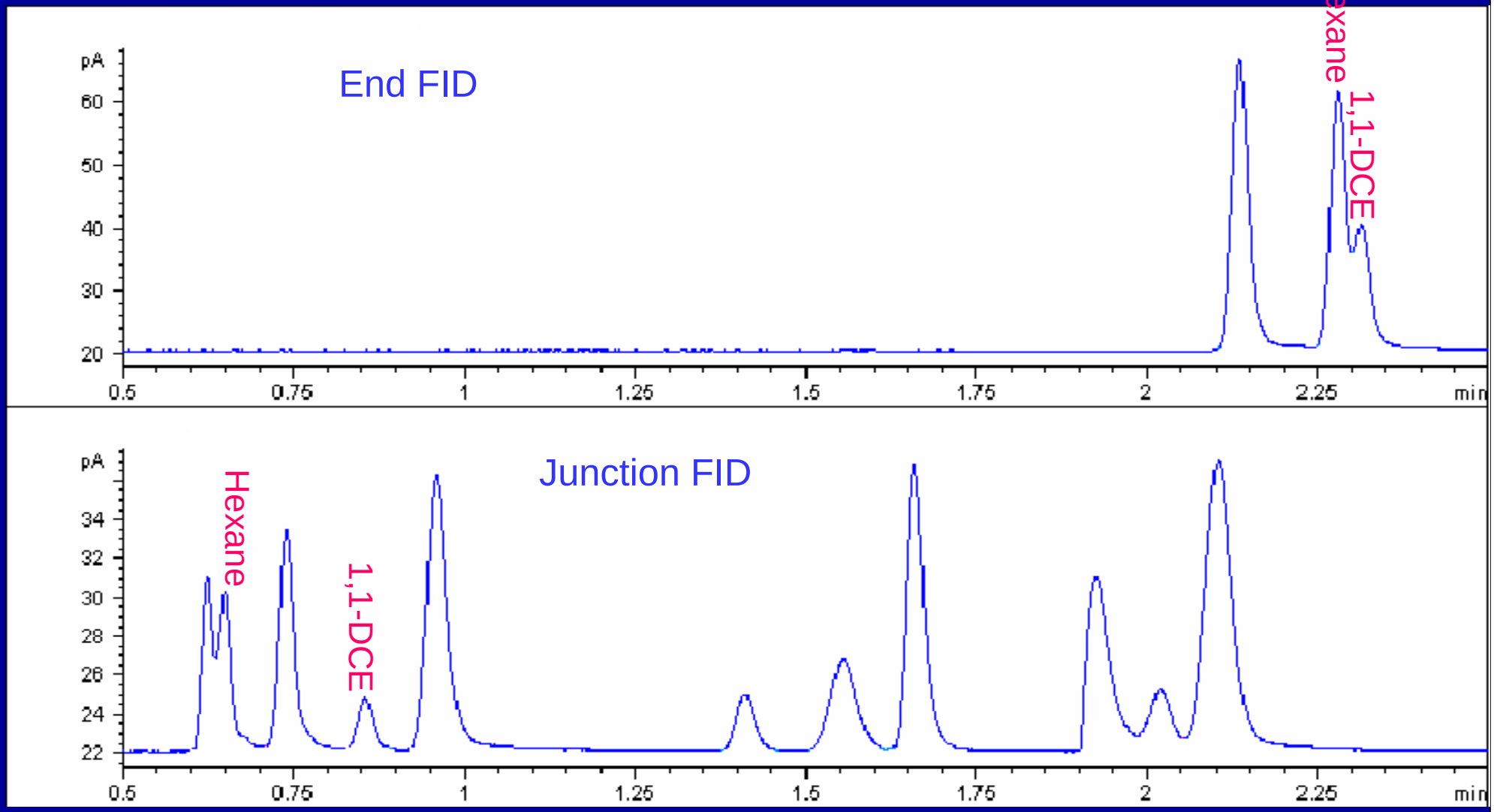
After Rtx-Stabilwax + Rtx-200 (30m x 0.25mm x 1.0μm)



