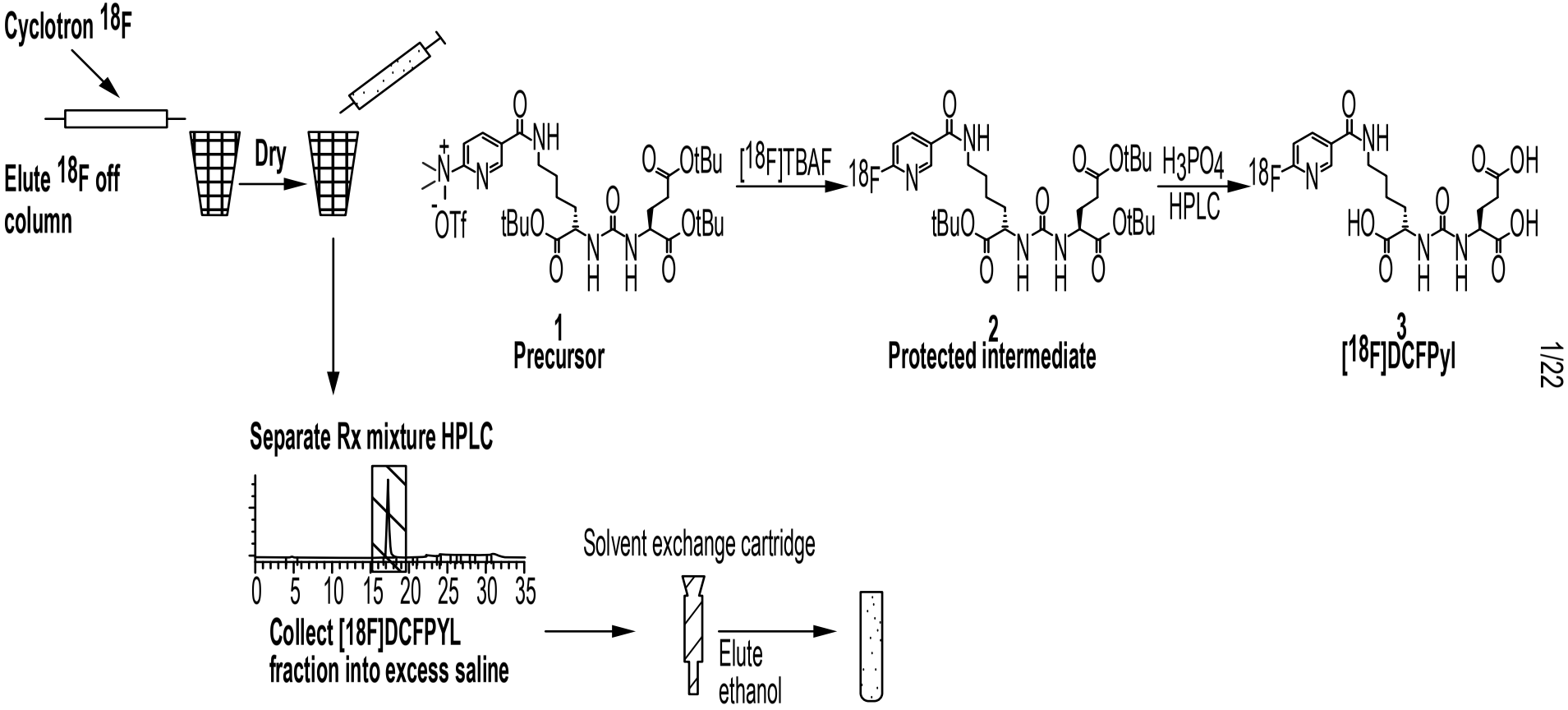

Cyclotron 18F
Elute 18F off column
Dry
1
Precursor
[18F]TBAF
2
Protected intermediate
H3PO4
HPLC
3
[18F]DCFPyl
Separate Rx mixture HPLC
0 5 10 15 20 25 30 35
Collect [18F]DCFPYL fraction into excess saline
Solvent exchange cartridge
Elute ethanol

FIG. 1

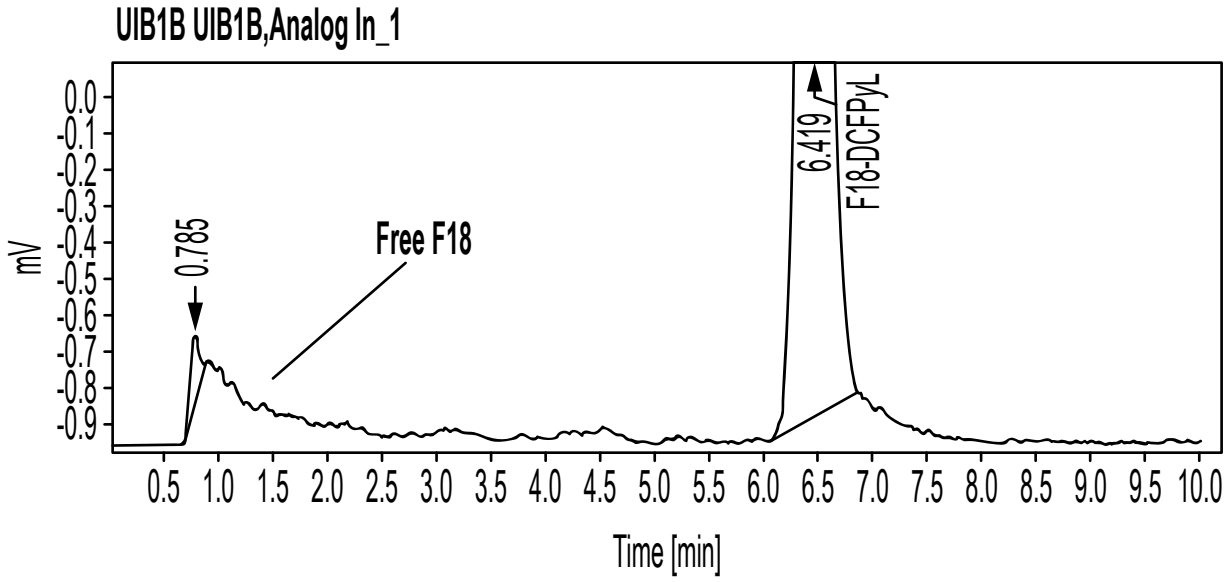

UIB1B UIB1B,Analog In_1
mV
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
0.785
Free F18
6.419
F18-DCFPyL
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0
Time [min]

FIG. 2

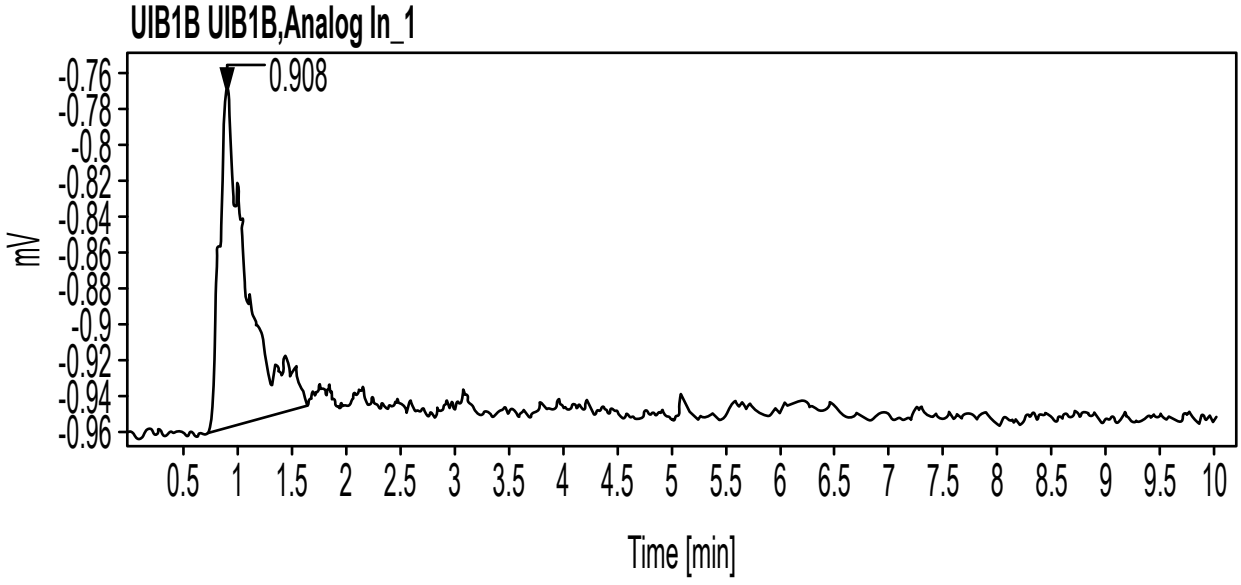

UIB1B UIB1B,Analog In_1
mV
-0.76
-0.78
-0.8
-0.82
-0.84
-0.86
-0.88
-0.9
-0.92
-0.94
-0.96
0.908
0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10
Time [min]

