Headspace Analysis of Residual Solvents in Pharmaceuticals, Using Flow-Modulation Chromatography.

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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:

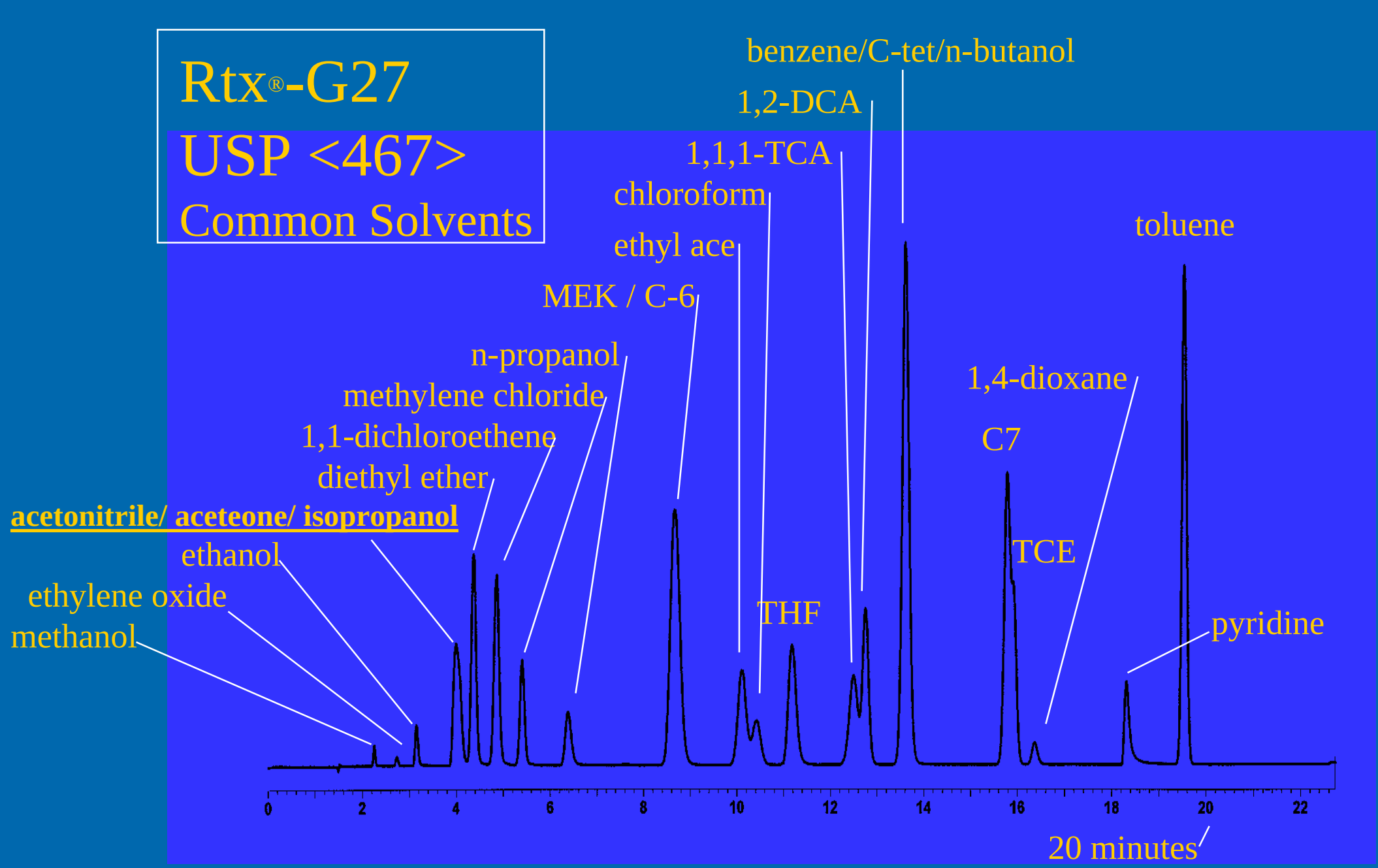
- Evaluate Existing Phases
- Develop a New Stationary Phase
- Stop-Flow GC Technology
  - Using Existing RT Data
  - Applying RT Data for Stop-Flow

Existing Phases Evaluated

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

- Column Design.