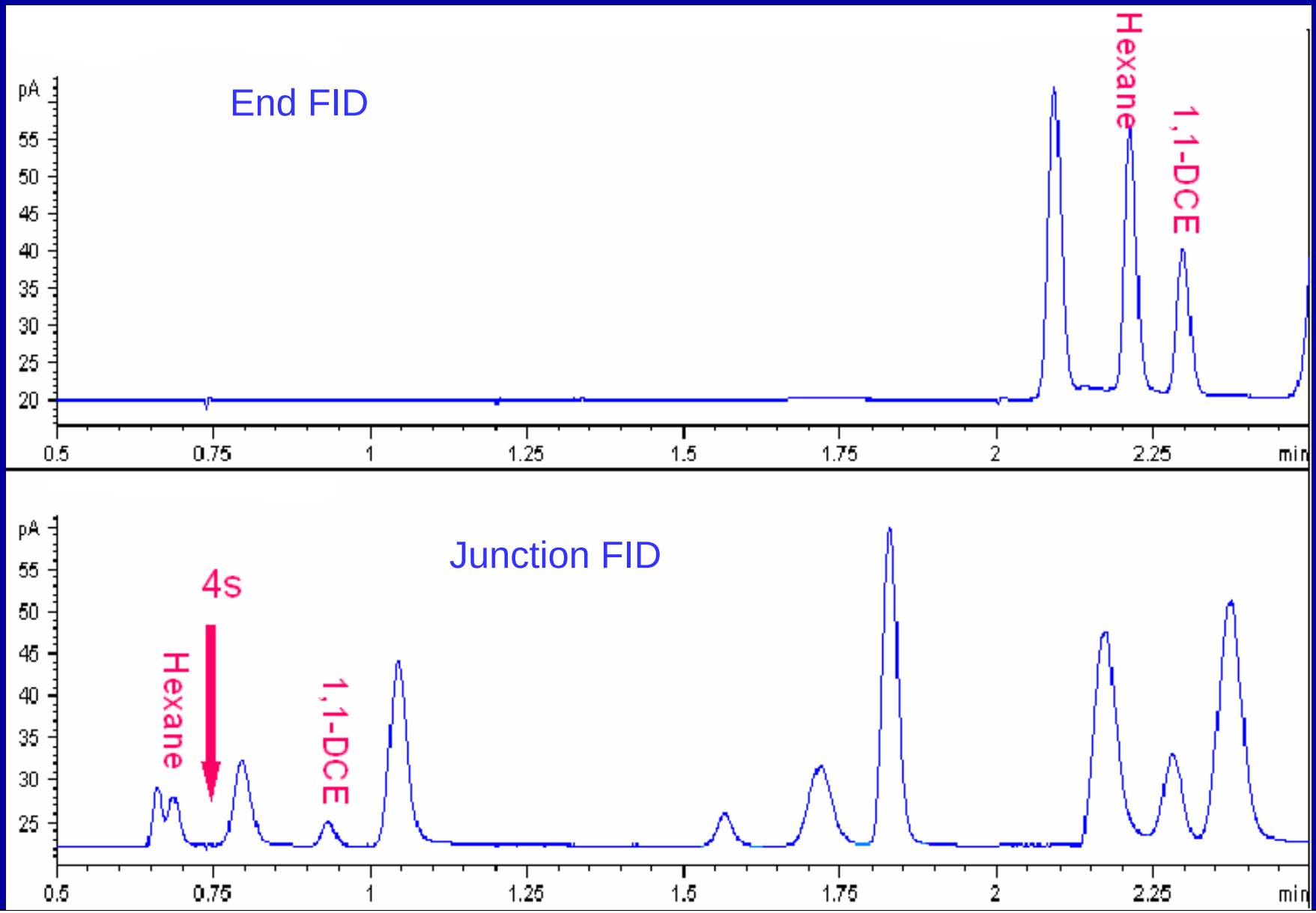
Residual Solvents: Run Conditions

	Standard Procedure	*Fast Procedure*
Analytical Columns	Stabilwax 15m x 0.25mm, 0.5μm Rtx-200 30m x 0.25mm, 1μm	Stabilwax 15m x 0.25mm, 0.5μm Rtx-200 30m x 0.25mm, 1μm
Oven Program	40°C (6 min. hold) to 100°C at 4°C/min., to 220°C at 15°C/min., 5 min. hold	40°C (1 min. hold) to 65°C at 