FIG. 3

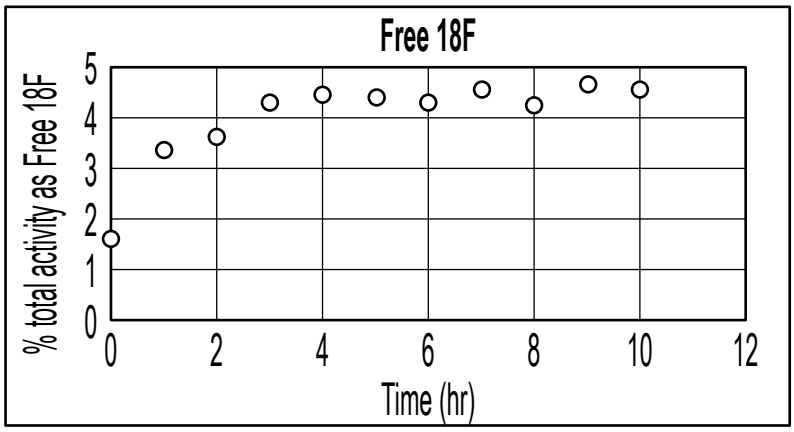


FIG. 4

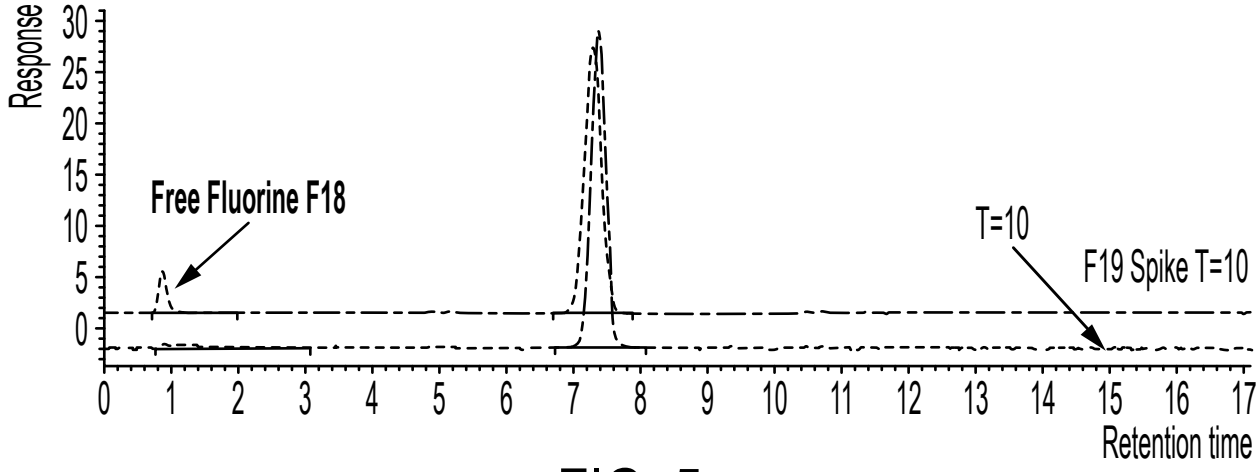


FIG. 5

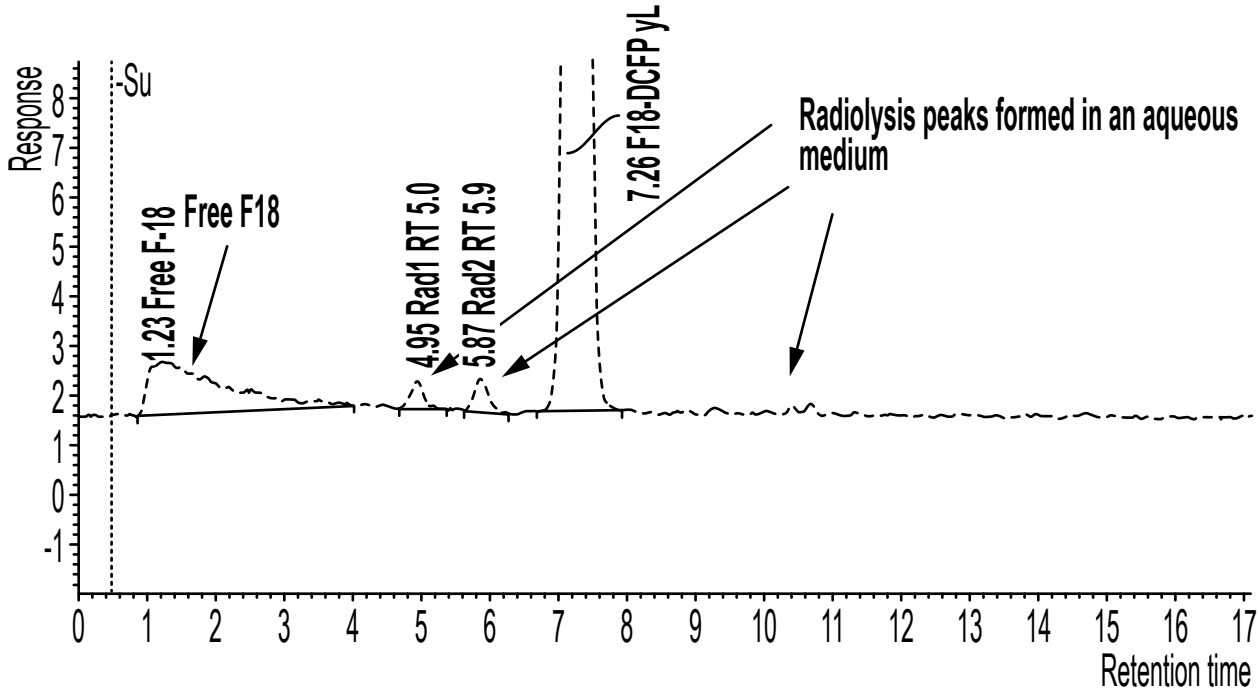


FIG. 6

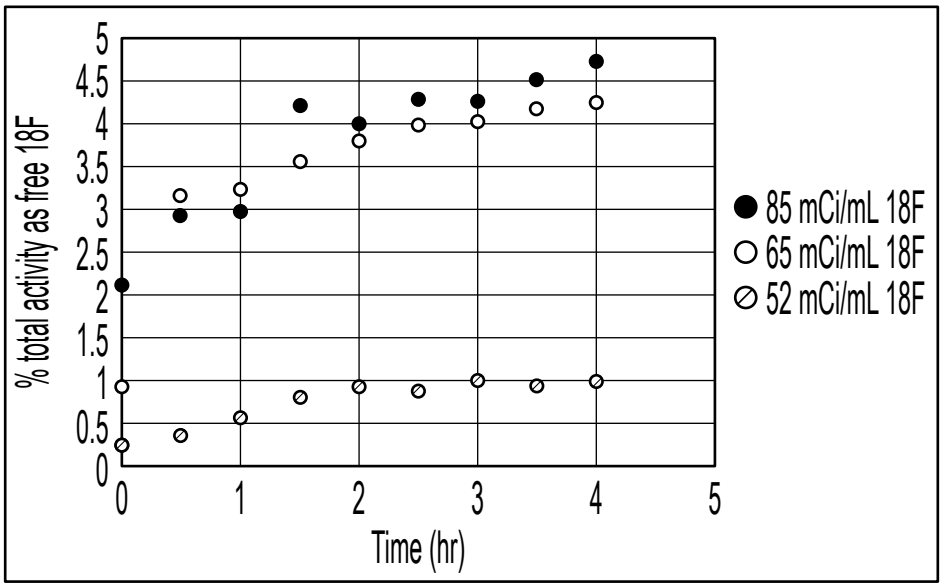


FIG. 7

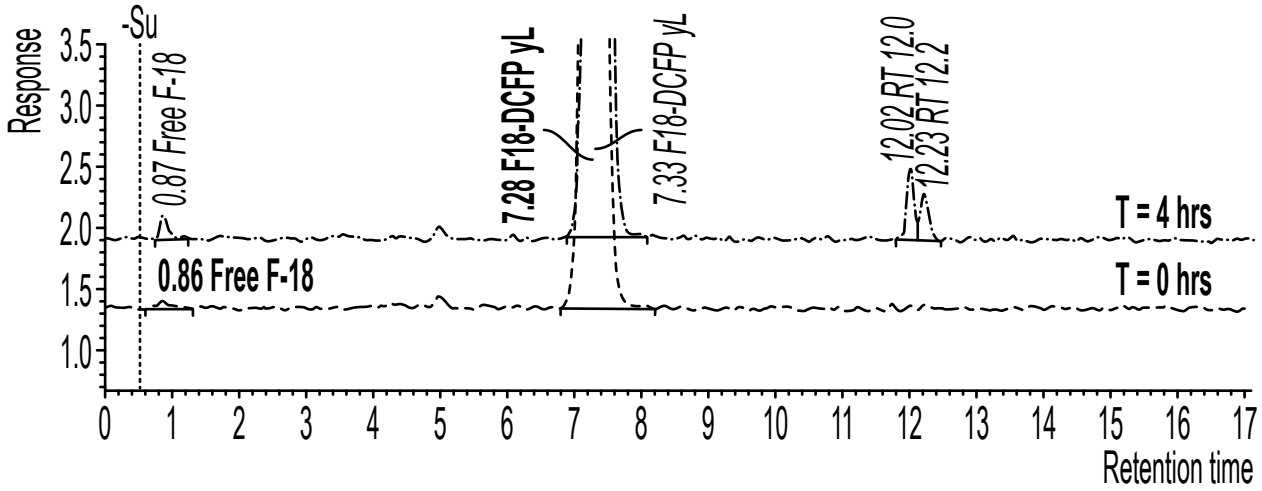


FIG. 8

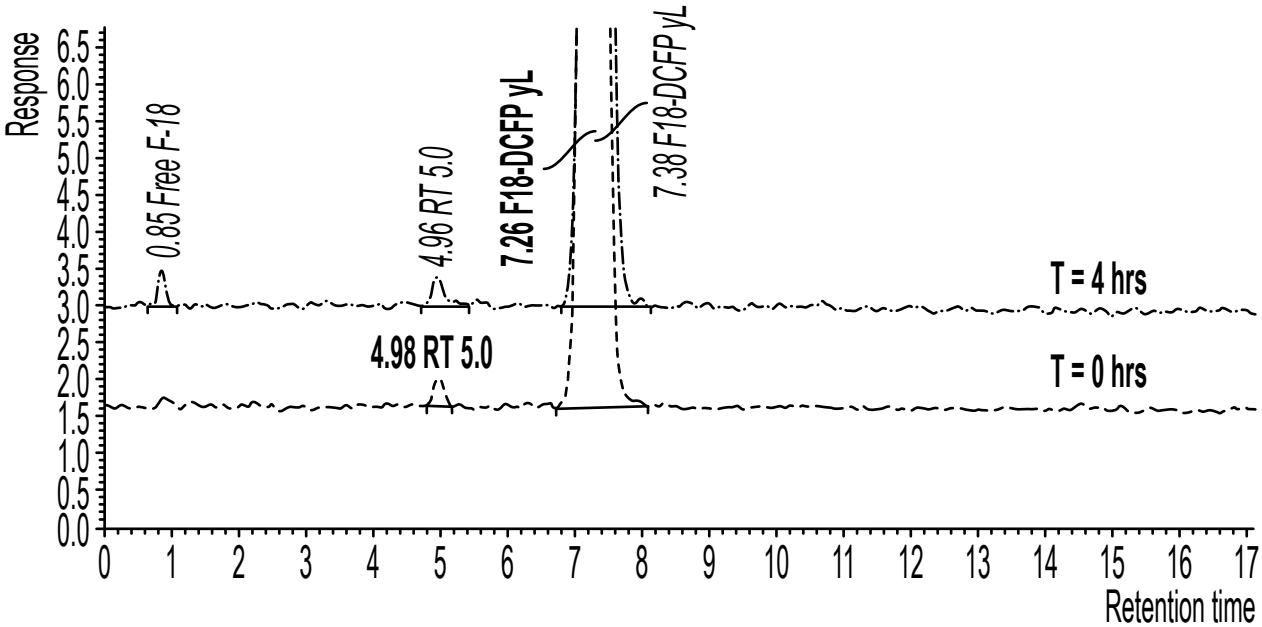


FIG. 9

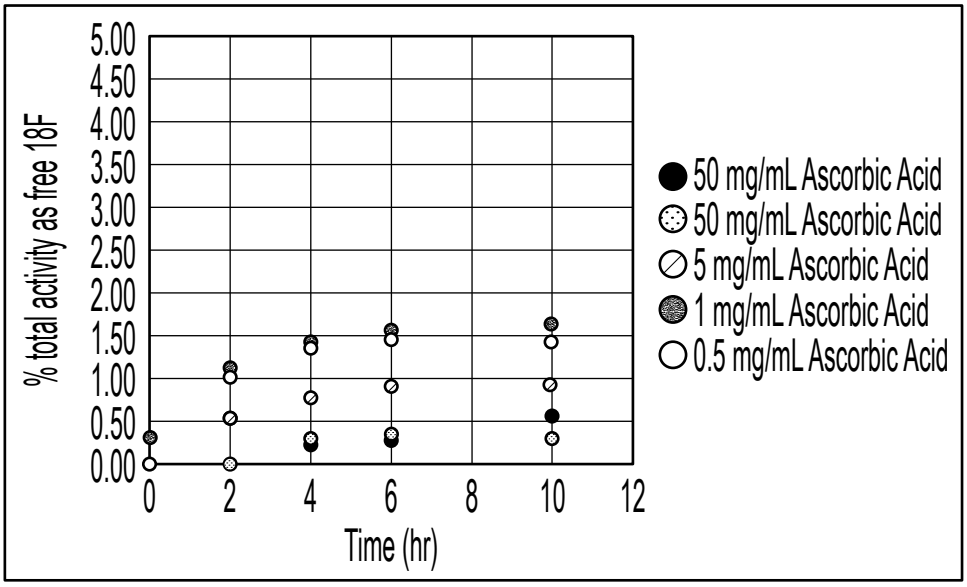

% total activity as free 18F
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
2
4
6
8
10
12
Time (hr)
50 mg/mL Ascorbic Acid
50 mg/mL Ascorbic Acid
5 mg/mL Ascorbic Acid
1 mg/mL Ascorbic Acid
0.5 mg/mL Ascorbic Acid

FIG. 10

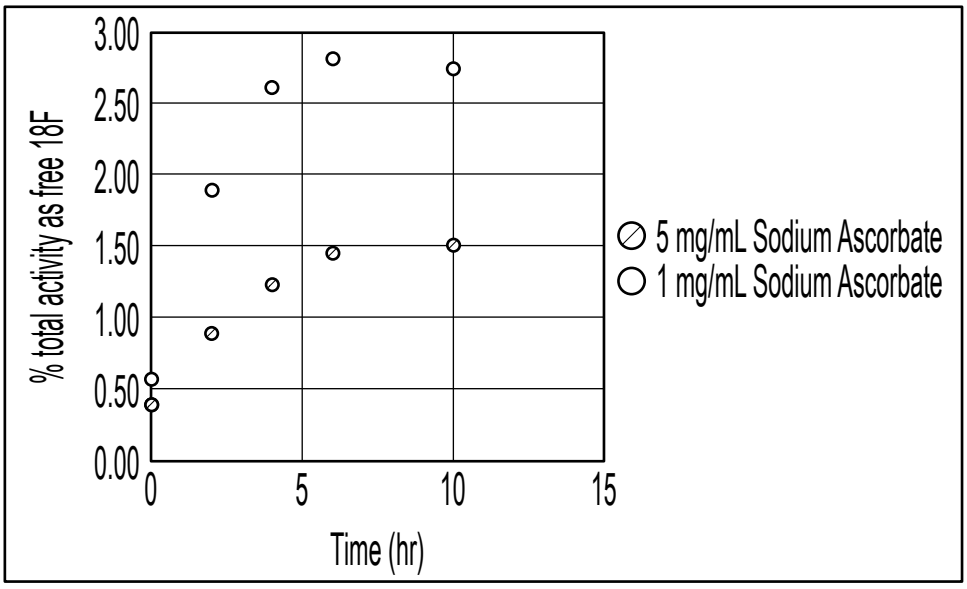

% total activity as free 18F
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
5
10
15
Time (hr)
5 mg/mL Sodium Ascorbate
1 mg/mL Sodium Ascorbate