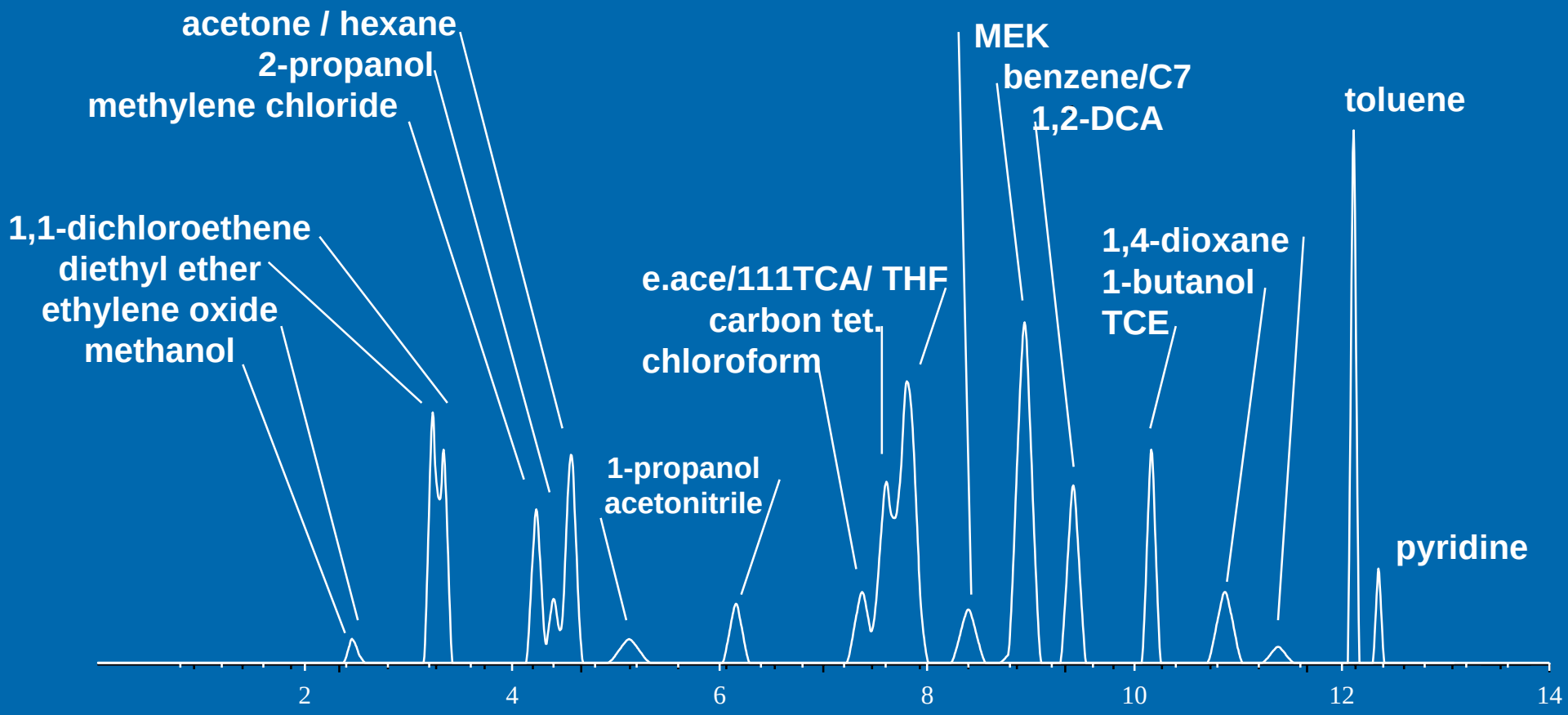
Rtx®-G27
USP <467>
Common Solvents



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

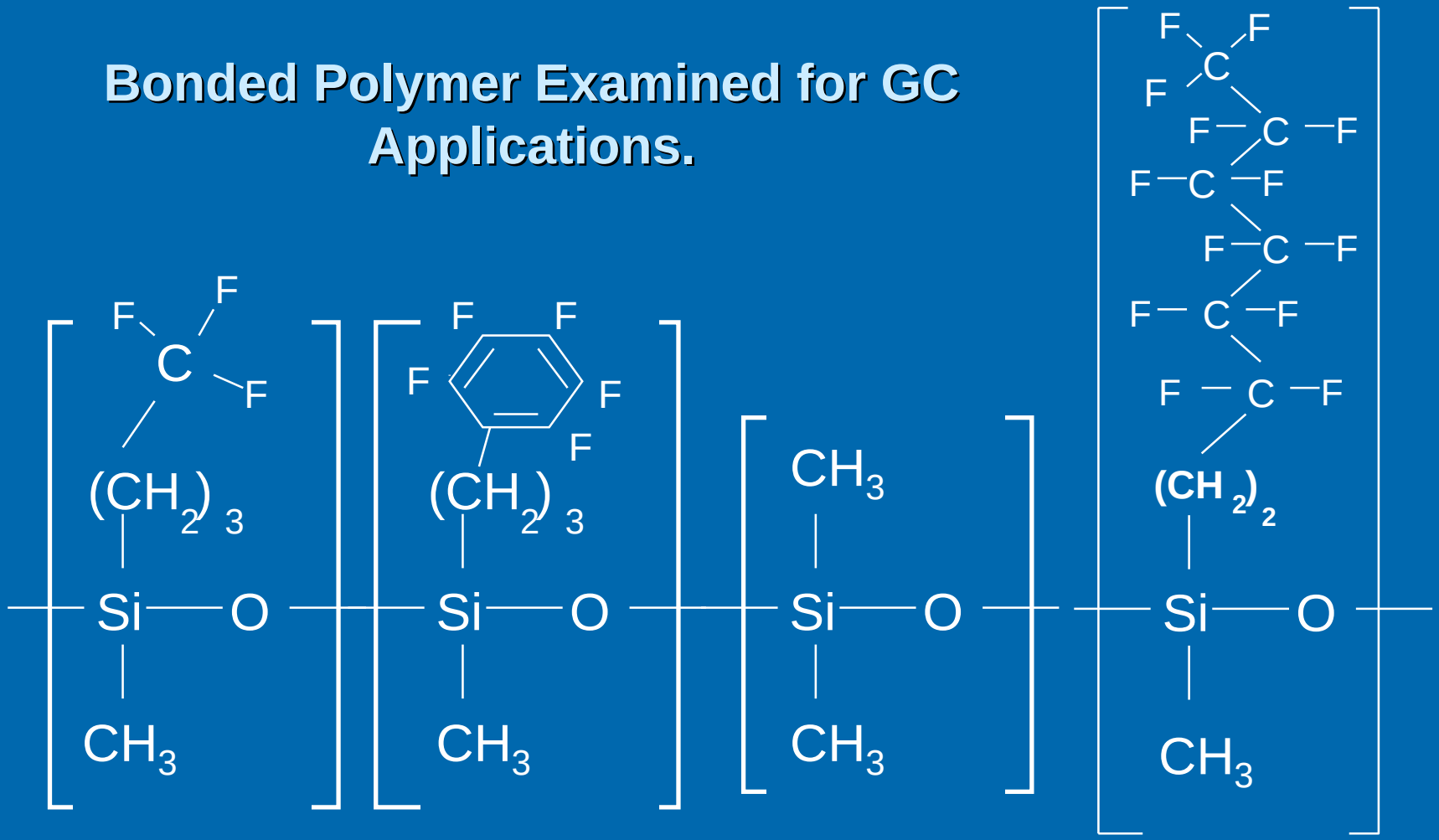


The Rtx-VGC Unresolved

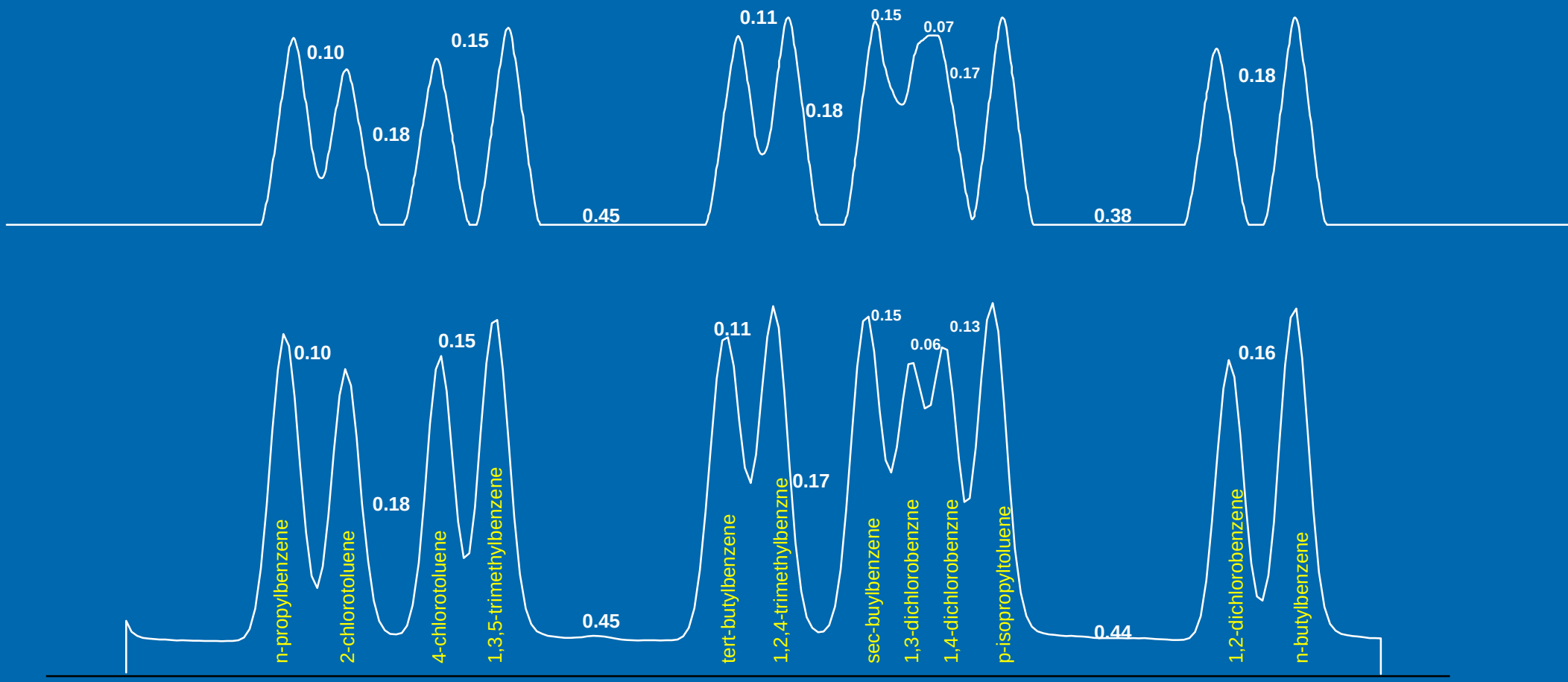
- acetone (III), C6 (II)
- E.ace (III),111TCA (I), THF (III)
- benzene (I), C7 (III)

Experimental Fluorinated Phase

Bonded Polymer Examined for GC Applications.