6°C/min., to 100°C at 12°C/min., to 250°C at 70°C/min., 1.8 min. hold
Column Flow	1.5 mL/min. constant flow	2.5 mL/min. to 9.5 min. 3.5 mL/min. at 10 min.
Injector	230°C	230°C
Injection	0.2 μL HS, 200:1 split	0.2 μL HS, 200:1 split
Detectors	Dual FIDs @ 250°C	Dual FIDs @ 250°C

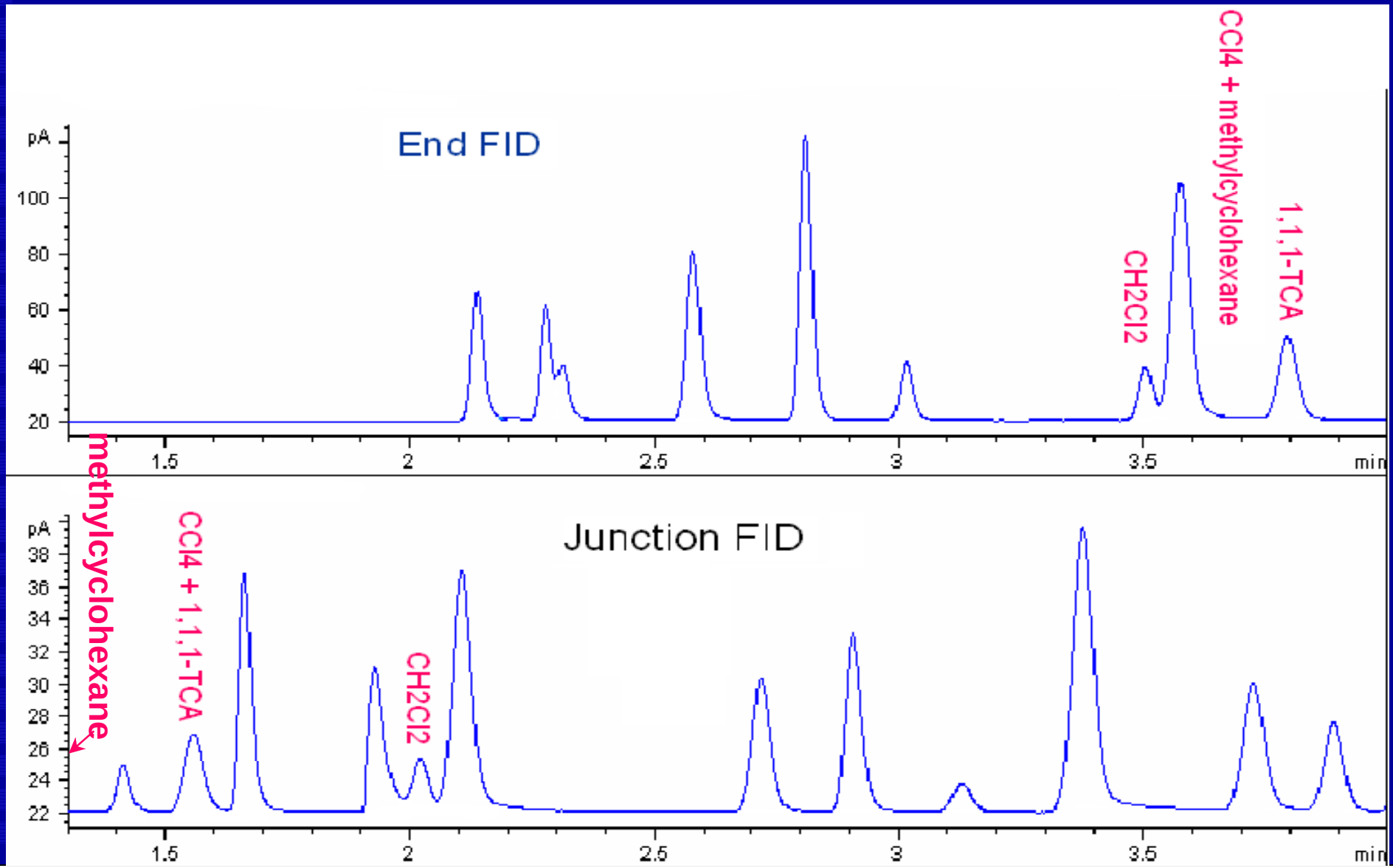
Class I & II Residual Solvents: No Pulses