FIG. 11

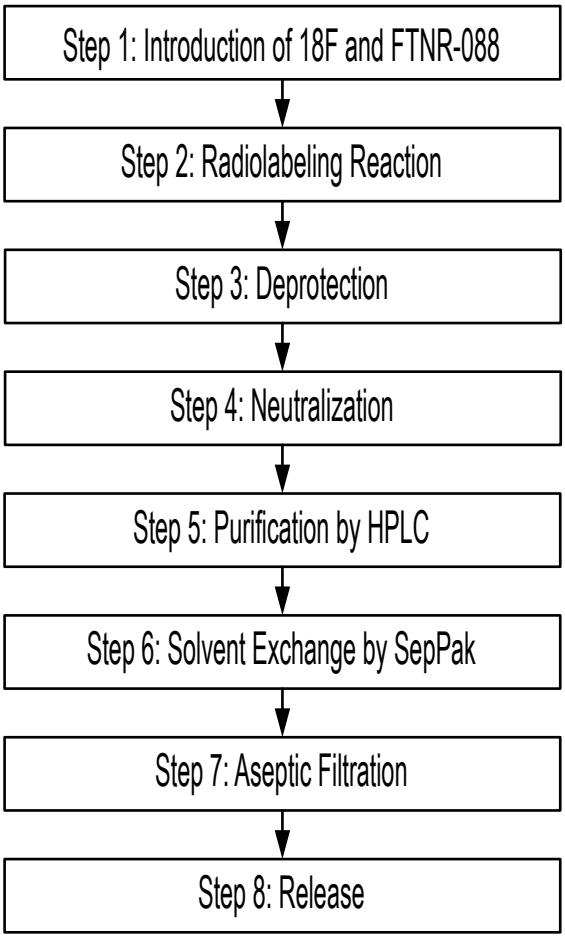
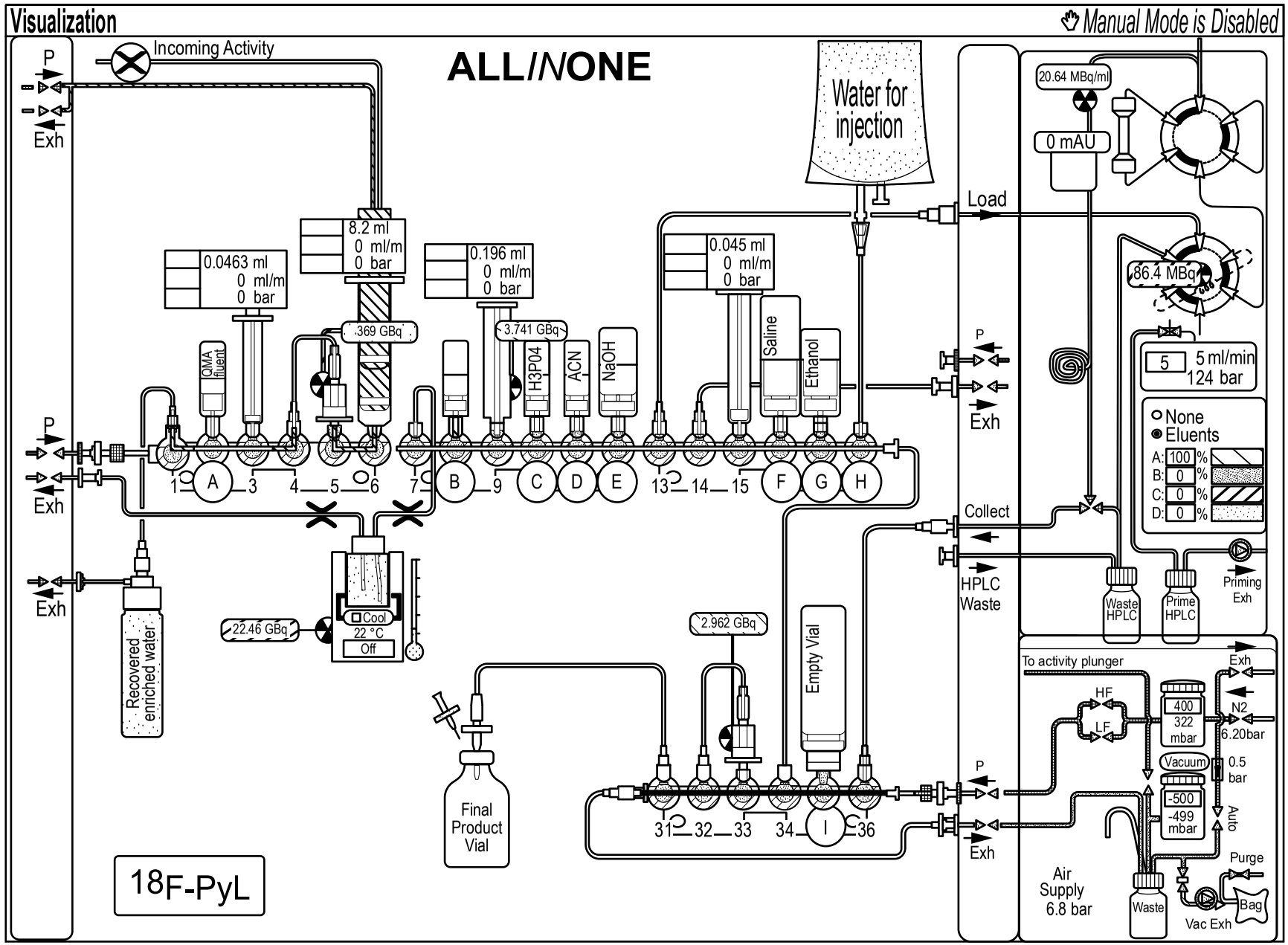

Step 1: Introduction of 18F and FTNR-088
Step 2: Radiolabeling Reaction
Step 3: Deprotection
Step 4: Neutralization
Step 5: Purification by HPLC
Step 6: Solvent Exchange by SepPak
Step 7: Aseptic Filtration
Step 8: Release

FIG. 12



A: QMA eluent Vial
B: Precursor Vial
C: Phosphoric Acid Vial
D: Acetonitrile Vial
E: Sodium Hydroxide Vial
F: Delivery Solution Vial
G: Ethanol Vial
H: SWFI Bag
I: Collection Vial with Ascorbic Acid Solution

FIG. 13

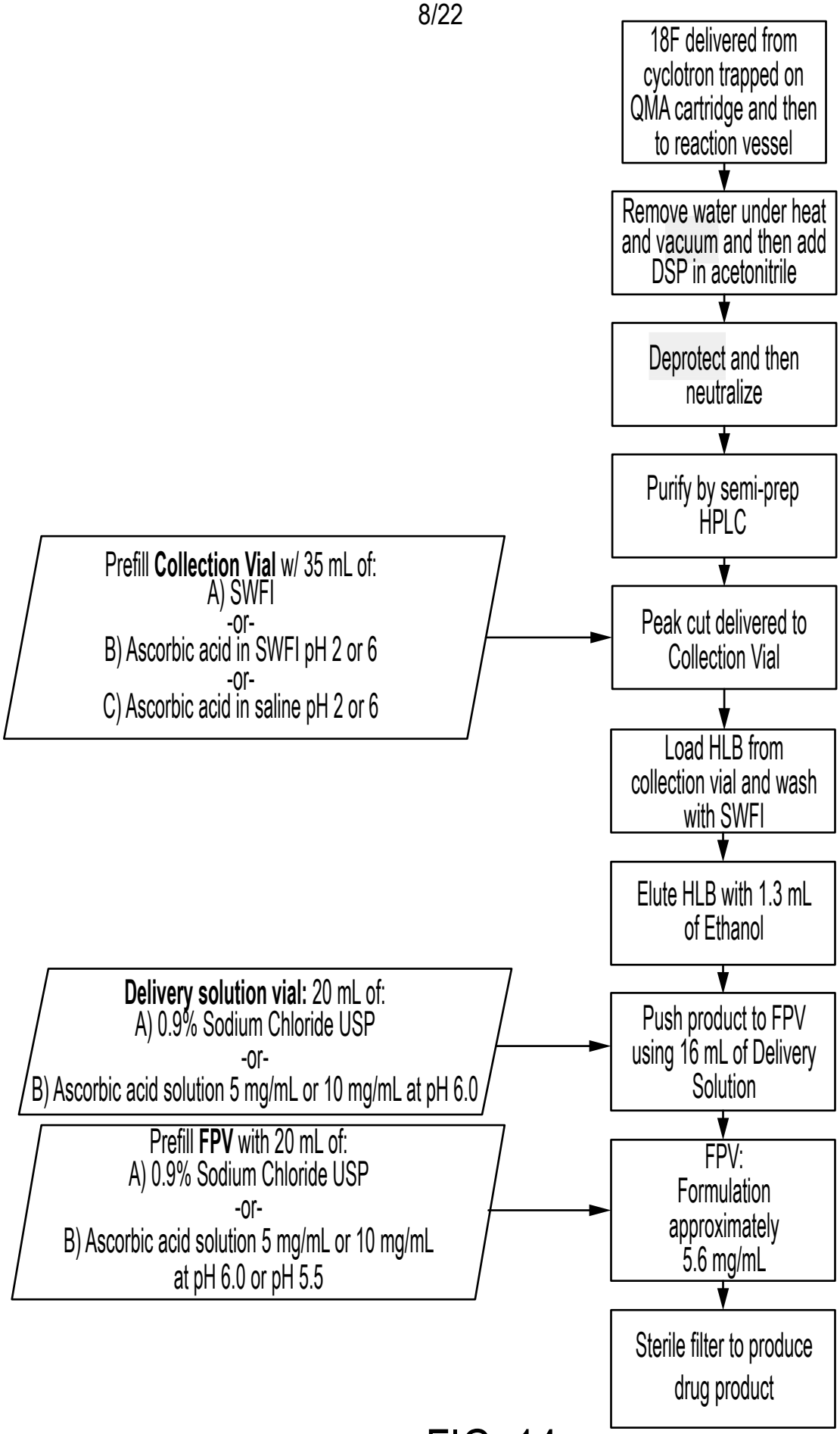

18F delivered from cyclotron trapped on QMA cartridge and then to reaction vessel
Remove water under heat and vacuum and then add DSP in acetonitrile
Deprotect and then neutralize
Purify by semi-prep HPLC
Prefill **Collection Vial** w/ 35 mL of:
A) SWFI
-or-
B) Ascorbic acid in SWFI pH 2 or 6
-or-
C) Ascorbic acid in saline pH 2 or 6
Peak cut delivered to Collection Vial
Load HLB from collection vial and wash with SWFI
Elute HLB with 1.3 mL of Ethanol
Delivery solution vial: 20 mL of:
A) 0.9% Sodium Chloride USP
-or-
B) Ascorbic acid solution 5 mg/mL or 10 mg/mL at pH 6.0
Push product to FPV using 16 mL of Delivery Solution
Prefill **FPV** with 20 mL of:
A) 0.9% Sodium Chloride USP
-or-
B) Ascorbic acid solution 5 mg/mL or 10 mg/mL at pH 6.0 or pH 5.5
FPV: Formulation approximately 5.6 mg/mL
Sterile filter to produce drug product

FIG. 14

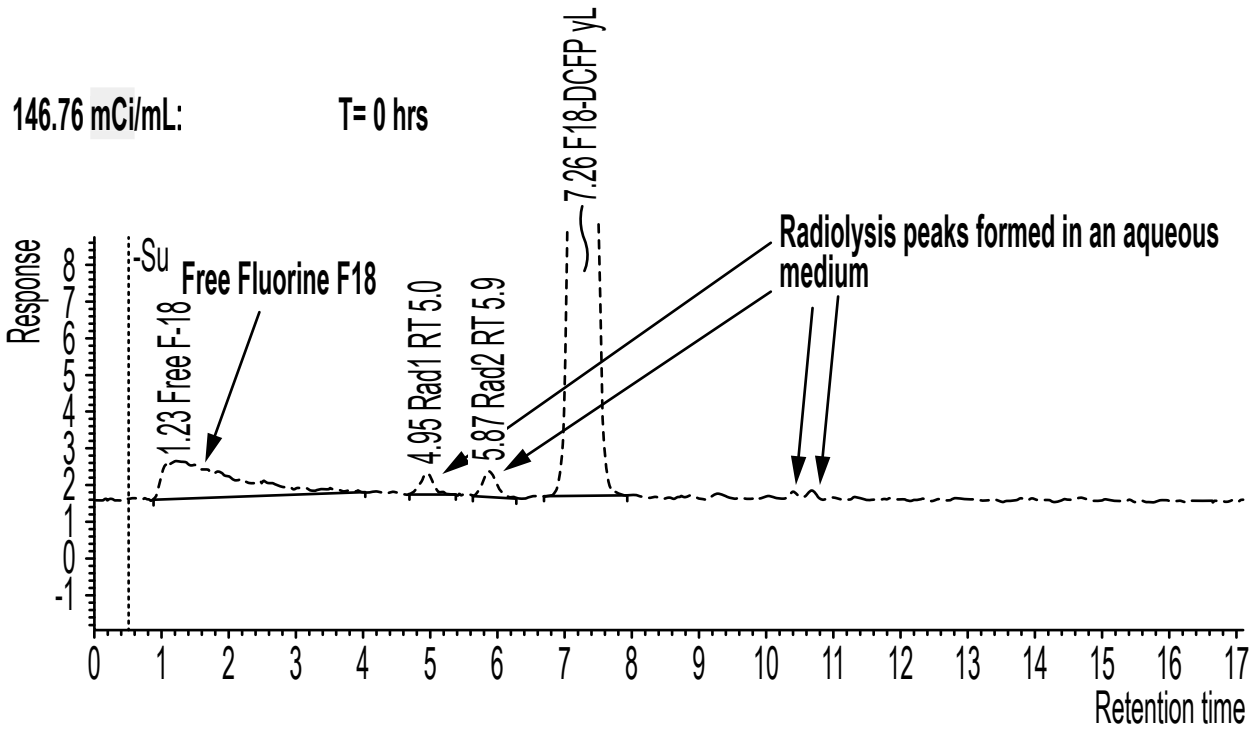

146.76 mCi/mL:
T= 0 hrs
7.26 F18-DCFP yL
Radiolysis peaks formed in an aqueous medium
Response
-Su
Free Fluorine F18
1.23 Free F-18
4.95 Rad1 RT 5.0
5.87 Rad2 RT 5.9
Retention time