Modeling for a New Bonded Phase



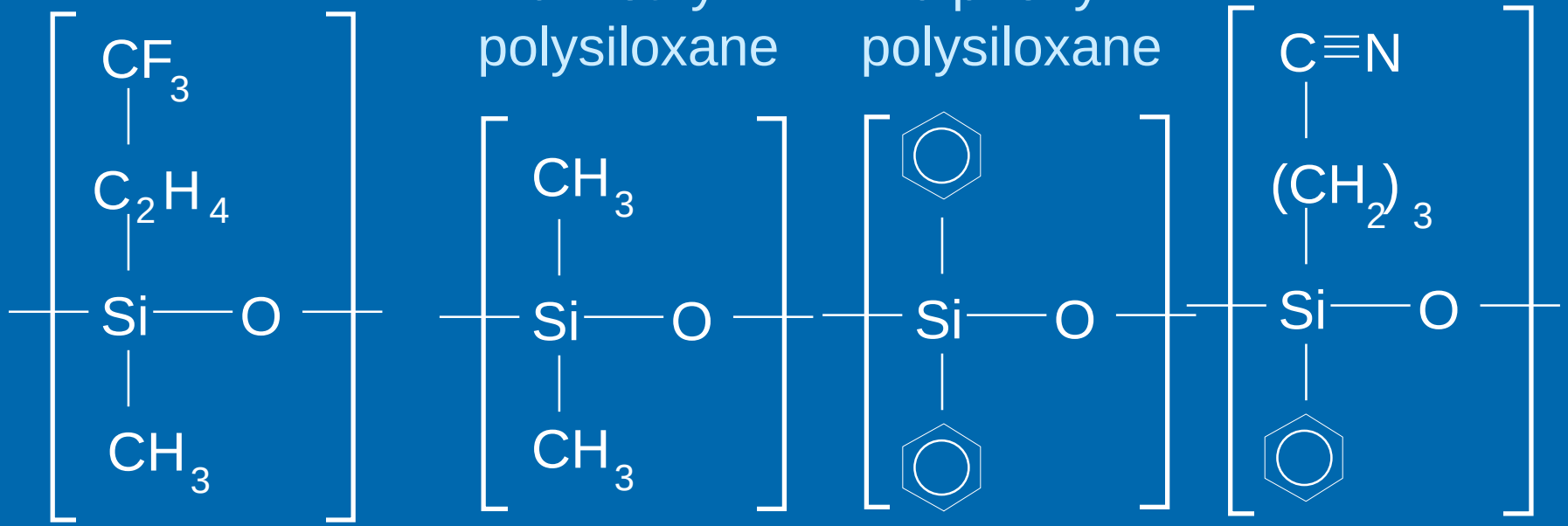
Stationary Phases Used for Modeling

trifluoropropylmethyl polysiloxane

dimethyl polysiloxane

diphenyl polysiloxane

cyanopropylphenyl polysiloxane

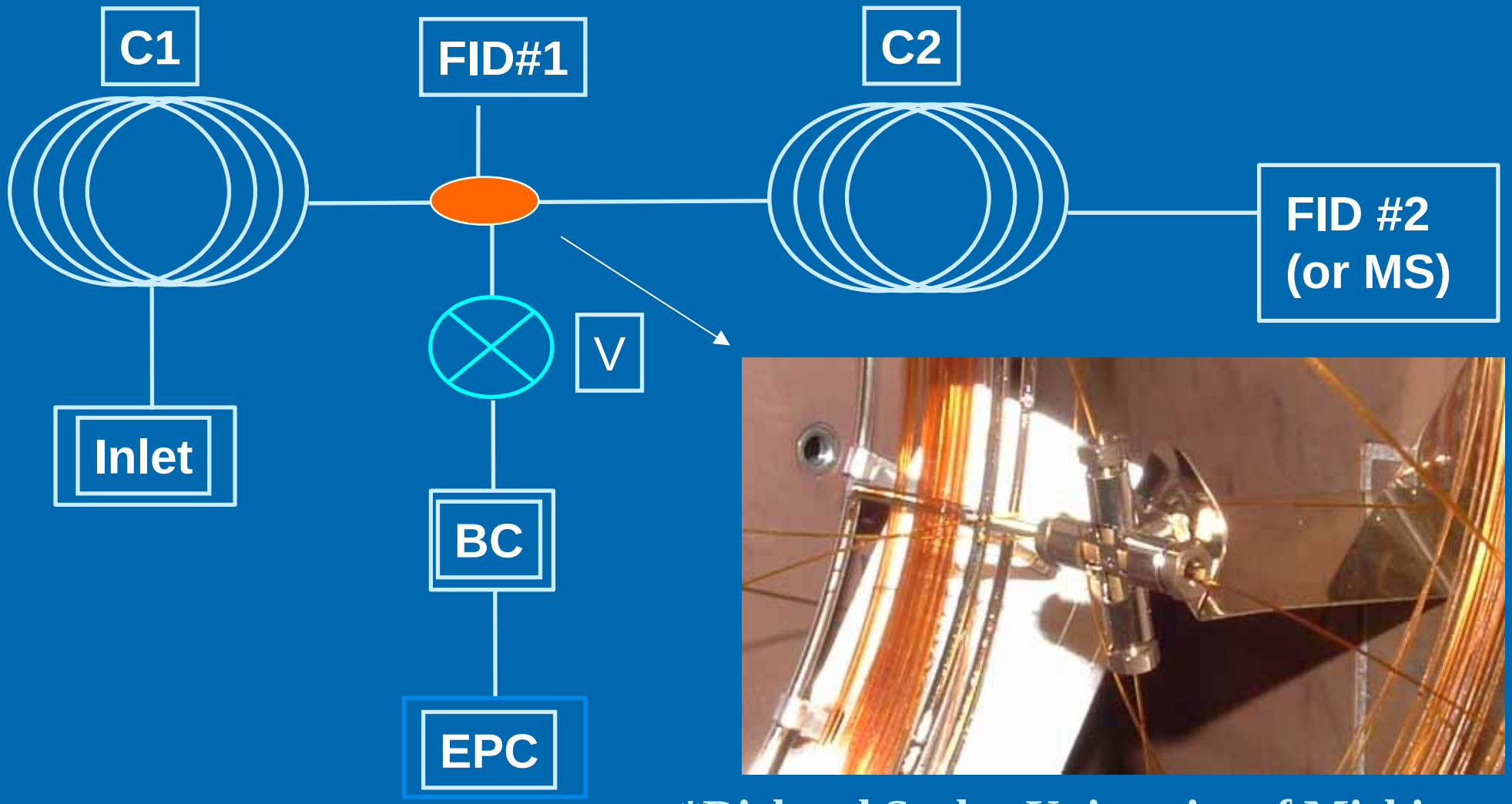


Current Issues with the ICH Compounds.