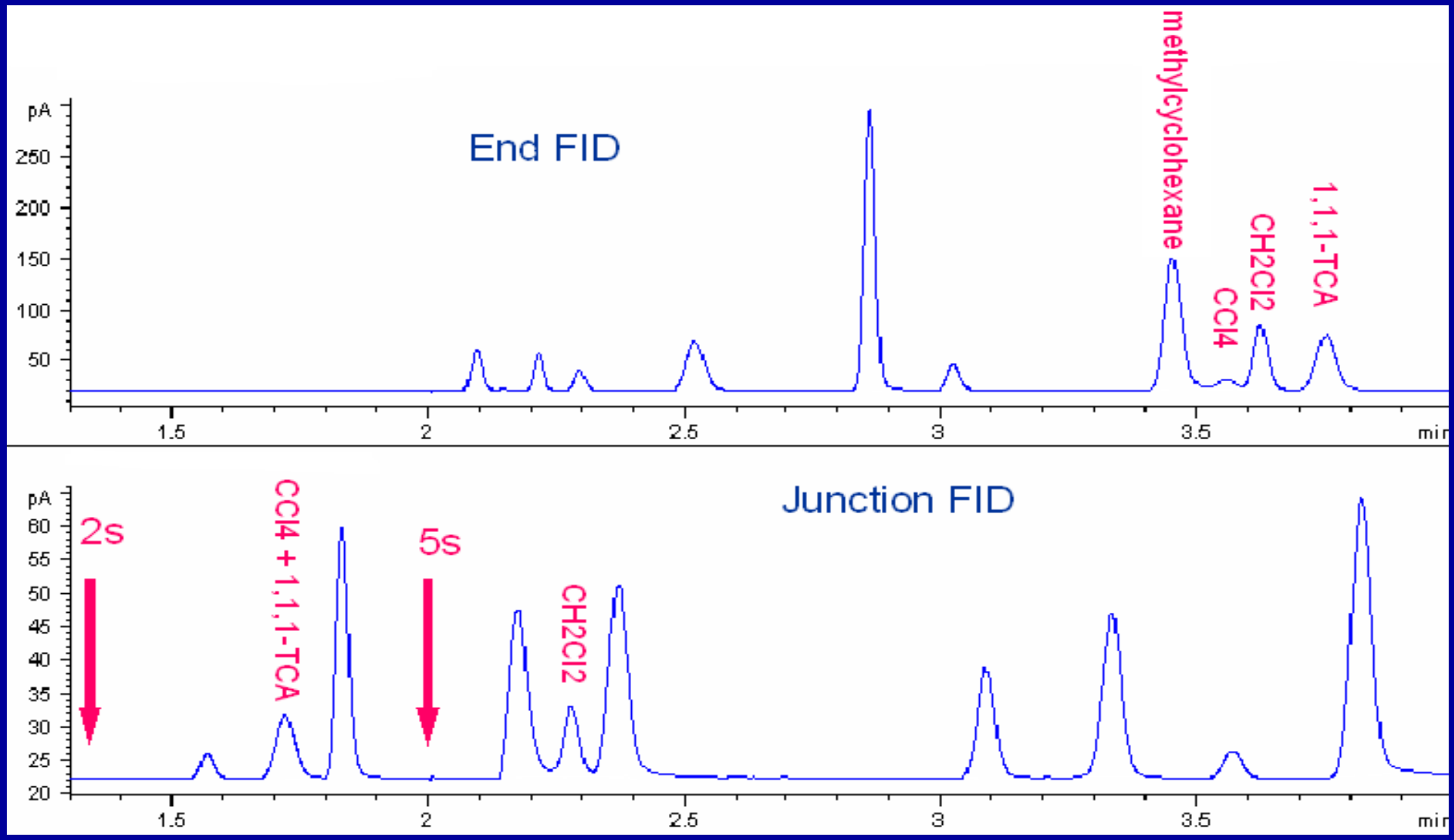
Residual Solvents: Pulse @ 44 sec.