FIG. 15

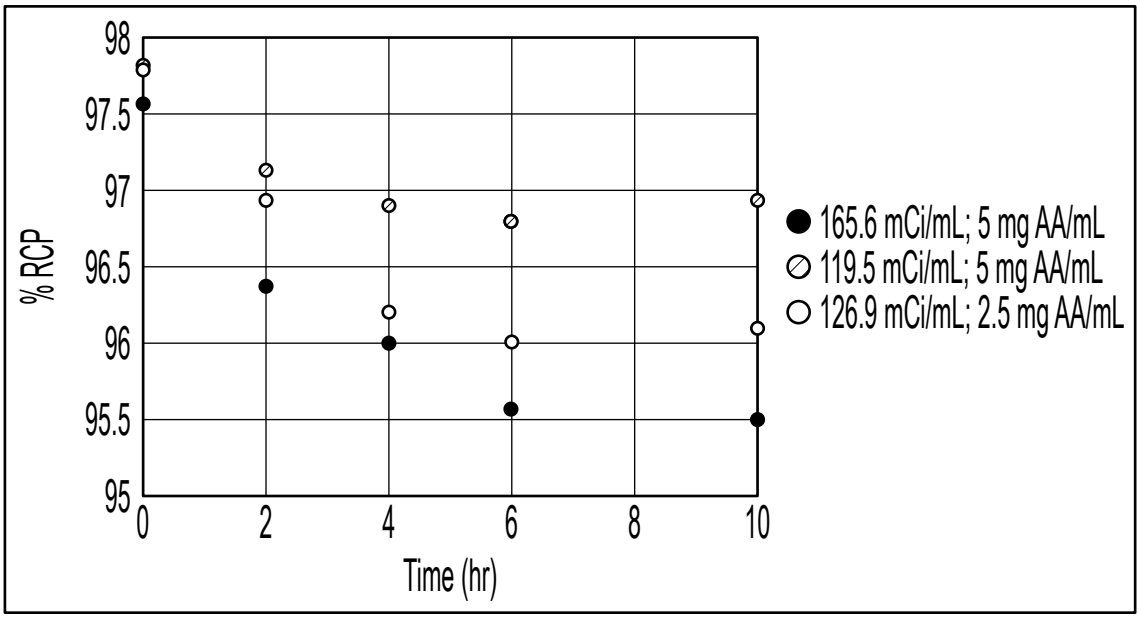

% RCP
Time (hr)
165.6 mCi/mL; 5 mg AA/mL
119.5 mCi/mL; 5 mg AA/mL
126.9 mCi/mL; 2.5 mg AA/mL

FIG. 16

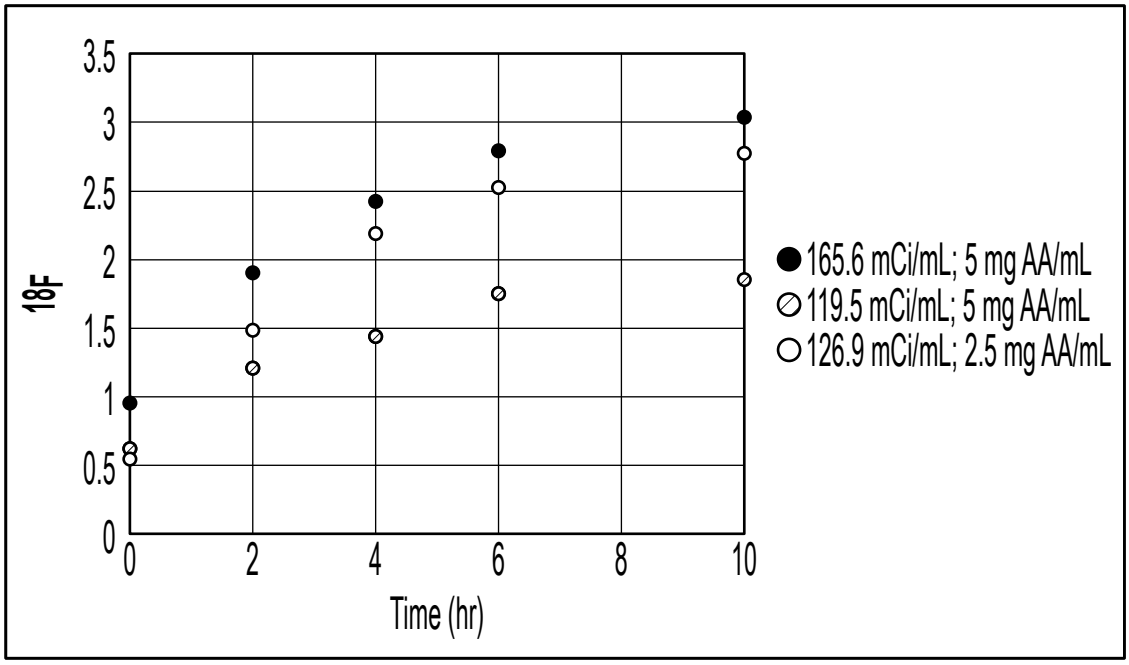

3.5
3
2.5
2
1.5
1
0.5
0
18F
0
2
4
6
8
10
Time (hr)
165.6 mCi/mL; 5 mg AA/mL
119.5 mCi/mL; 5 mg AA/mL
126.9 mCi/mL; 2.5 mg AA/mL

FIG. 17

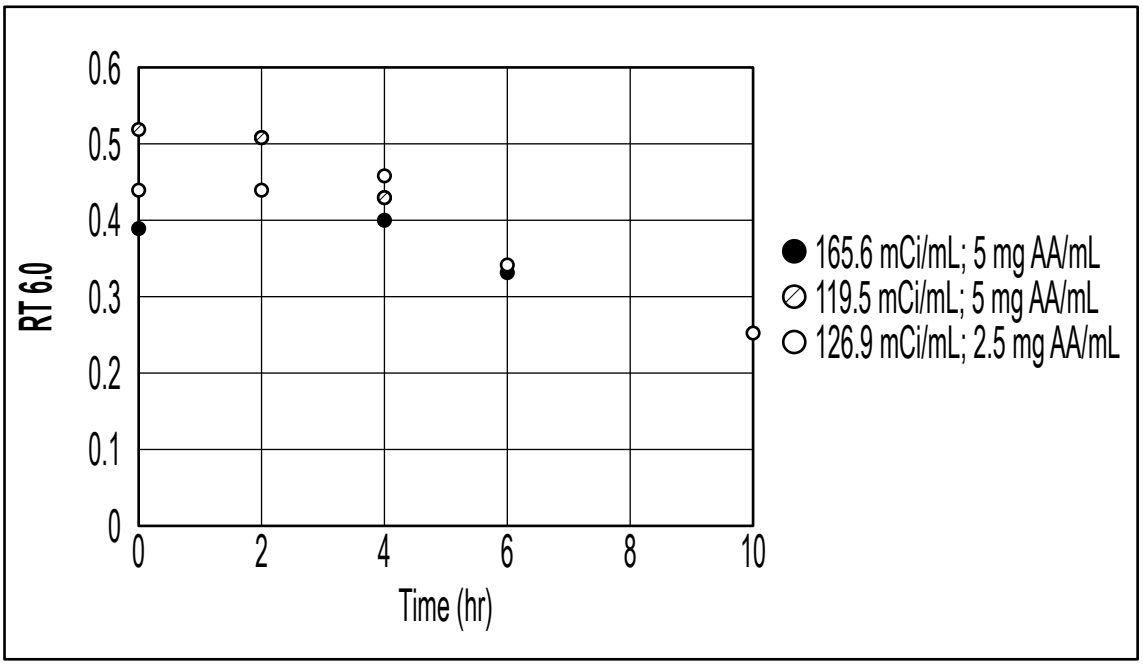

0.6
0.5
0.4
0.3
0.2
0.1
0
RT 6.0
0
2
4
6
8
10
Time (hr)
165.6 mCi/mL; 5 mg AA/mL
119.5 mCi/mL; 5 mg AA/mL
126.9 mCi/mL; 2.5 mg AA/mL

FIG. 18

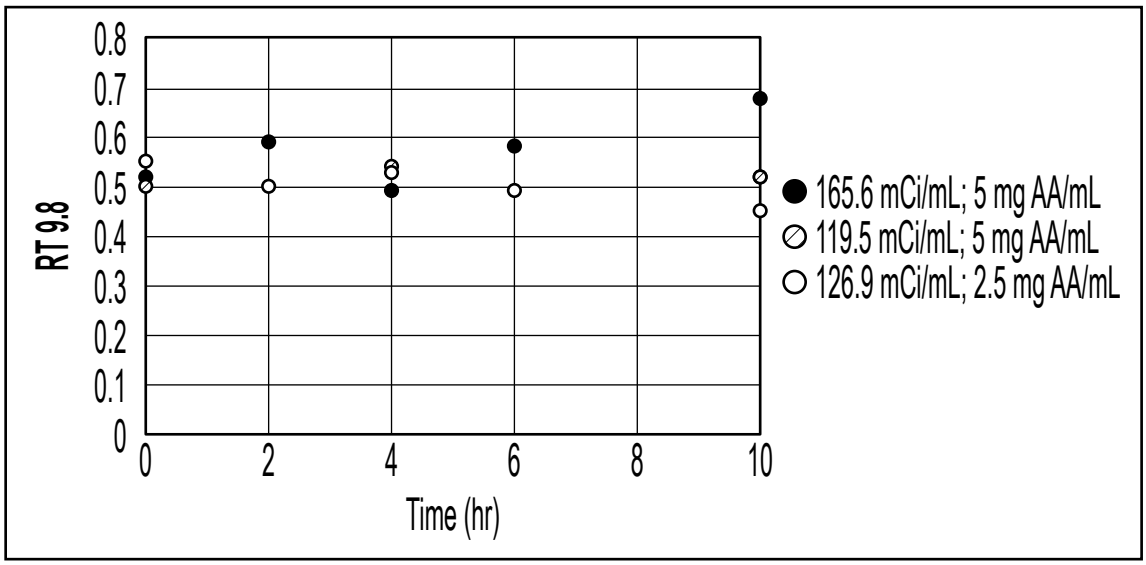

RT 9.8
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
Time (hr)
165.6 mCi/mL; 5 mg AA/mL
119.5 mCi/mL; 5 mg AA/mL
126.9 mCi/mL; 2.5 mg AA/mL

FIG. 19

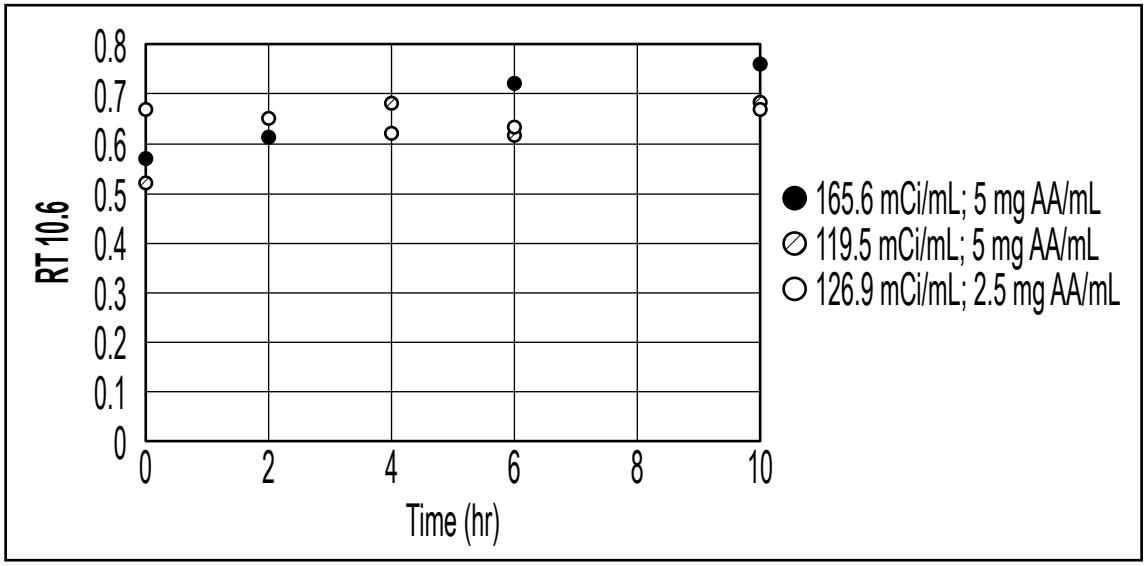

RT 10.6
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
Time (hr)
165.6 mCi/mL; 5 mg AA/mL
119.5 mCi/mL; 5 mg AA/mL
126.9 mCi/mL; 2.5 mg AA/mL