Separation
Concentration

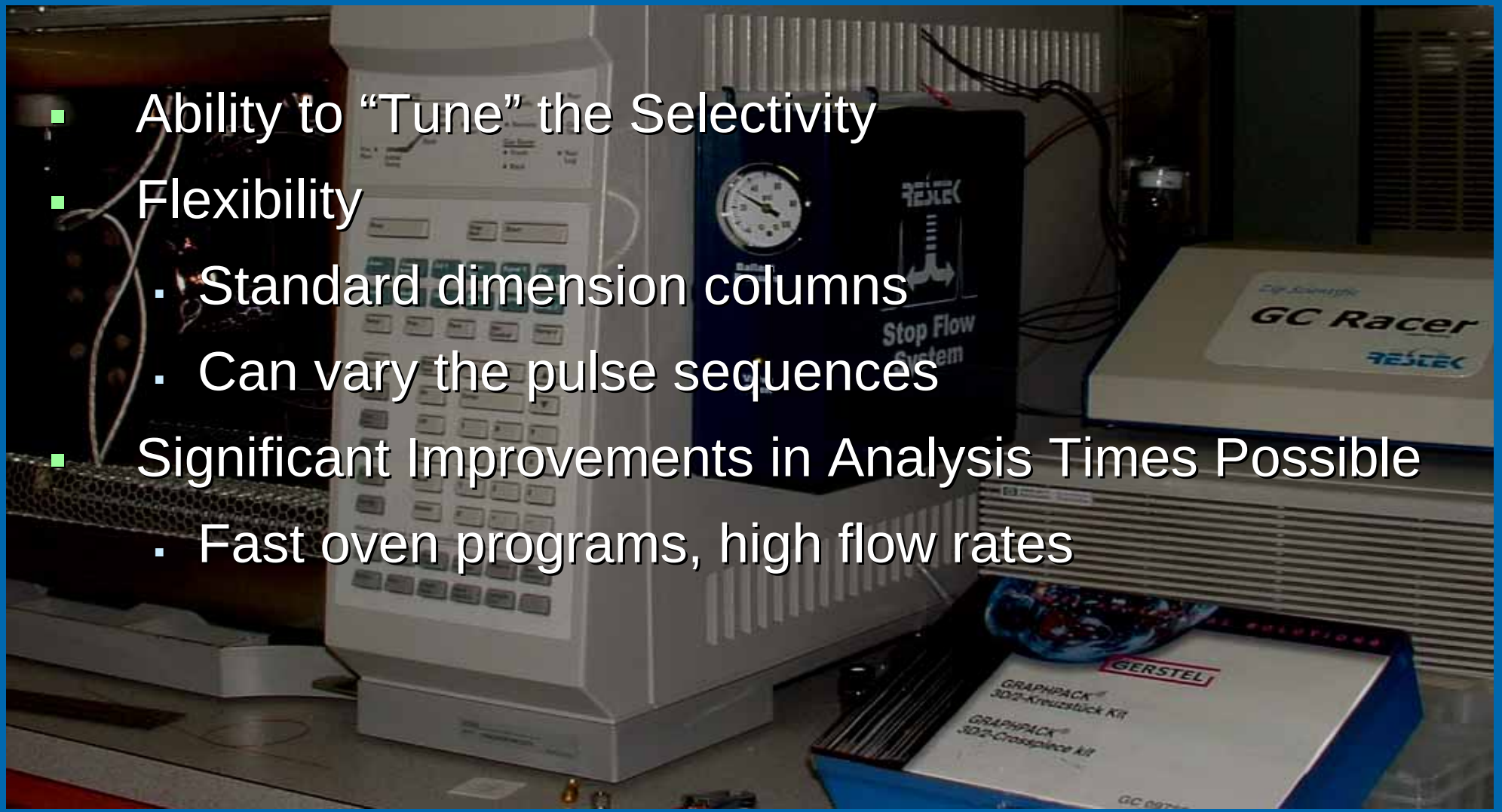
Headspace & Stop Flow

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

Coelutions by Phase
Class I & II

Rtx-1

1,2-dichloroethane / methyl cyclopentane

1,4-dioxane / trichloroethene

p-xylene / m-xylene

Rtx-200

hexane / methylene chloride

1,2-dichloroethane / trichloroethene

2-ethoxyethanol / toluene

Stabilwax

carbon tetrachloride / 1,1,1-trichloroethane

cis-1,2-dichloroethene / trichloroethene

Rtx-VMS

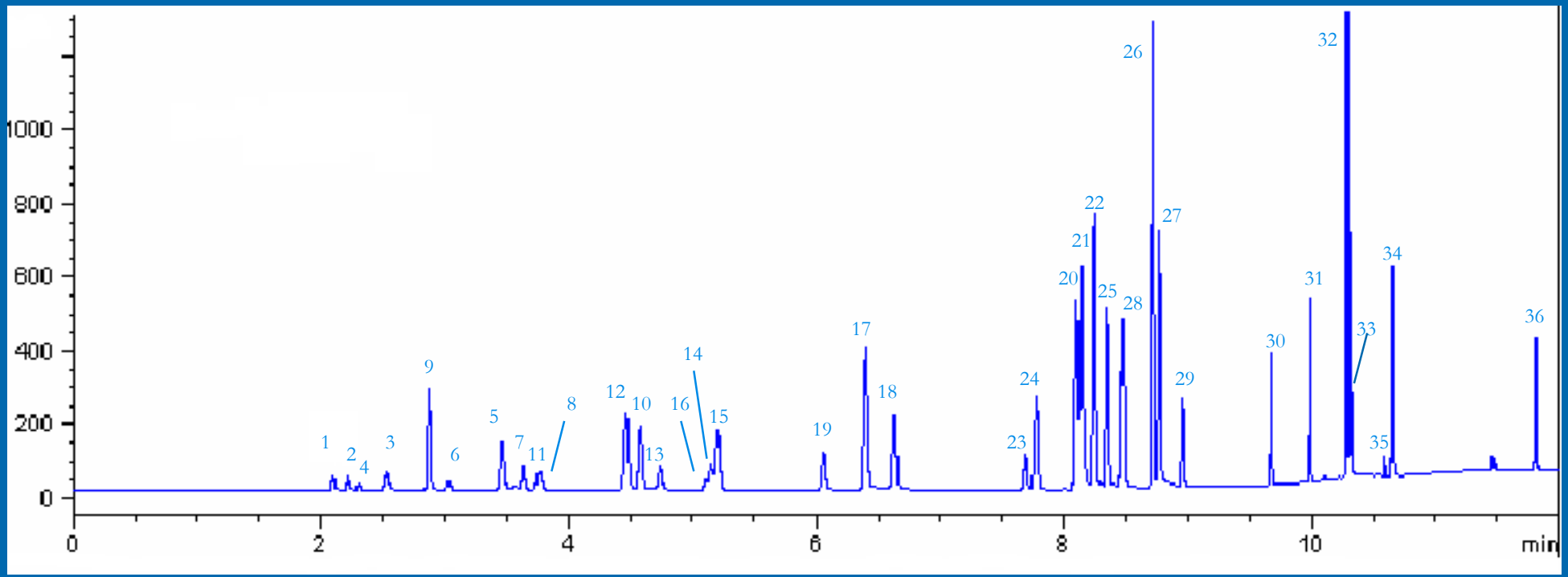
Carbon tetrachloride / 1,1,1-trichloroethane (close pair)

Trichloroethene / methyl cyclohexane

p-xylene / m-xylene

Class I & II OVIs: Total of 9 Pulses

At the End Detector – all 36 resolved

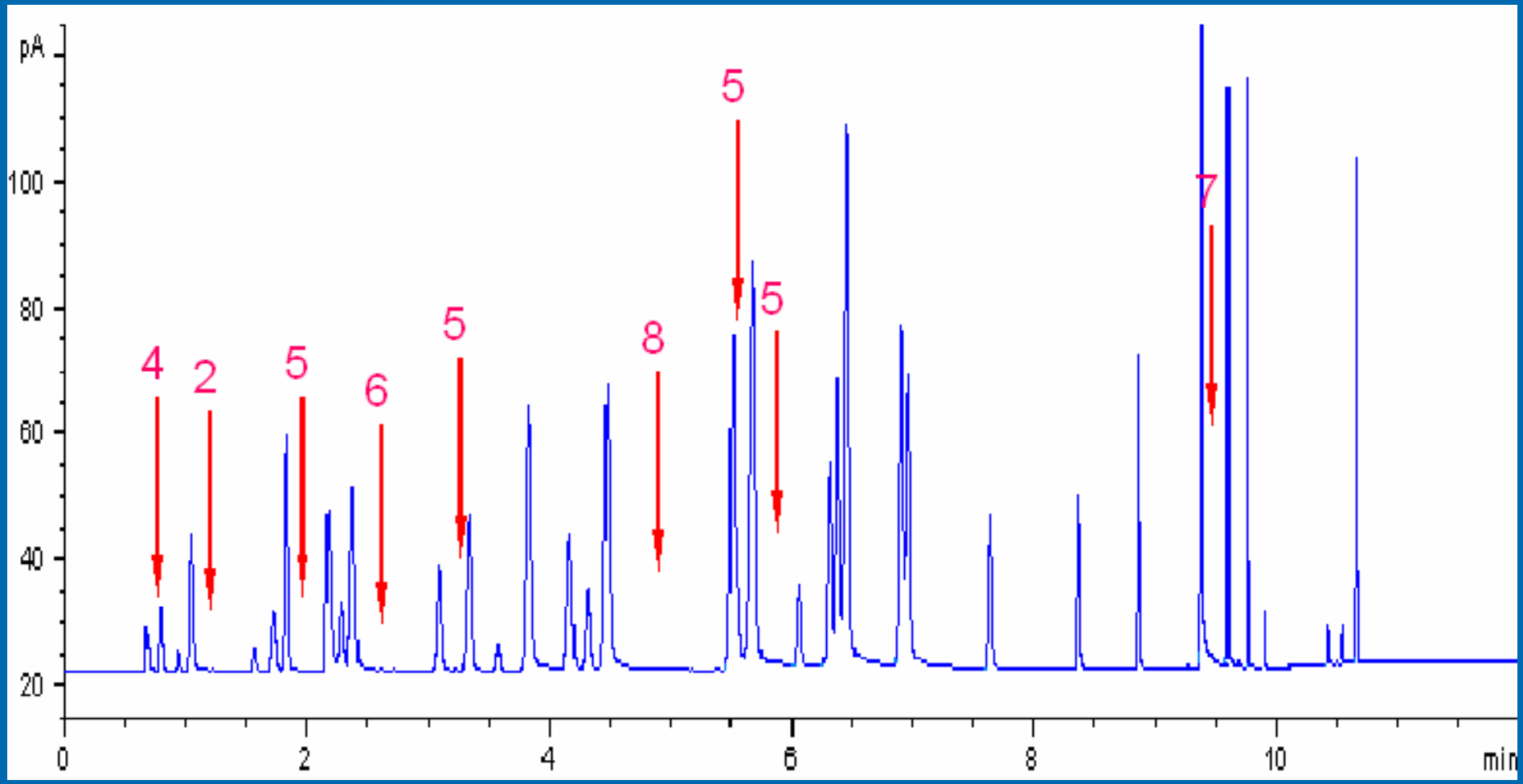


Residual Solvents: Run Conditions

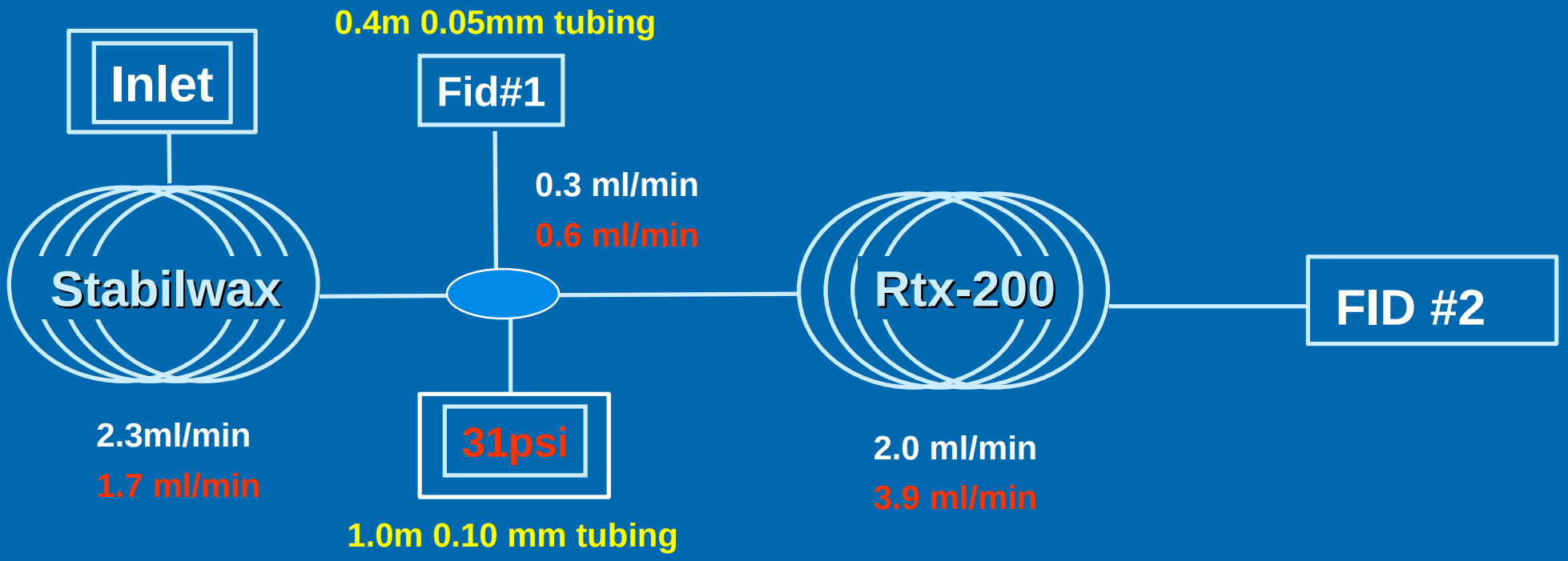
	Standard Procedure	*Fast Procedure*
Analytical Columns	**Stabilwax 15m x 0.25mm, 0.5μm Rtx-200 30m x 0.25mm, 1μm**	**Stabilwax 15m x 0.25mm, 0.5μm Rtx-200 30m x 0.25mm, 1μm**
Oven Program	**40°C (6 min. hold) to 100°C at 4°C/min., to 220°C at 15°C/min., 5 min. hold**	**40°C (1 min. hold) to 65°C at 6°C/min., 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 OVIs: Total of 9 Pulses