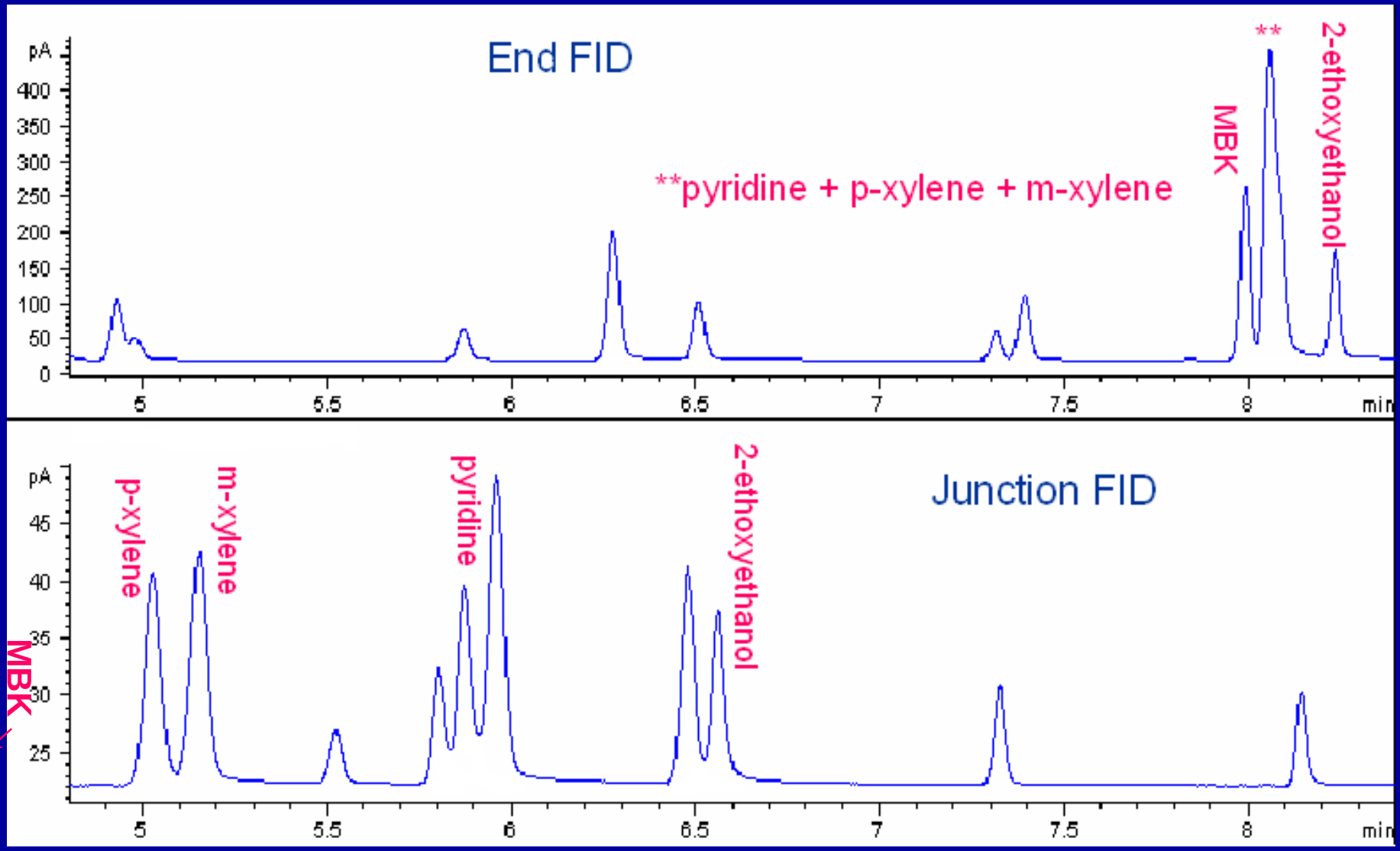
Residual Solvents: No Pulses