FIG. 20

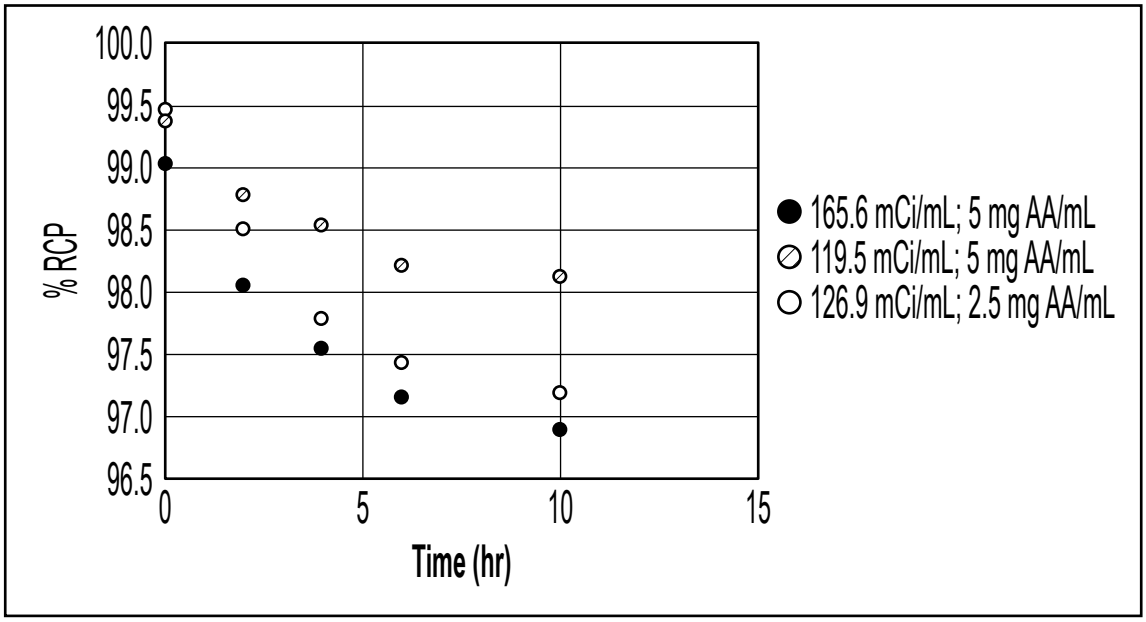

100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
% RCP
0
5
10
15
Time (hr)
165.6 mCi/mL; 5 mg AA/mL
119.5 mCi/mL; 5 mg AA/mL
126.9 mCi/mL; 2.5 mg AA/mL

FIG. 21

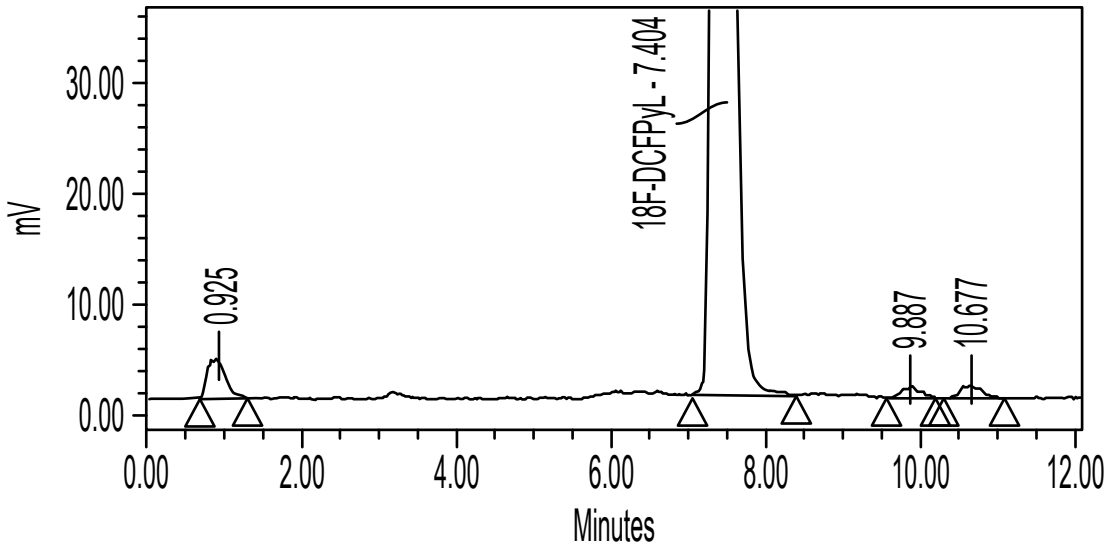

30.00
20.00
10.00
0.00
mV
18F-DCFPyL - 7.404
0.925
9.887
10.677
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes

FIG. 22

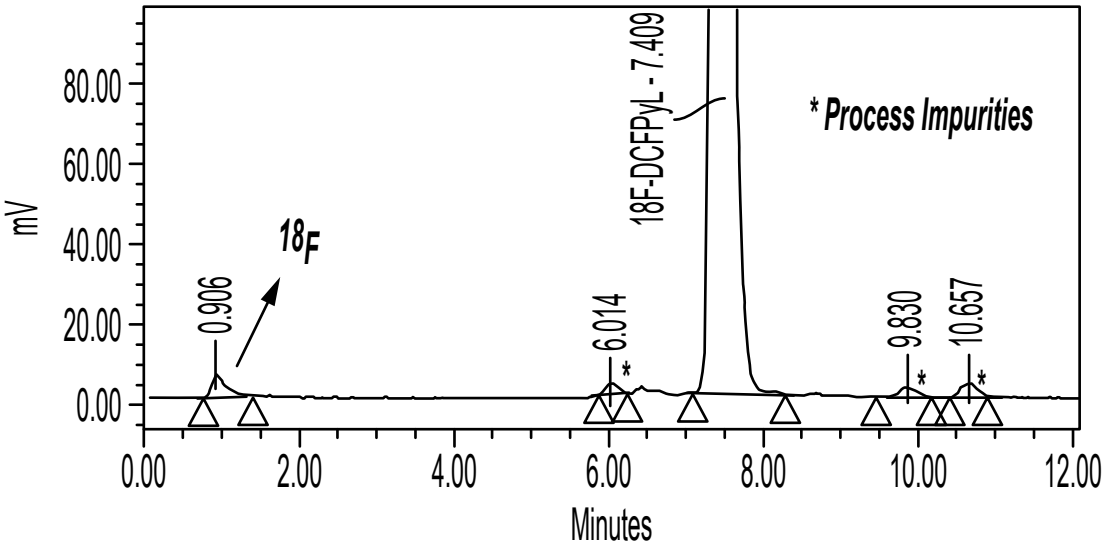

mV
80.00
60.00
40.00
20.00
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes
0.906
18F
6.014
18F-DCFPyL - 7.409
9.830
10.657
* Process Impurities

FIG. 23

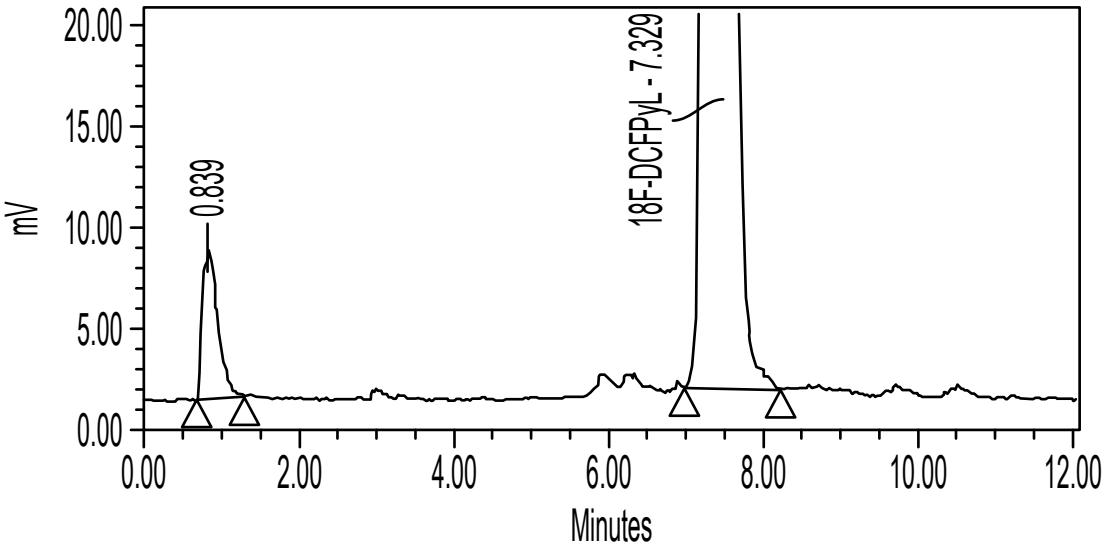

mV
20.00
15.00
10.00
5.00
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes
0.839
18F-DCFPyL - 7.329

FIG. 24

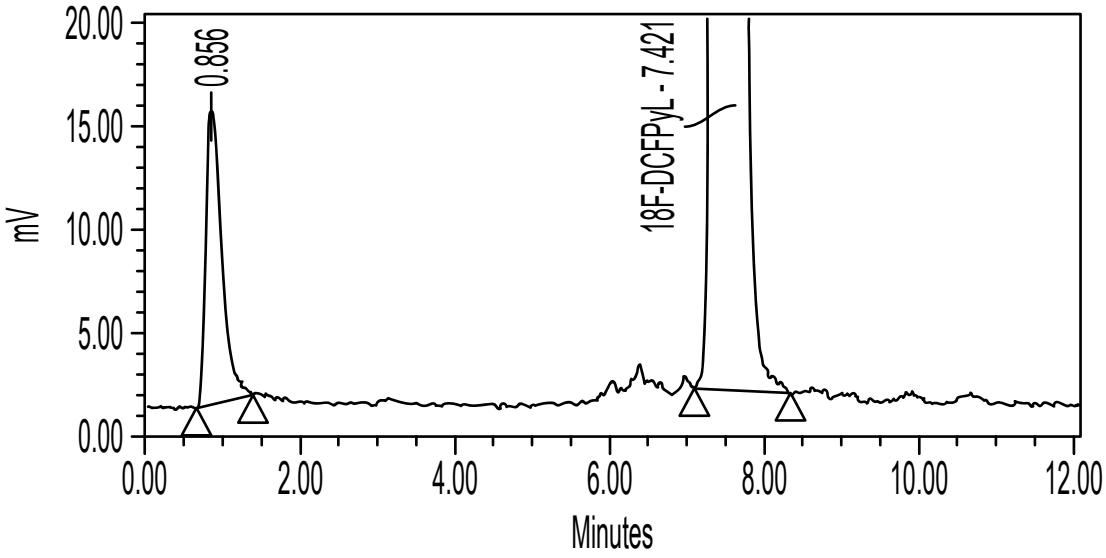

20.00
15.00
10.00
5.00
0.00
mV
0.856
18F-DCFPyL - 7.421
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes

FIG. 25

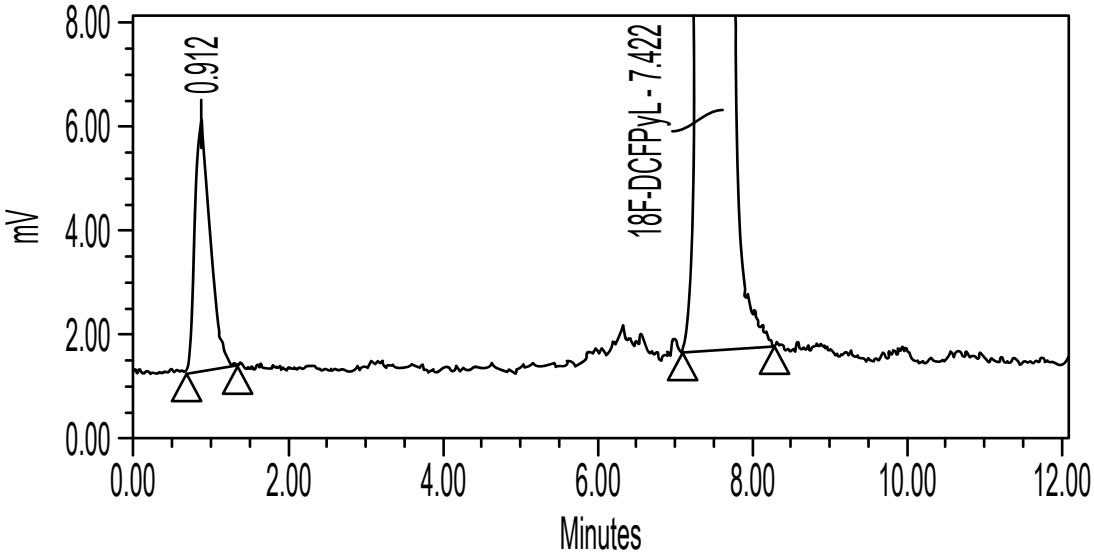

8.00
6.00
4.00
2.00
0.00
mV
0.912
18F-DCFPyL - 7.422
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes