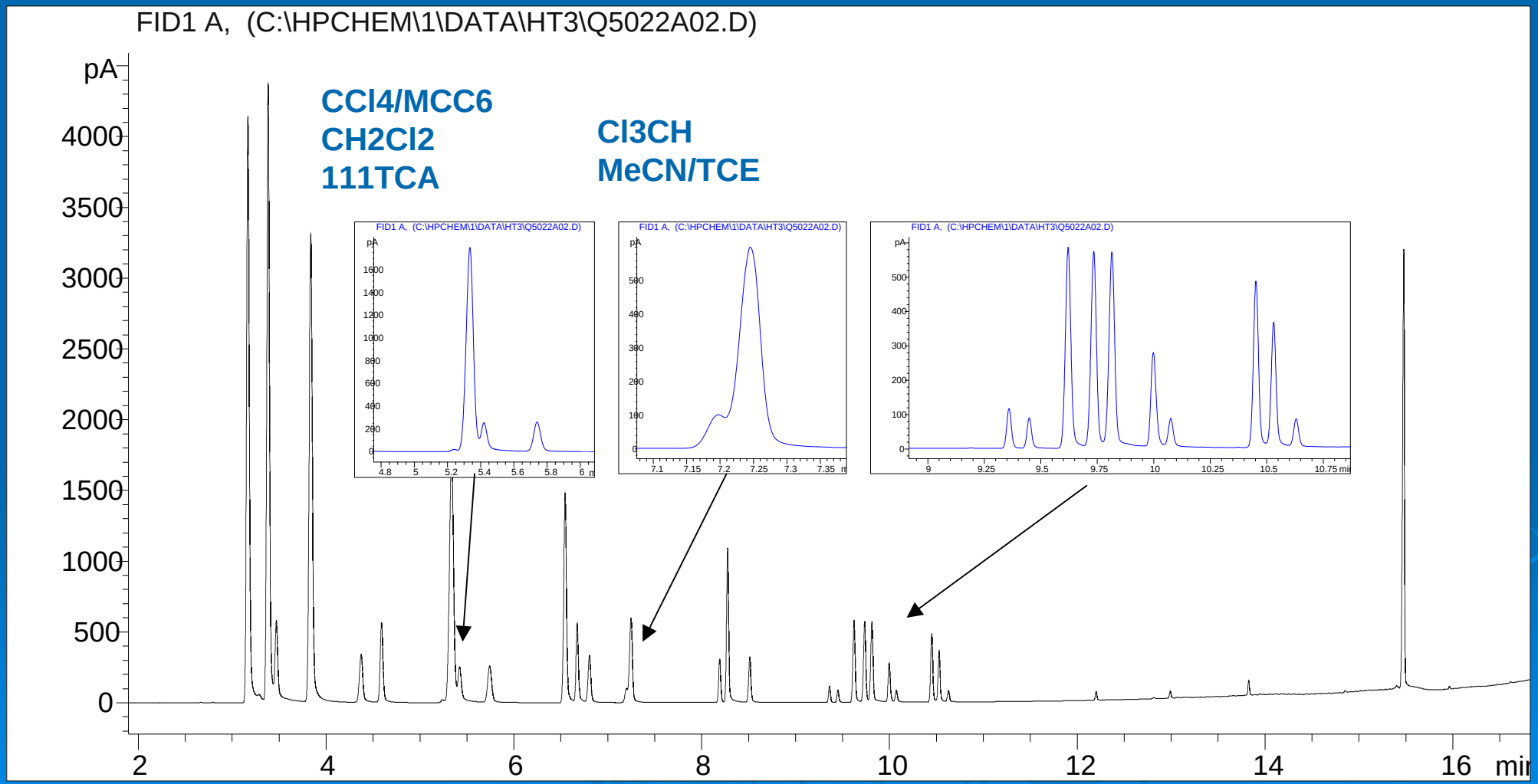
At the Junction



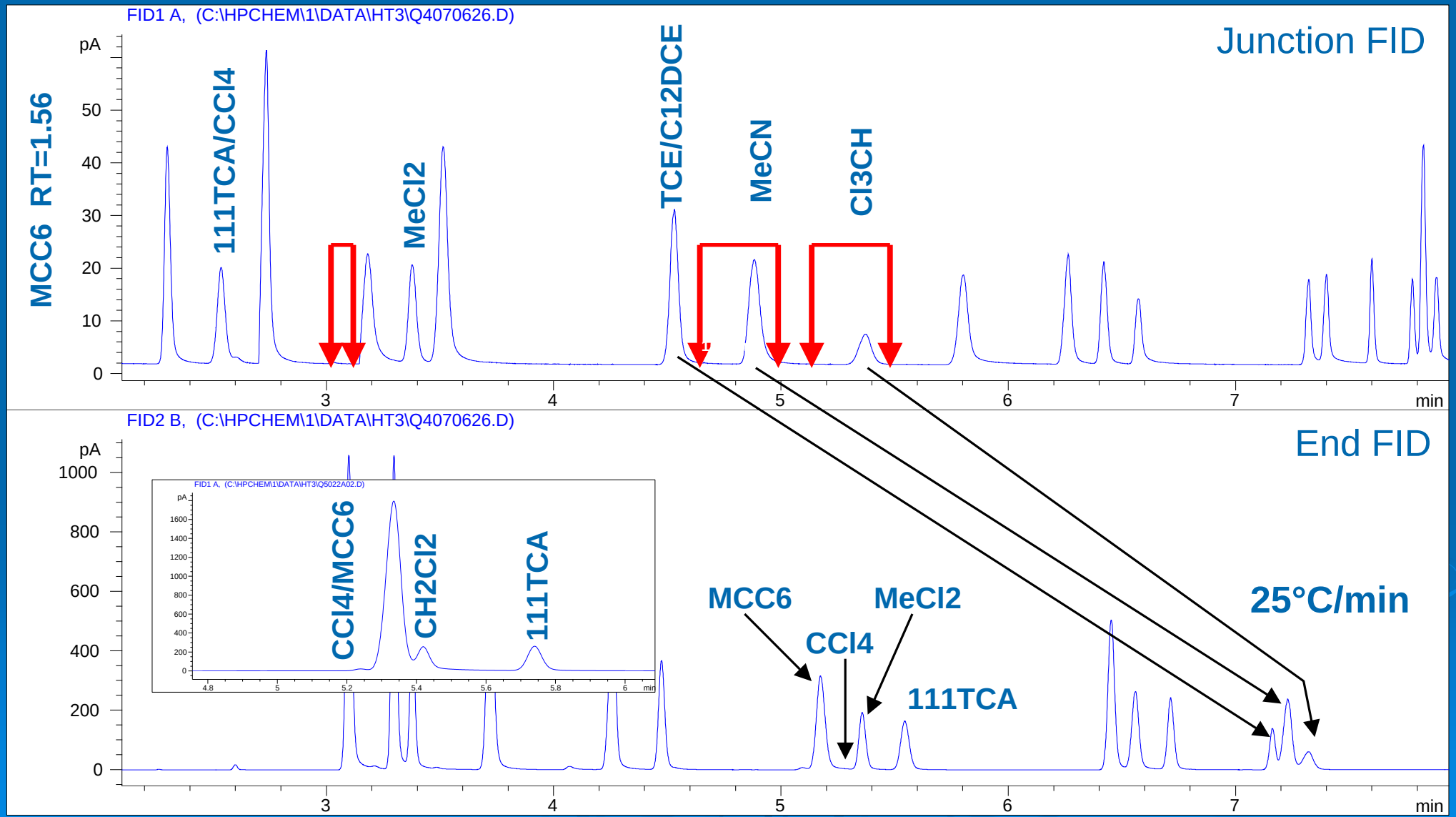
Flow Modulation Pulses



Stabilwax 15m x 0.25mm x 0.5df
Rtx-200 30m x 0.25mm x 1.0df
Analysis without Pulses 2nd FID