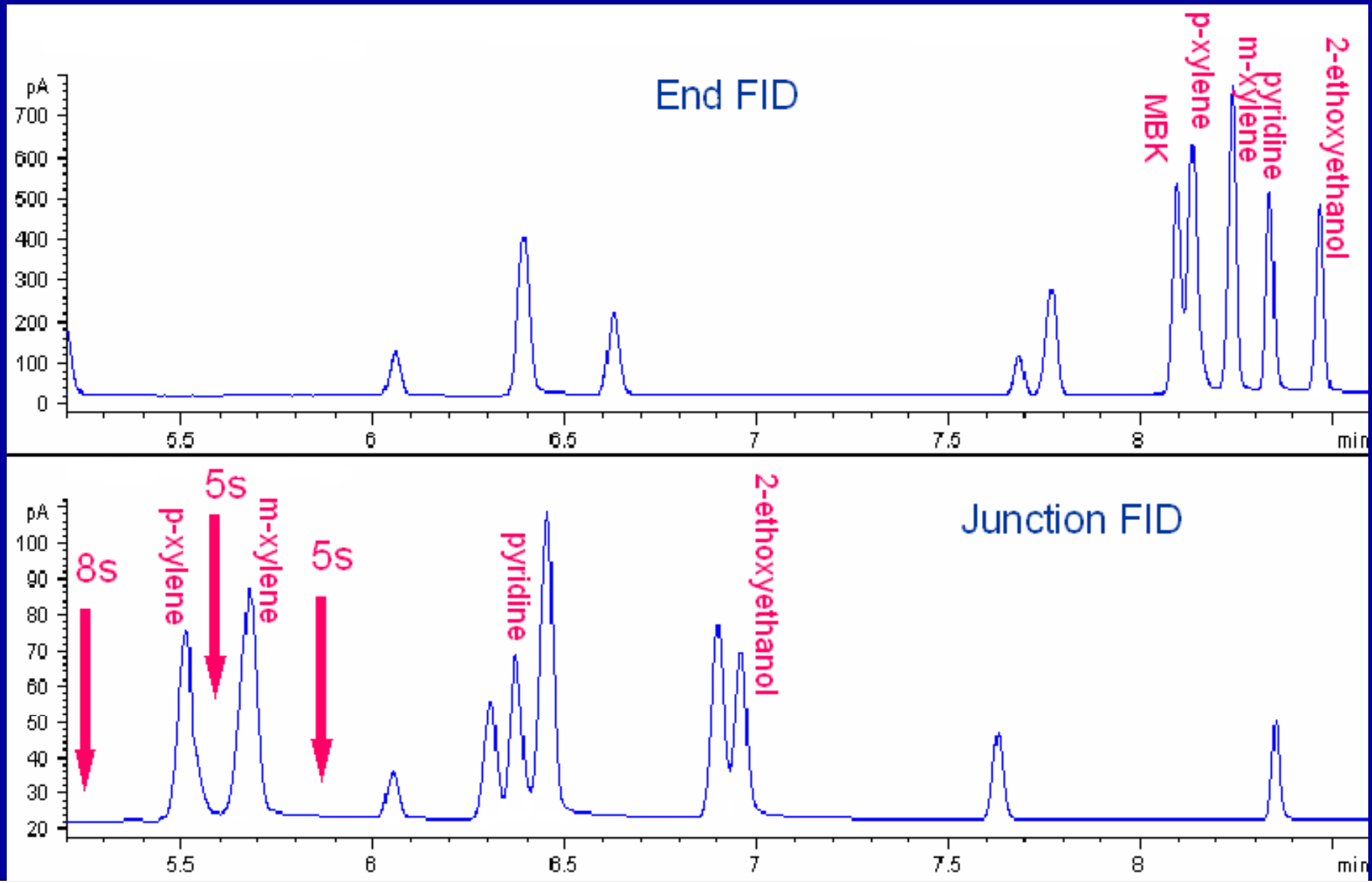
Residual Solvents: Pulses @ 72 & 120 sec.