FIG. 26

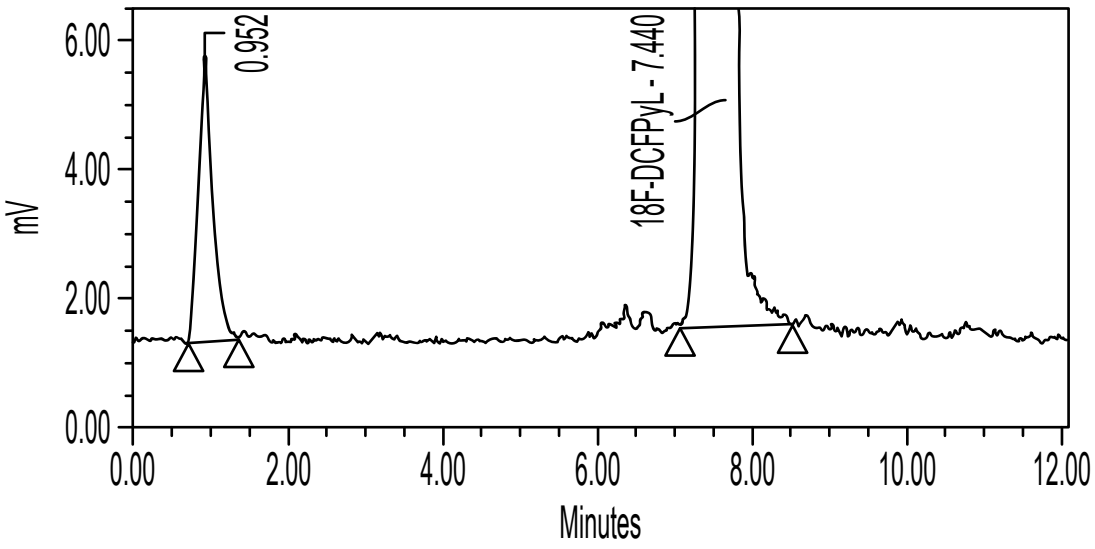

0.952
18F-DCFPyL - 7.440
mV
6.00
4.00
2.00
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes

FIG. 27

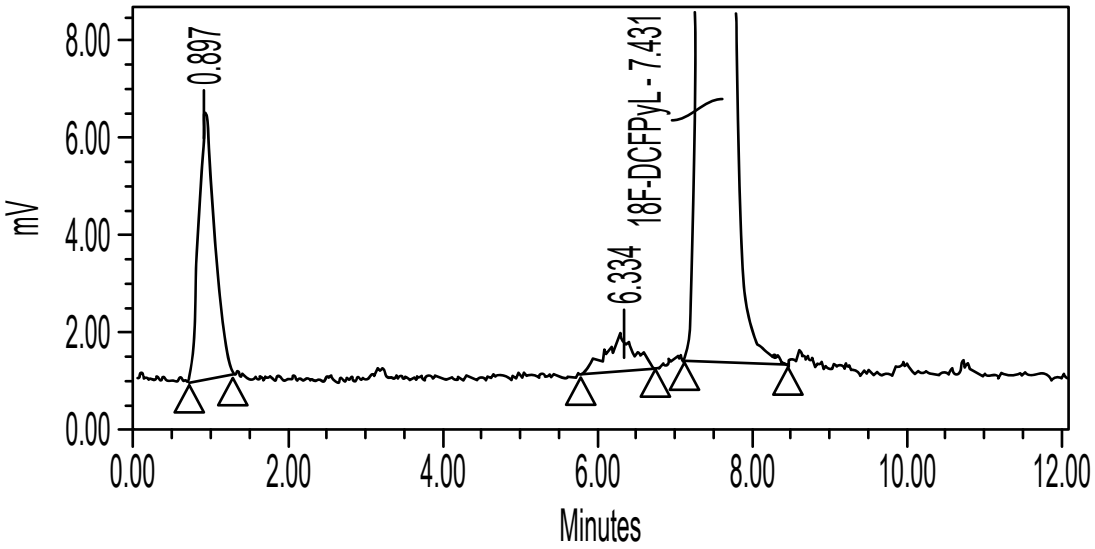

0.897
18F-DCFPyL - 7.431
6.334
mV
8.00
6.00
4.00
2.00
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes

FIG. 28

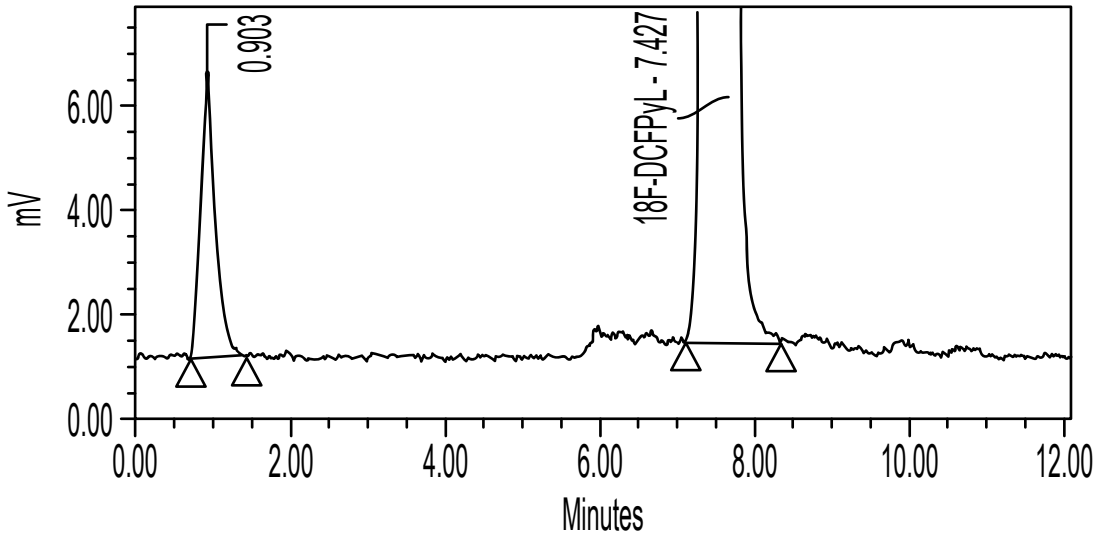

0.903
18F-DCFPyL - 7.427
mV
6.00
4.00
2.00
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes

FIG. 29

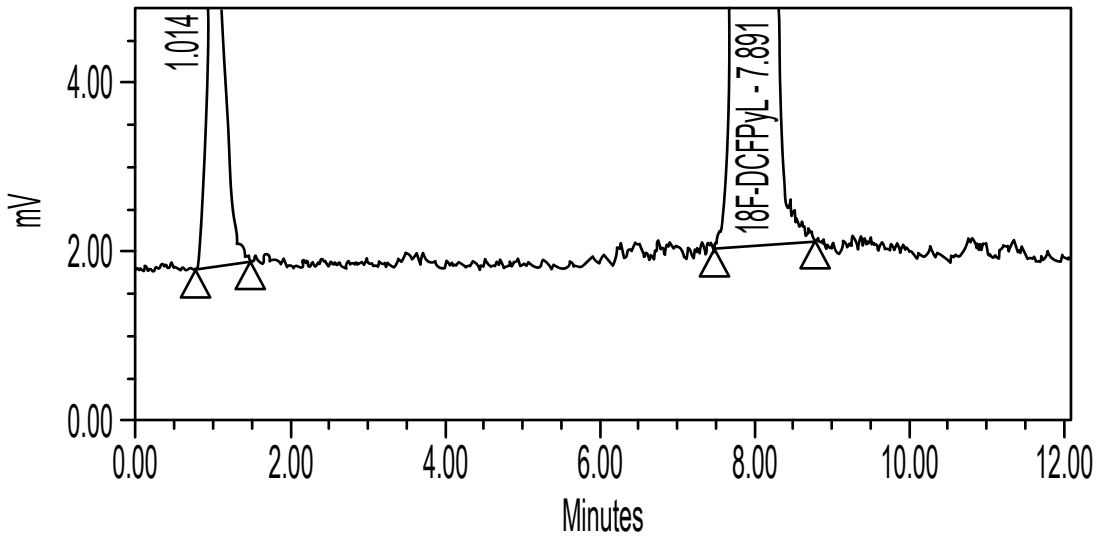

1.014
18F-DCFPyL - 7.891
mV
4.00
2.00
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
Minutes