Three Flow Modulation Pulses



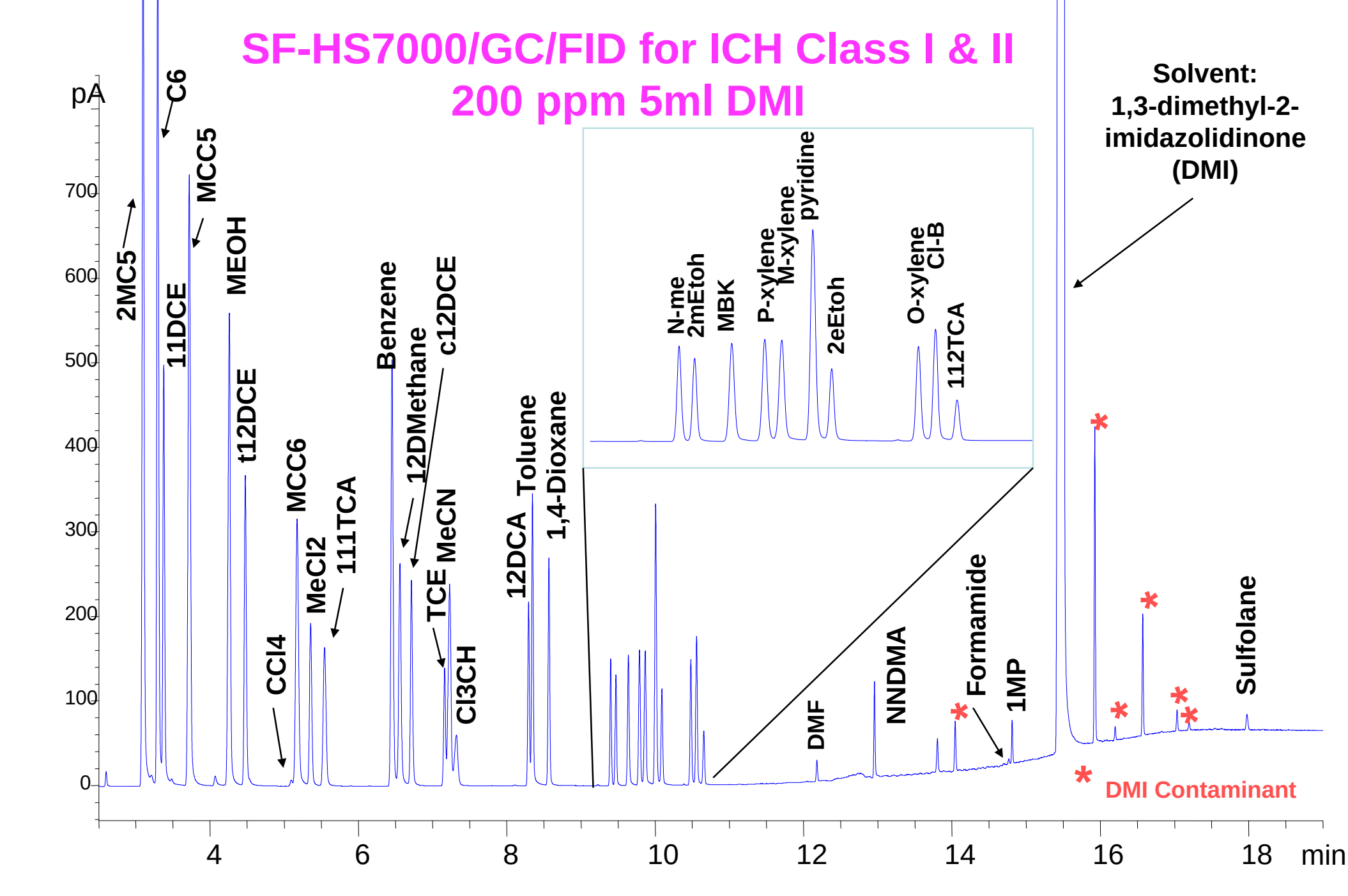
Teledyne Tekmar HT7000

Platen Temperature:	140°C
Sample Equilibration Time:	5 minutes
Mixing Time:	10 minutes
Mixing Power:	2
Mixture Stabilization Time:	1
Pressure Time:	0.2 minutes
Pressure Equilibrium:	0.3 minutes
Loop Fill Time:	0.1 minutes
Loop Equilibration Time:	0.05 minutes
Injection Time:	1.0 minutes
Loop/Line Temperature:	250°C
Vial Size:	22ml high temperature vials
Sample Loop Size:	Silcosteel 1ml Standard Size.
Static Vial Pressure:	3.5 PSI Helium
Vial Pressurization:	8 PSI Helium
Variable Injection Pressure (VIPR)	5 PSI Helium
Concentration:	200ppm each component.
Solvent:	1,3-dimethyl-2-imidazolidinone (DMI)
Interface:	plumbed through injection port 1:20 split

GC	Agilent 6890
Injection Port Temperature:	250°C
Carrier gas:	helium, constant flow
Flow rate:	2.3 ml/min, 25.6psi @ 40°C.
Oven temperature:	40°C (hold 2 min.) to 55°C @ 4°C/min. (no hold) to 110°C @ 25°C/min. (hold 2 min.) to 250°C @ 25°C/min (hold 5 minutes)
Total Runtime:	20.55 minutes
	Agilent Dual Flame Ionization Detectors

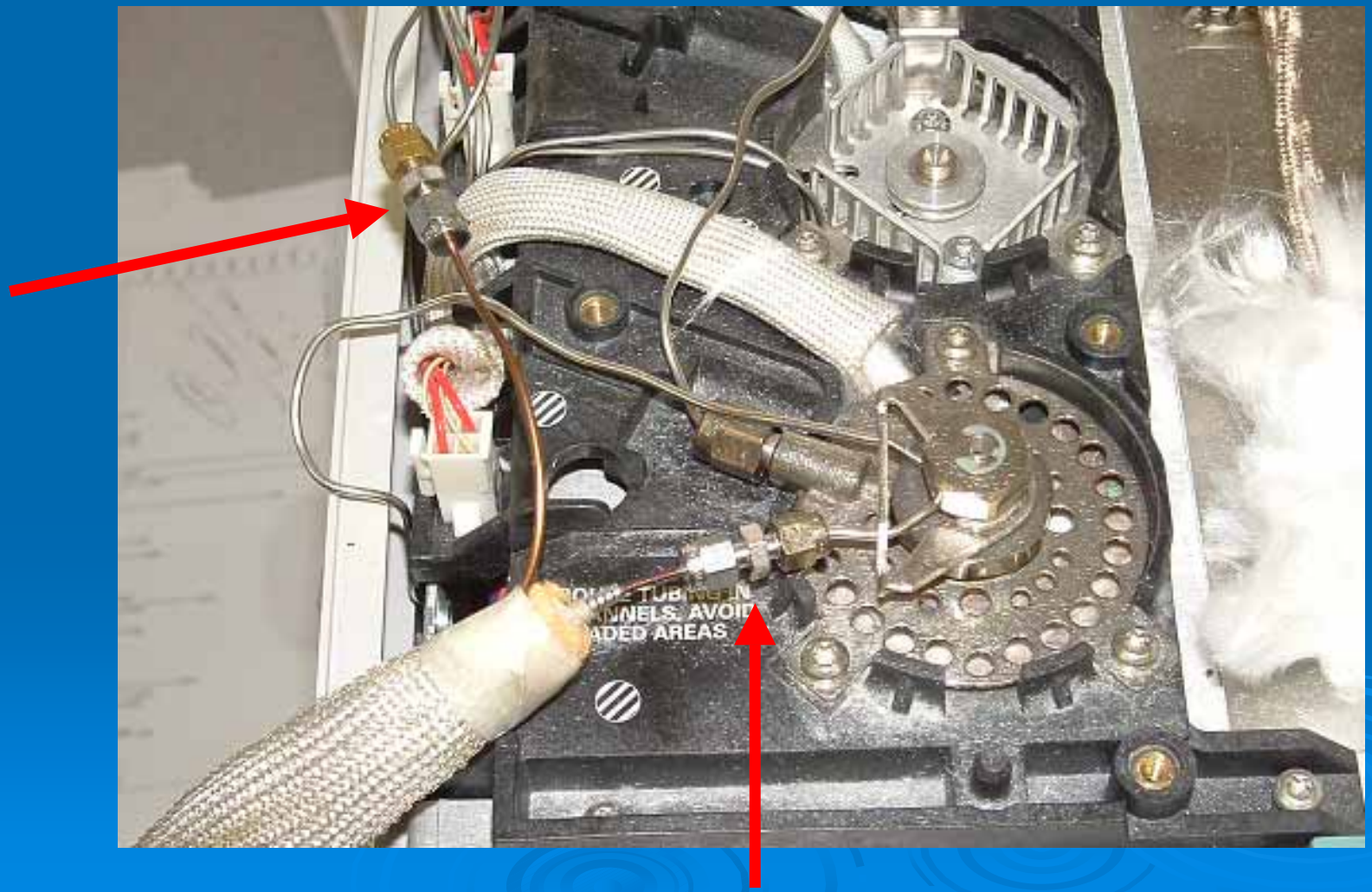
Restek's Stop-Flow Unit Pulse Settings:

Injection Port Connection:	cool-on-column injector.	
Pressure:	31.0 PSI constant pressure	
Pulses:	Valve Closed	0.00 minutes.
	Valve Open	3.00 minutes
	Valve Closed	3.15 minutes
	Valve Open	4.65 minutes
	Valve Closed	5.02 minutes
	Valve Open	5.10 minutes
	Valve Closed	5.40 minutes


SF-HS7000/GC/FID for ICH Class I & II
200 ppm 5ml DMI
pA
700
600
500
400
300
200
100
0
4
6
8
10
12
14
16
18
min
2MC5
C6
11DCE
MCC5
MEOH
t12DCE
MCC6
MeCl2
111TCA
CCl4
Benzene
12DMethane
c12DCE
TCE
MeCN
Cl3CH
12DCA
Toluene
1,4-Dioxane
DMF
NNDMA
Formamide
1MP
Sulfolane
Solvent:
1,3-dimethyl-2-
imidazolidinone
(DMI)
N-me
2mEtoh
MBK
P-xylene
M-xylene
pyridine
2eEtoh
O-xylene
Cl-B
112TCA
DMI Contaminant