Residual Solvents: No Pulses

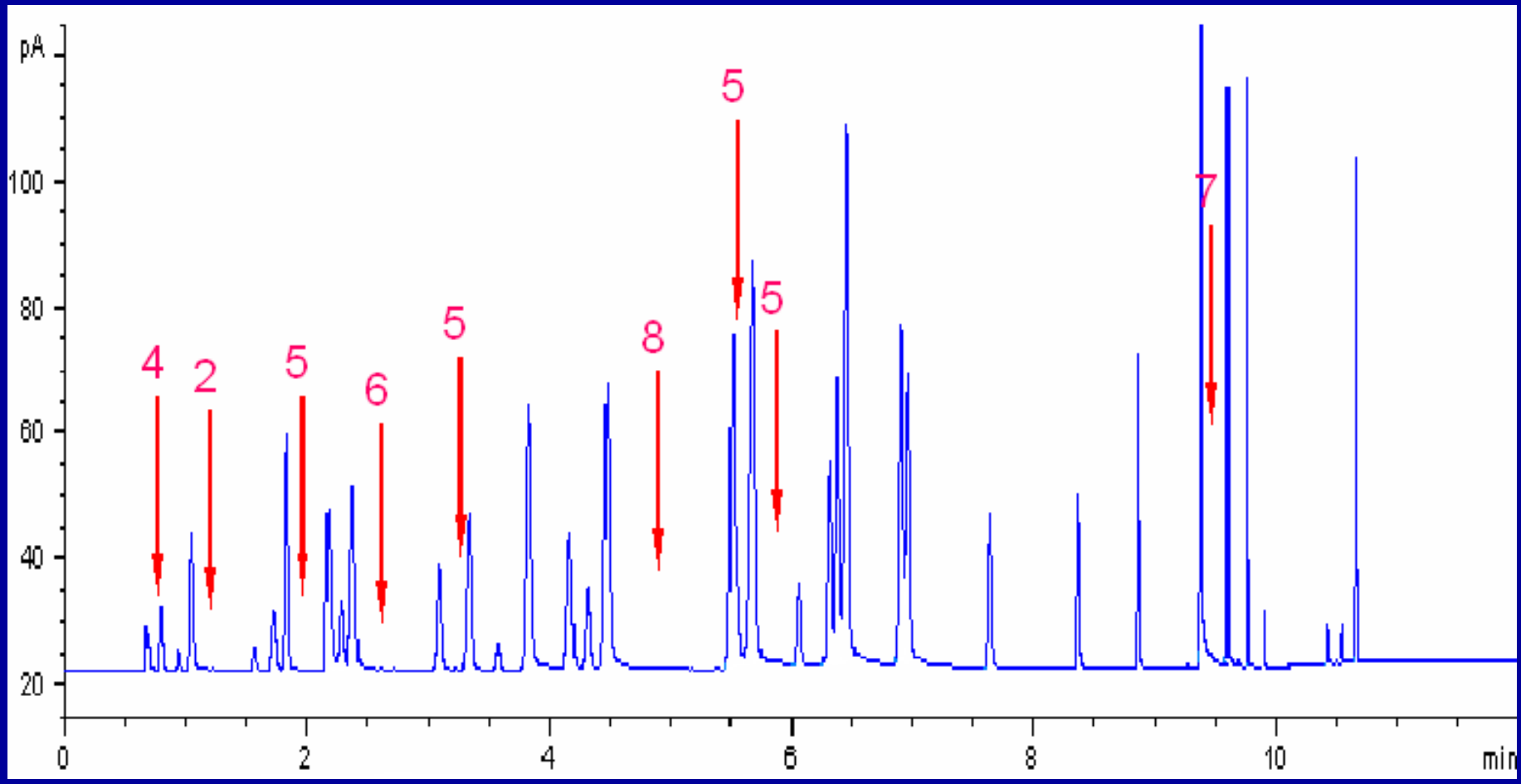


Residual Solvents: Pulses @ 290, 330, & 346 sec.



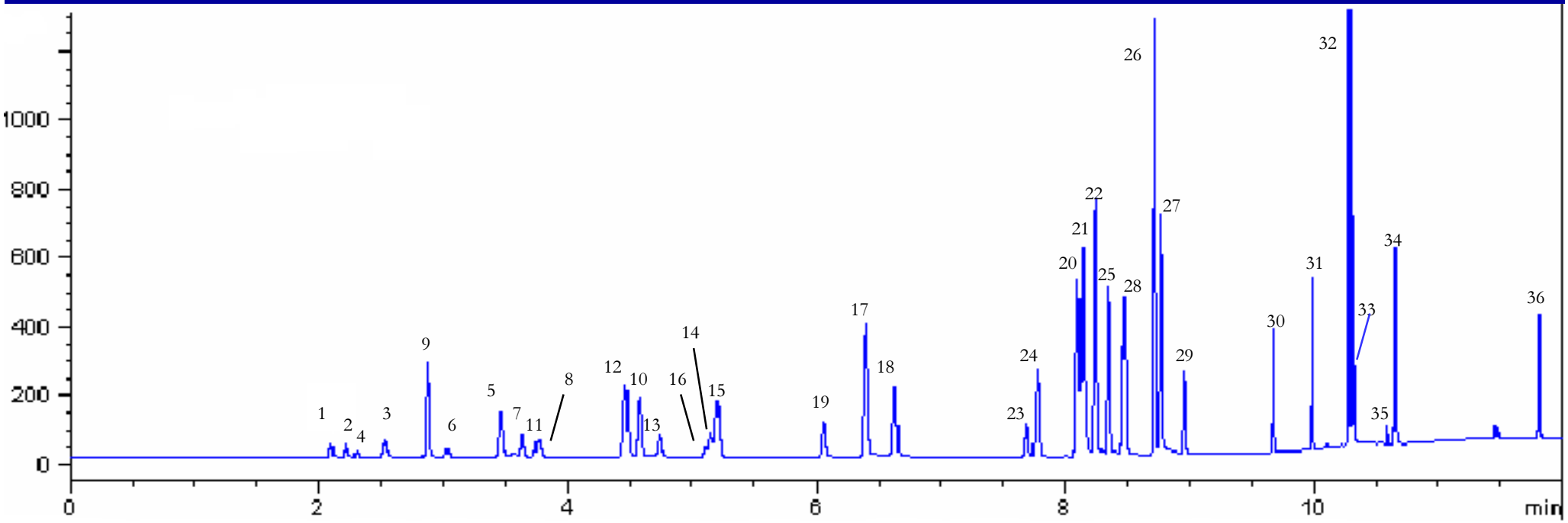
Class I & II OVIs: Total of 9 Pulses

At the Junction



Class I & II OVIs: Total of 9 Pulses

At the End Detector – all 36 resolved



Summary of Stop-Flow GC

- Ability to “Tune” the Selectivity
- Flexibility
  - Standard dimension columns
  - Can vary the pulse sequences
- Significant Improvements in Analysis Times Possible
  - Fast oven programs, high flow rates

Conclusions

- Completed evaluation of current phases
- Continue work on a new stationary phases
  - Using computer modeling
  - Goal: resolve 76 compounds
- Continue with Stop-Flow technology

For More Information...

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