FIG. 30

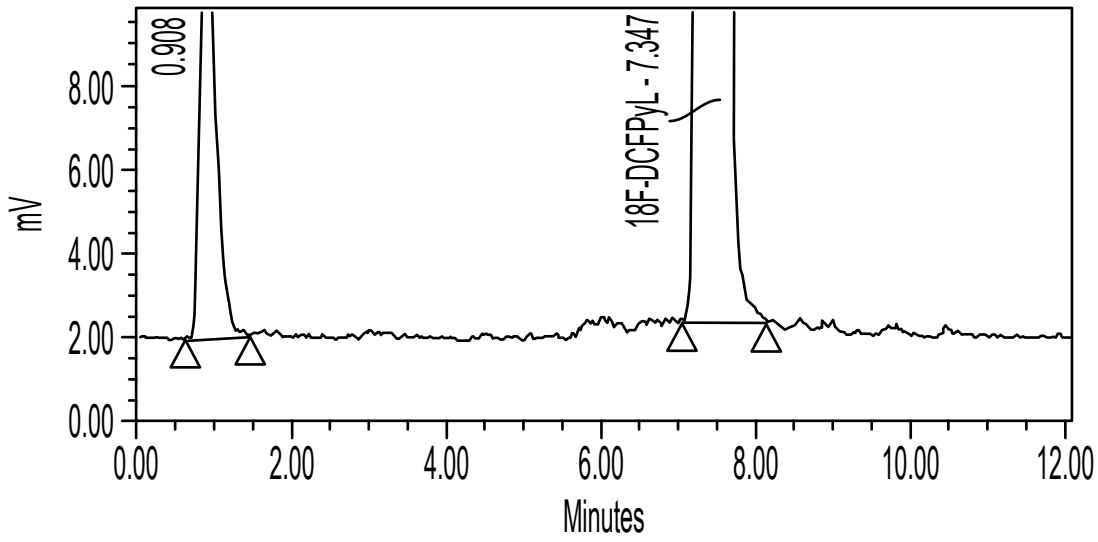


FIG. 31

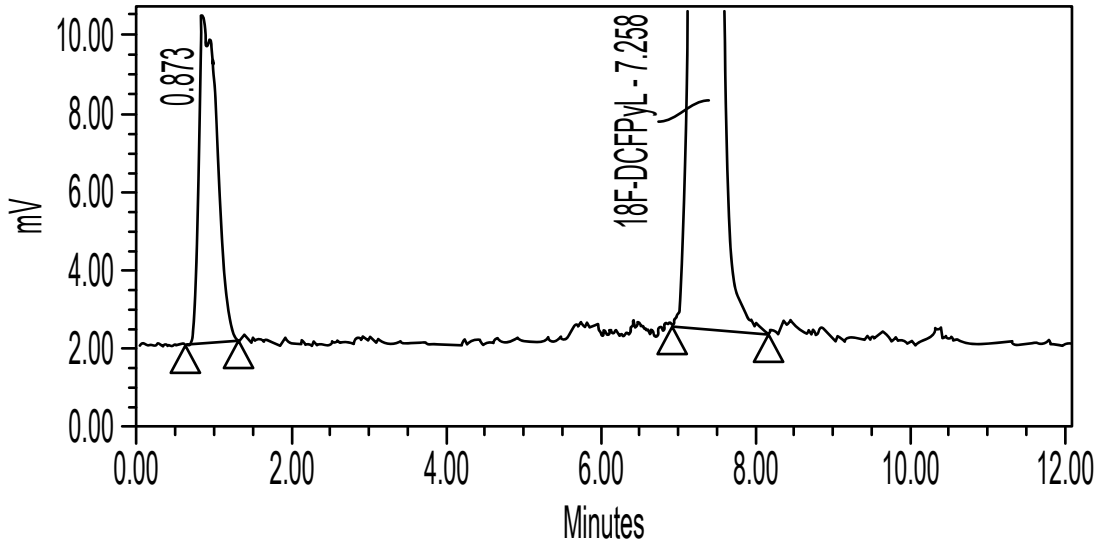


FIG. 32

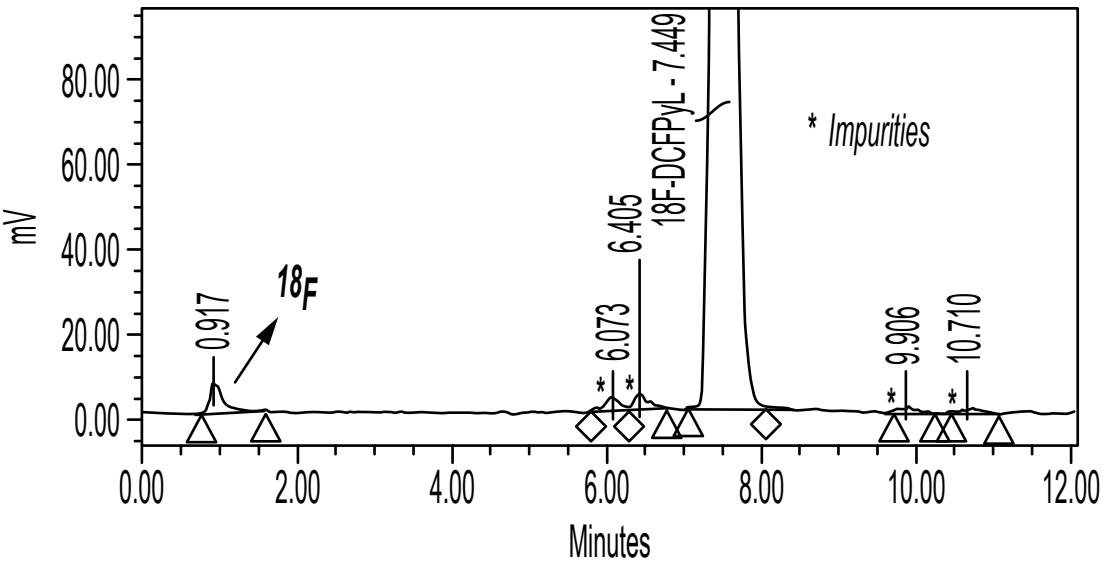


FIG. 33

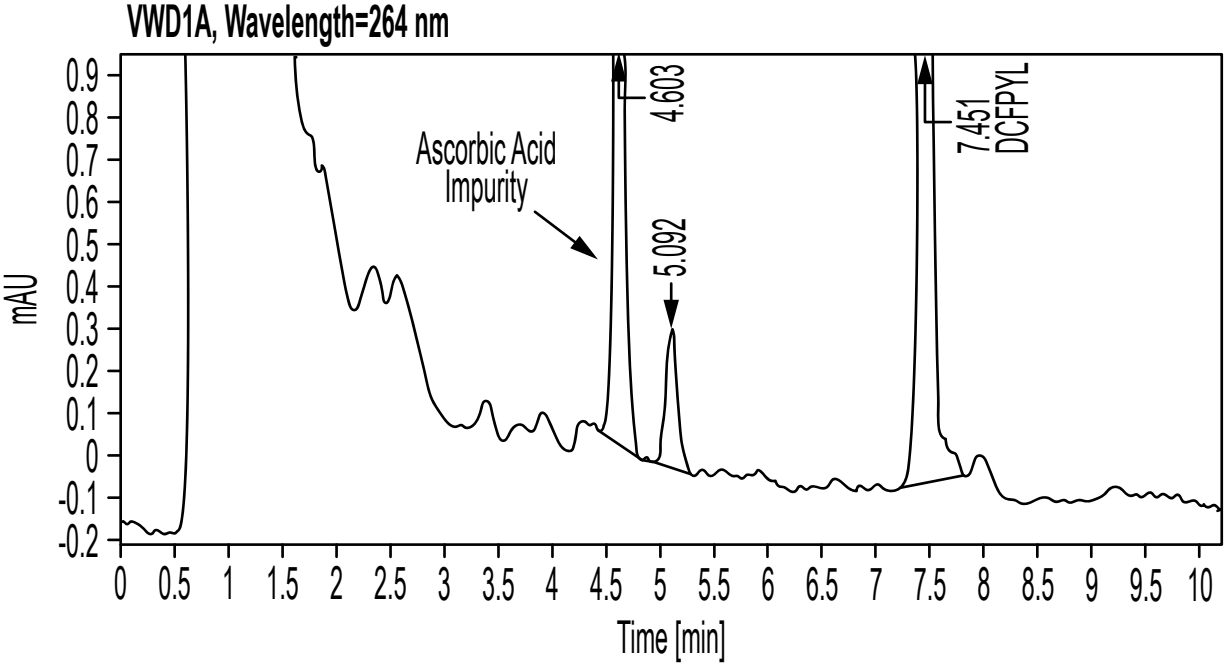

VWD1A, Wavelength=264 nm
mAU
Ascorbic Acid Impurity
4.603
5.092
7.451
DCFPYL
Time [min]

FIG. 34

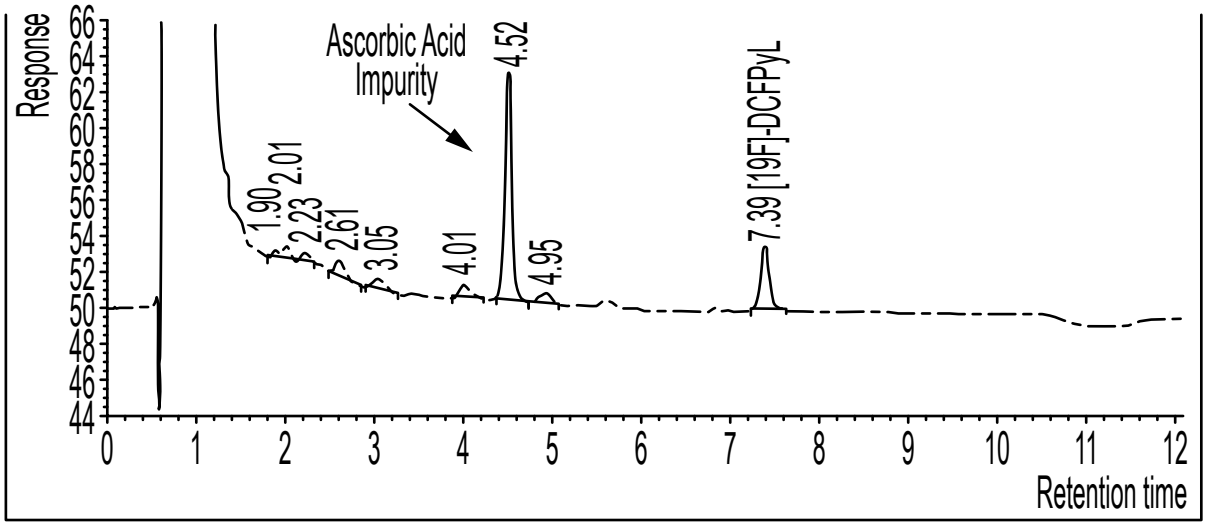

Response
Ascorbic Acid Impurity
1.90
2.01
2.23
2.61
3.05
4.01
4.52
4.95
7.39 [19F]-DCFPyL
Retention time

FIG. 35

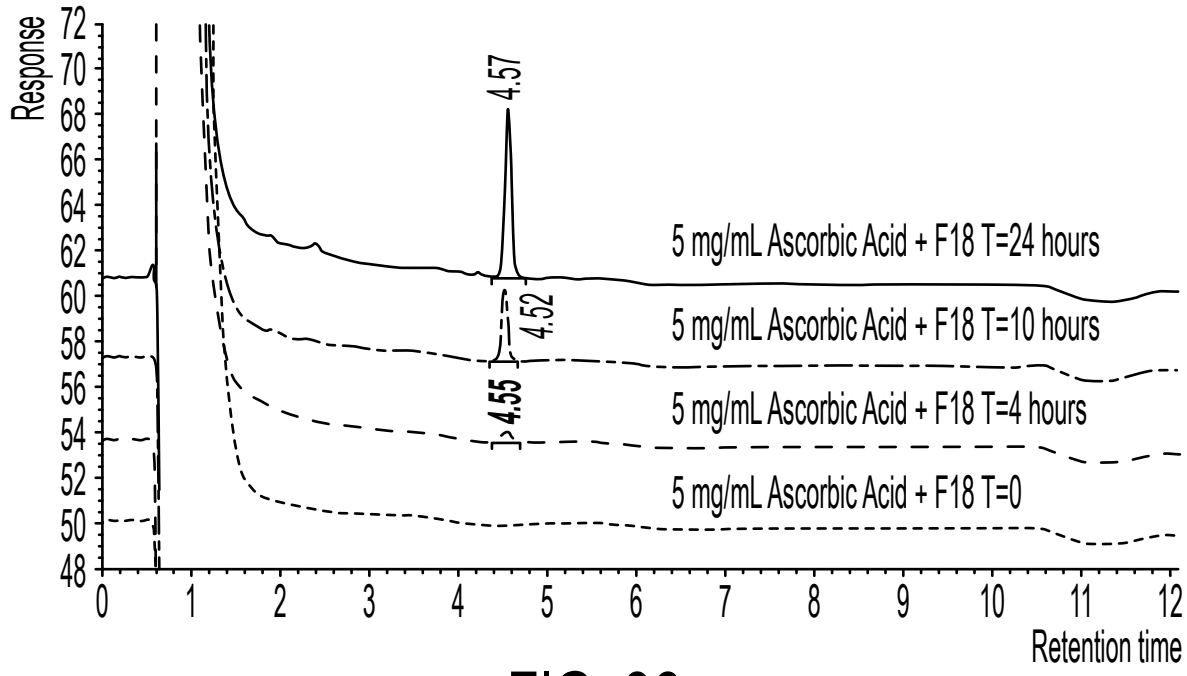

Response
72
70
68
66
64
62
60
58
56
54
52
50
48
0
1
2
3
4
5
6
7
8
9
10
11
12
Retention time
4.57
4.52
4.55
5 mg/mL Ascorbic Acid + F18 T=24 hours
5 mg/mL Ascorbic Acid + F18 T=10 hours
5 mg/mL Ascorbic Acid + F18 T=4 hours
5 mg/mL Ascorbic Acid + F18 T=0

FIG. 36

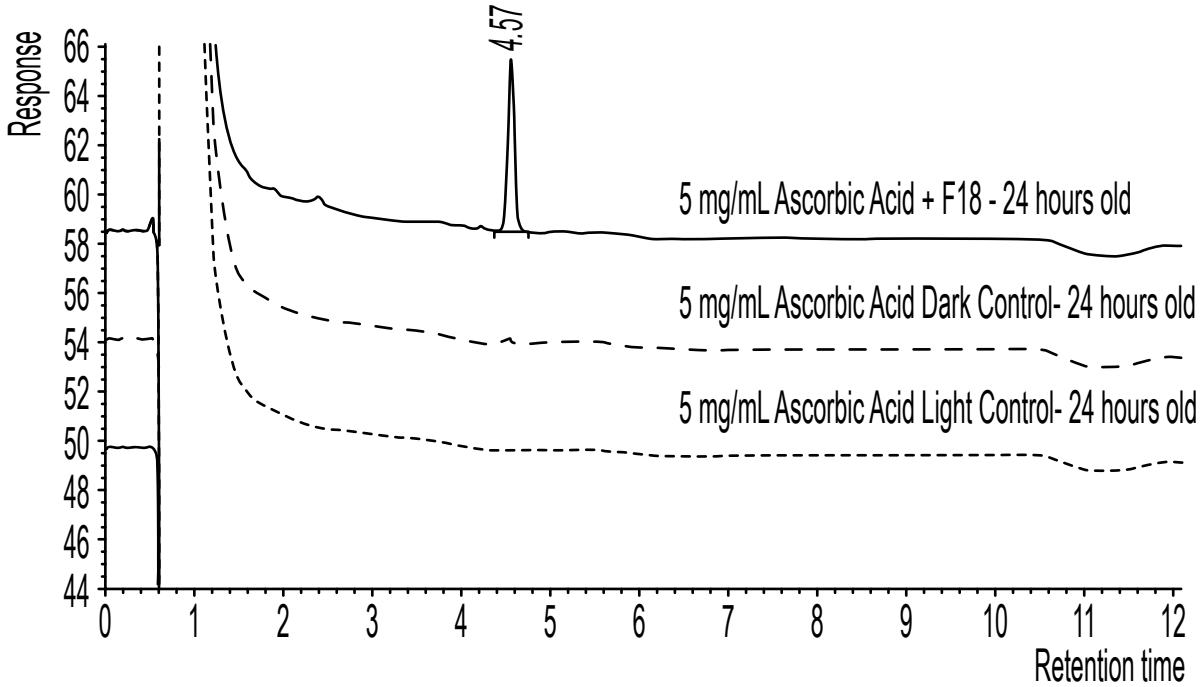

Response
66
64
62
60
58
56
54
52
50
48
46
44
0
1
2
3
4
5
6
7
8
9
10
11
12
Retention time
4.57
5 mg/mL Ascorbic Acid + F18 - 24 hours old
5 mg/mL Ascorbic Acid Dark Control- 24 hours old
5 mg/mL Ascorbic Acid Light Control- 24 hours old