Teledyne Tekmar HT3 HS/HS-Trap

Instrument Setup



HT3 Conditions Using DMI

Constant Heat Time	ON
G.C. Cycle Time	23.00 min
Valve Oven Temp	150 C
Transfer Line Temp	150 C
Standby Flow Rate	50mL/min
Platen / Sample Temp	150 C
Platen Temp Equil. Time	0.10 min
Sample Equil. Time	1.00 min
Mixer	ON
Mixing Time	10.00 min
Mixing Level	Level 5
Mixer Stabilize Time	0.50 min
Pressure	8 PSIG
Pressure Time	2.00 min
Pressure Equil. Time	0.50 min
Loop Fill Pressure	5 PSIG
Loop Fill Time	2.00 min
Loop Fill Equil. Time	0.50 min
Inject Time	1.00 min

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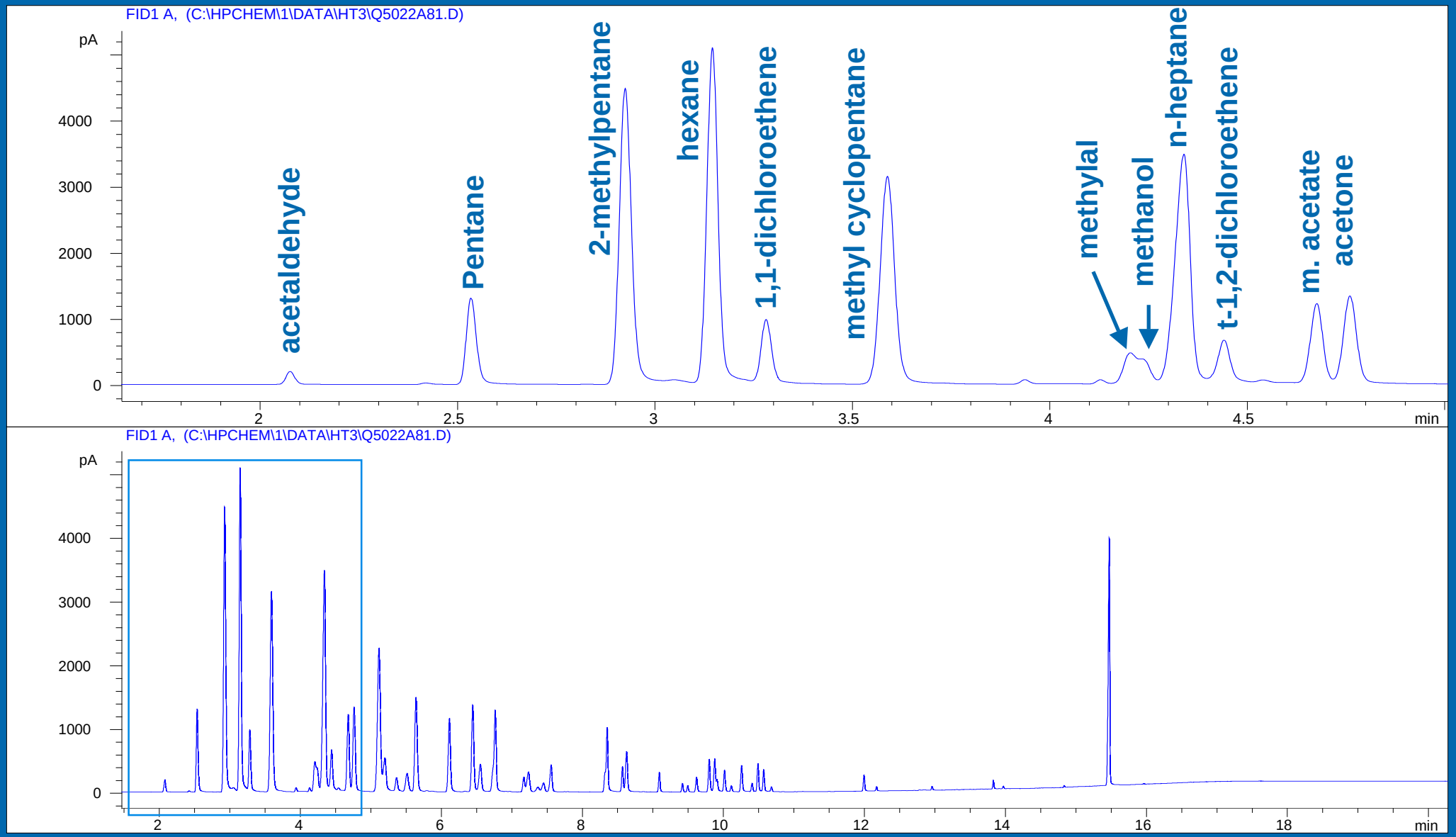
17	toluene	35	formamide
18	1,4-dioxane	36	sulfolone

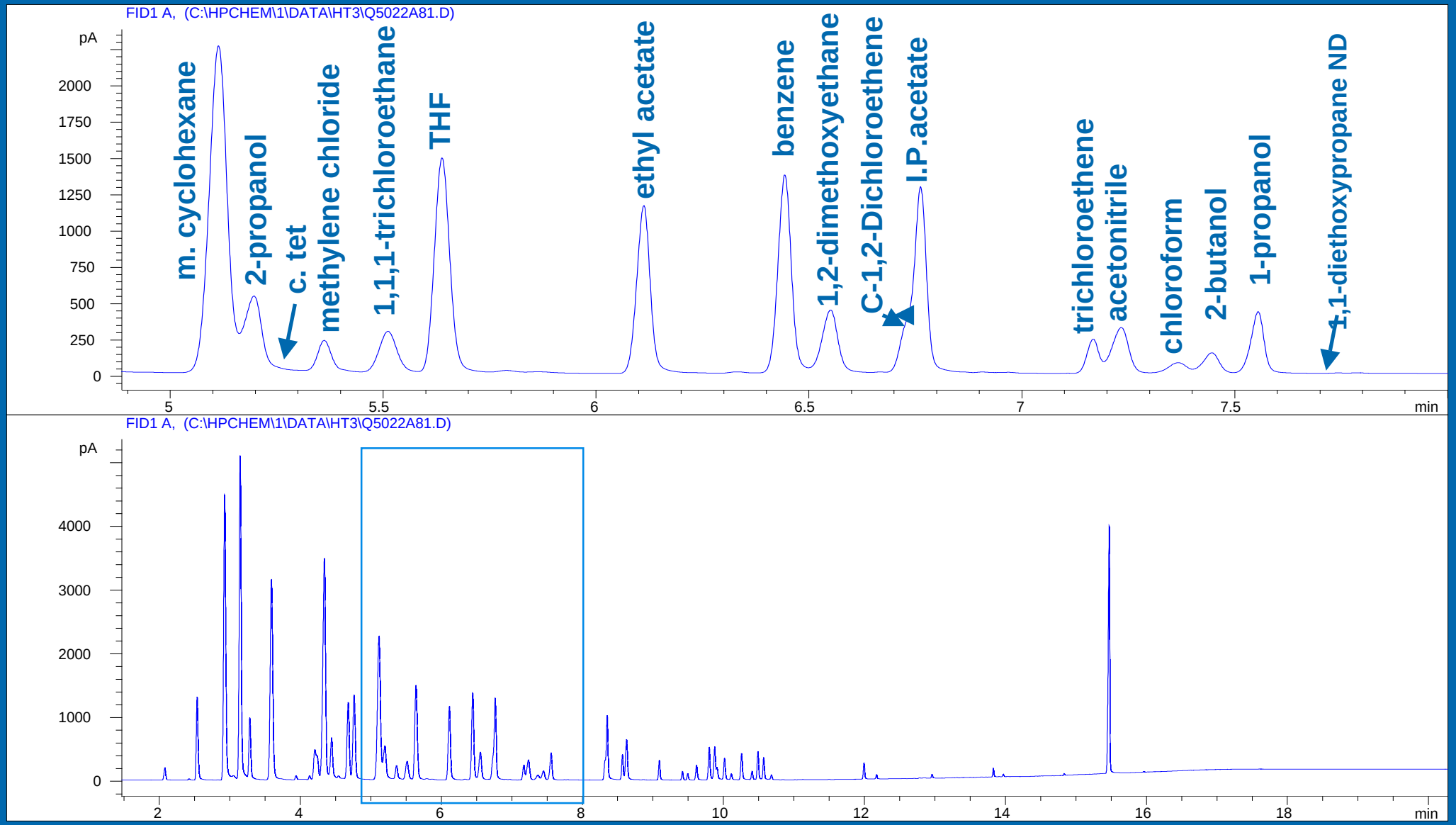
Class III Added Residual Solvents

compound	class
pentane	3
methylal	4
pentane	3
n-heptane (C7)	3
methyl acetate	3
acetone	3
2-propanol	3
tetrahydrofuran	3
ethyl acetate	3
isopropyl acetate	3
2-butanol	3
1-propanol	3
1,1-diethoxypropane	4
hexanone (MIBK)	3
1-butanol	3
isoamyl alcohol	3
isoamyl acetate	s
1-pentanol	3
anisole	3
dimethyl sulfoxide	3

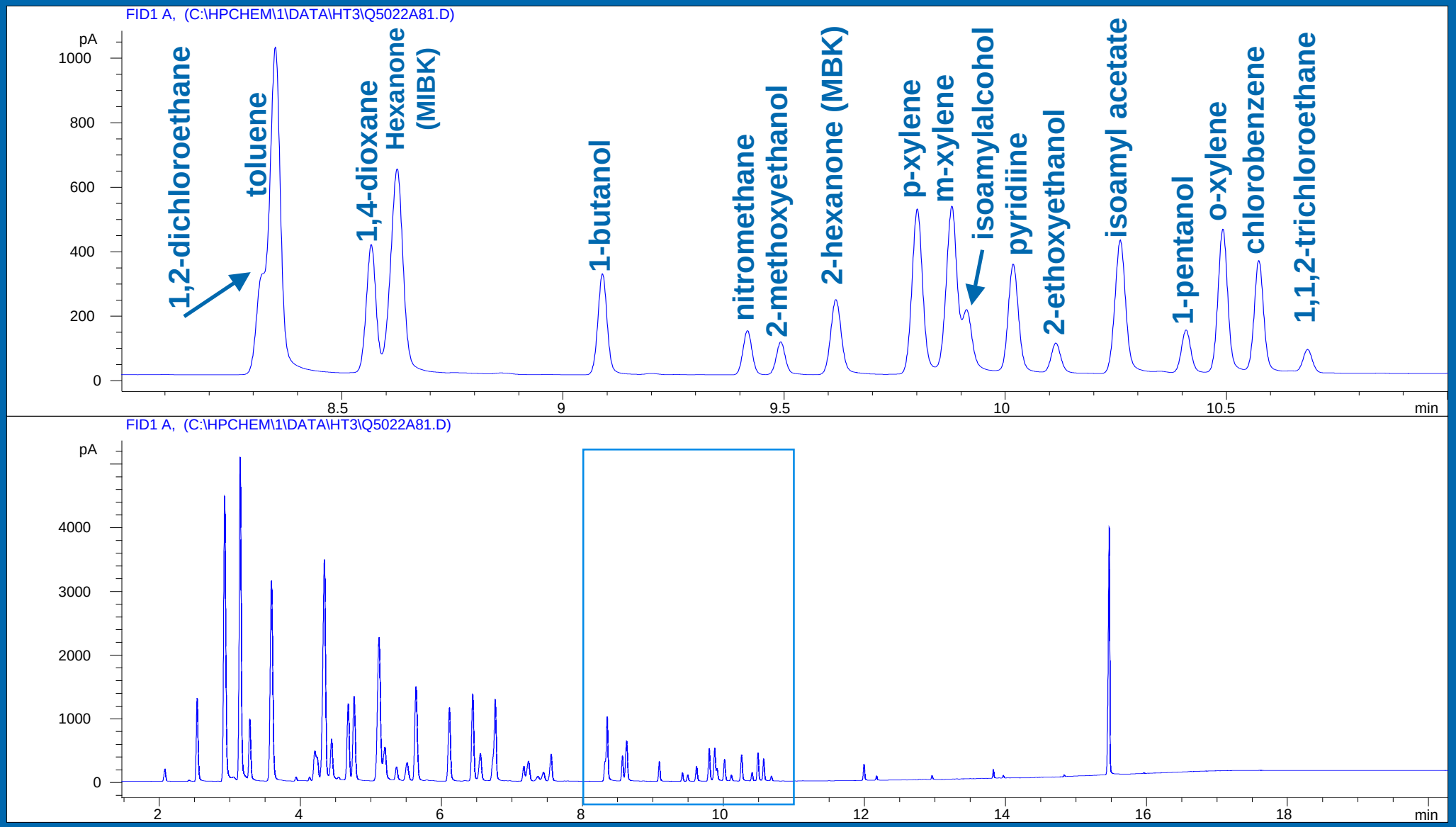
Class I,II,III 2nd FID by HS



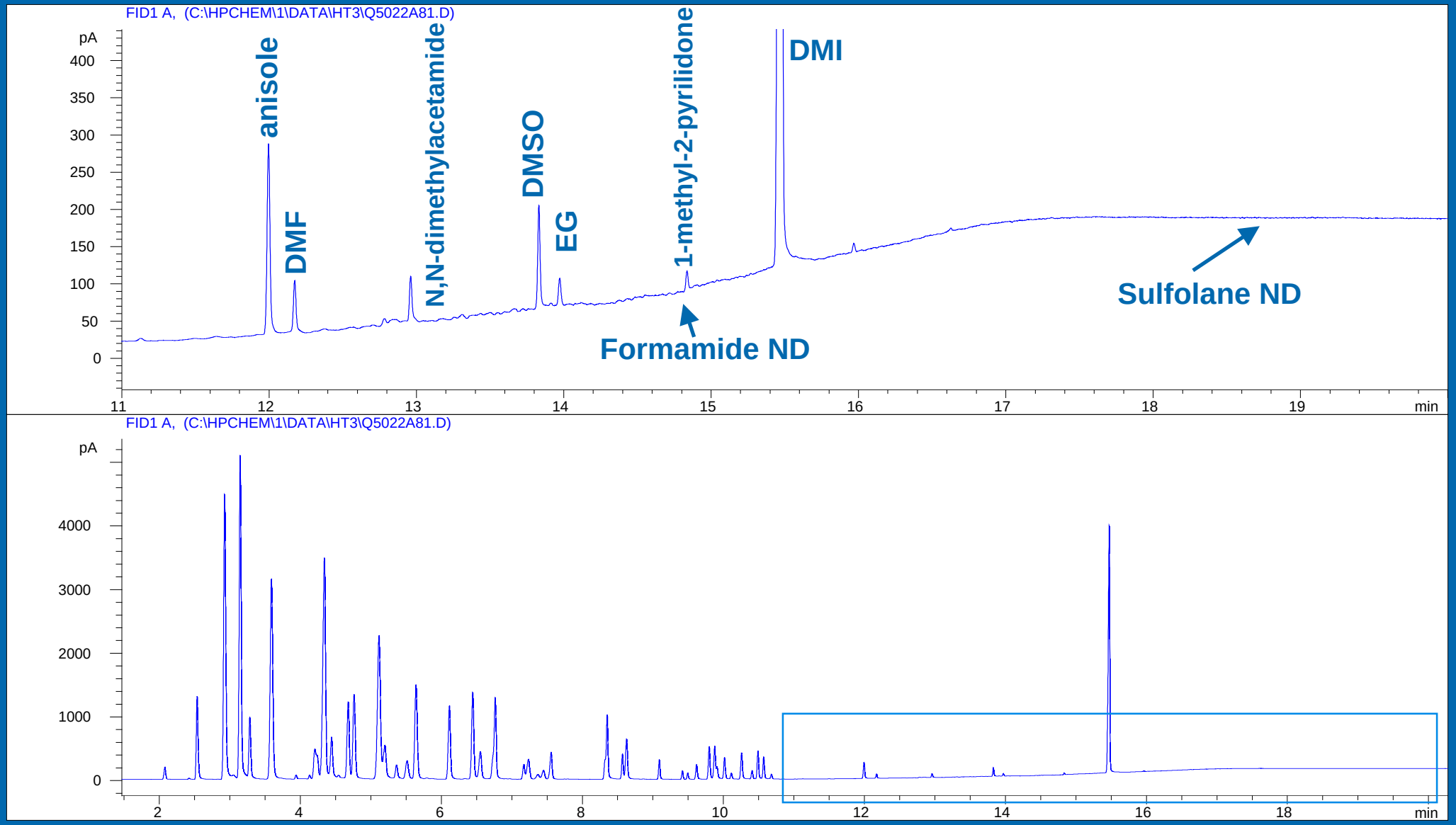
Class I,II,III 2nd FID by HS



Class I,II,III 2nd FID by HS



Class I,II,III 2nd FID by HS (spiked @ 400ppm)



Stabilwax / Rtx-200 Unresolved

Under Current Conditions

- methylal (s) / methanol (II)
- n-heptane (III) / isooctane (s)
- t-1,2-DCE (II) / ethyl formate (III)
- ethanol (III) / methyl cyclohexane (II)
- 2-butanone (III) / 1,2-dimethoxyethane (II)
- isobutyl acetate (III) / hexanone (III)
- 1-pentanol (III) / isopropylbenzene (III)
- c-1,2-dichloroethene (II) / isopropyl acetate (III)

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

- Continue evaluation of current phases
- Continue work on a new stationary phases
  - Using computer modeling
  - Goal: resolve Class I, II, III, other solvents.
- Continue with Stop-Flow technology

Special Thanks to Ed Price, Eric Heggs, Brian Wallace & Terry Jeffers of Teledyne Tekmar for their assistance in setup and operation of the HT3 Headspace unit.