FIG. 37

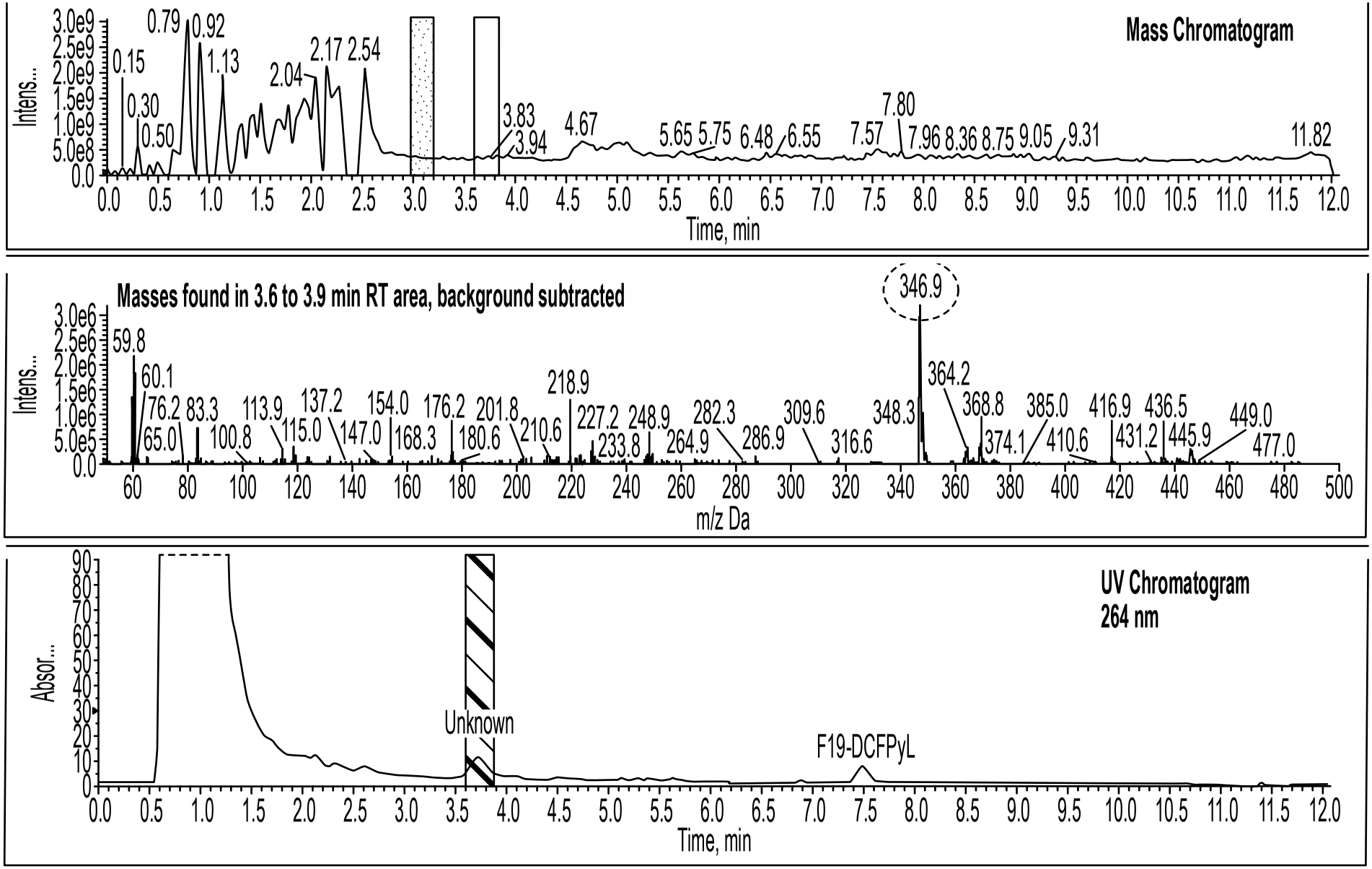

Mass Chromatogram
Intens...
Time, min
Masses found in 3.6 to 3.9 min RT area, background subtracted
Intens...
m/z Da
UV Chromatogram
264 nm
Absor...
Unknown
F19-DCFPyL
Time, min

FIG. 38

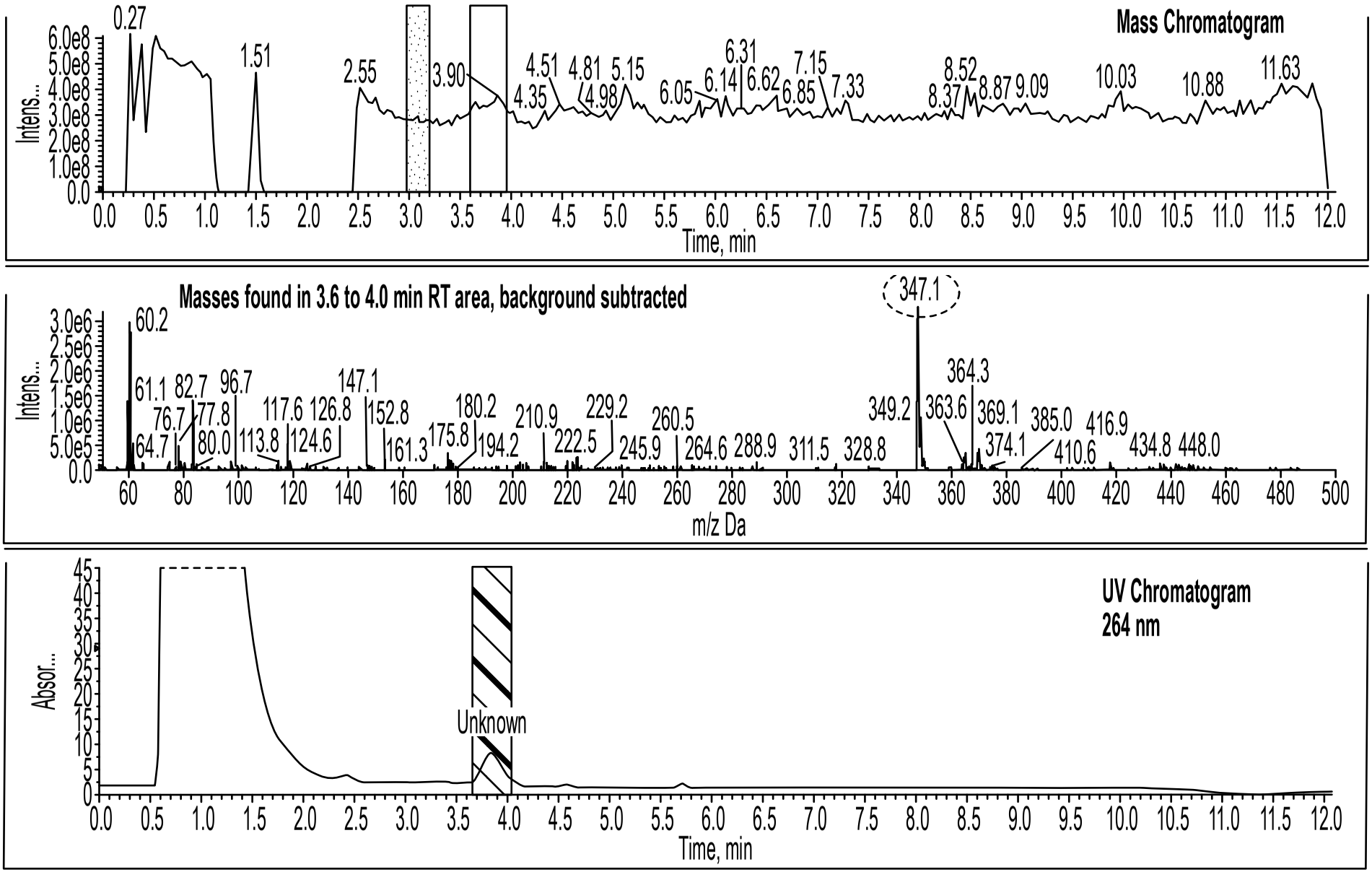

Mass Chromatogram
Intens...
Time, min
Masses found in 3.6 to 4.0 min RT area, background subtracted
m/z Da
UV Chromatogram
264 nm
Absor...
Unknown
Time, min

FIG. 39

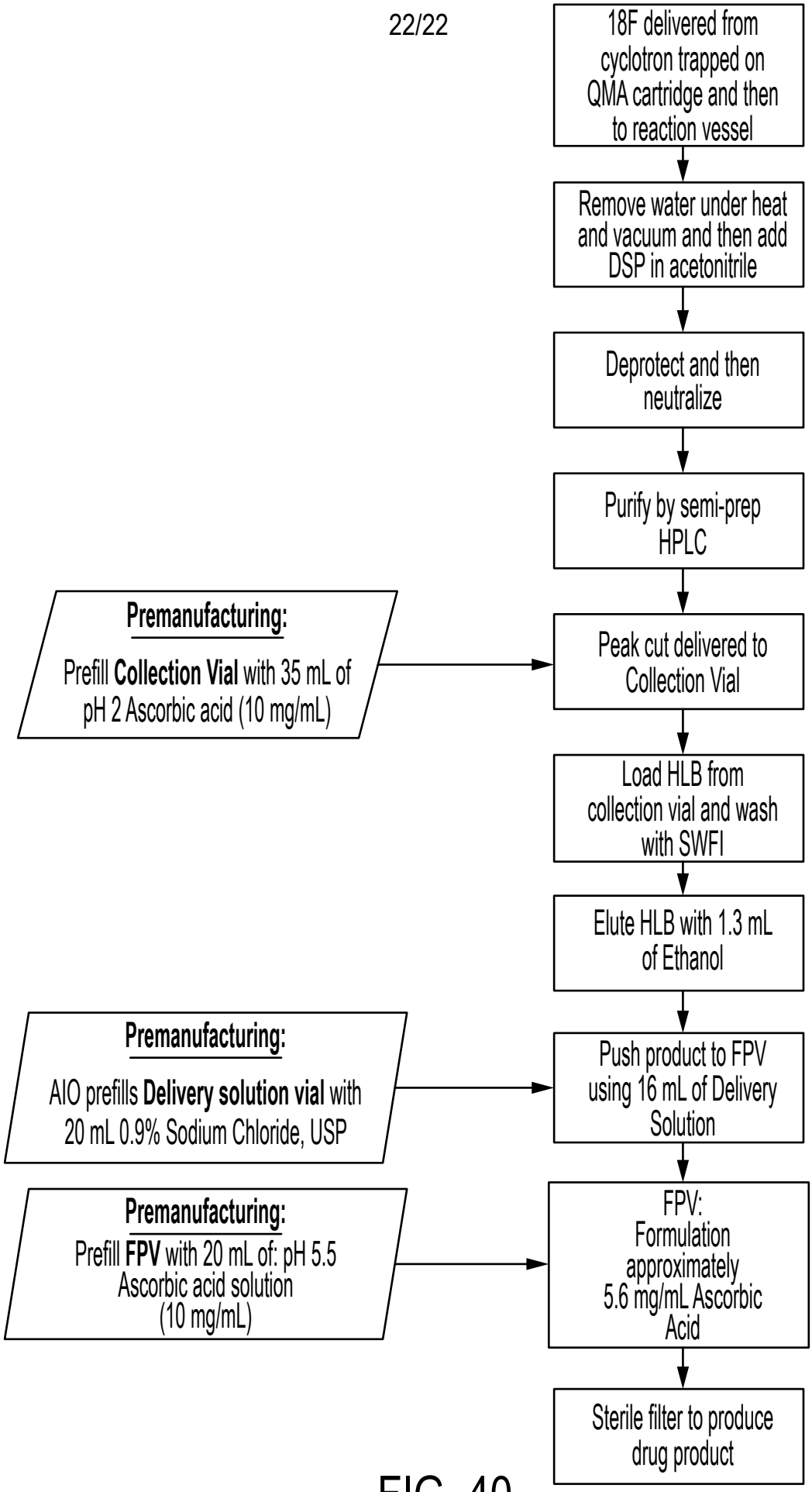

18F delivered from cyclotron trapped on QMA cartridge and then to reaction vessel
Remove water under heat and vacuum and then add DSP in acetonitrile
Deprotect and then neutralize
Purify by semi-prep HPLC
Premanufacturing:
Prefill Collection Vial with 35 mL of pH 2 Ascorbic acid (10 mg/mL)
Peak cut delivered to Collection Vial
Load HLB from collection vial and wash with SWFI
Elute HLB with 1.3 mL of Ethanol
Premanufacturing:
AIO prefills Delivery solution vial with 20 mL 0.9% Sodium Chloride, USP
Push product to FPV using 16 mL of Delivery Solution
Premanufacturing:
Prefill FPV with 20 mL of: pH 5.5 Ascorbic acid solution (10 mg/mL)
FPV: Formulation approximately 5.6 mg/mL Ascorbic Acid
Sterile filter to produce drug product

FIG. 40