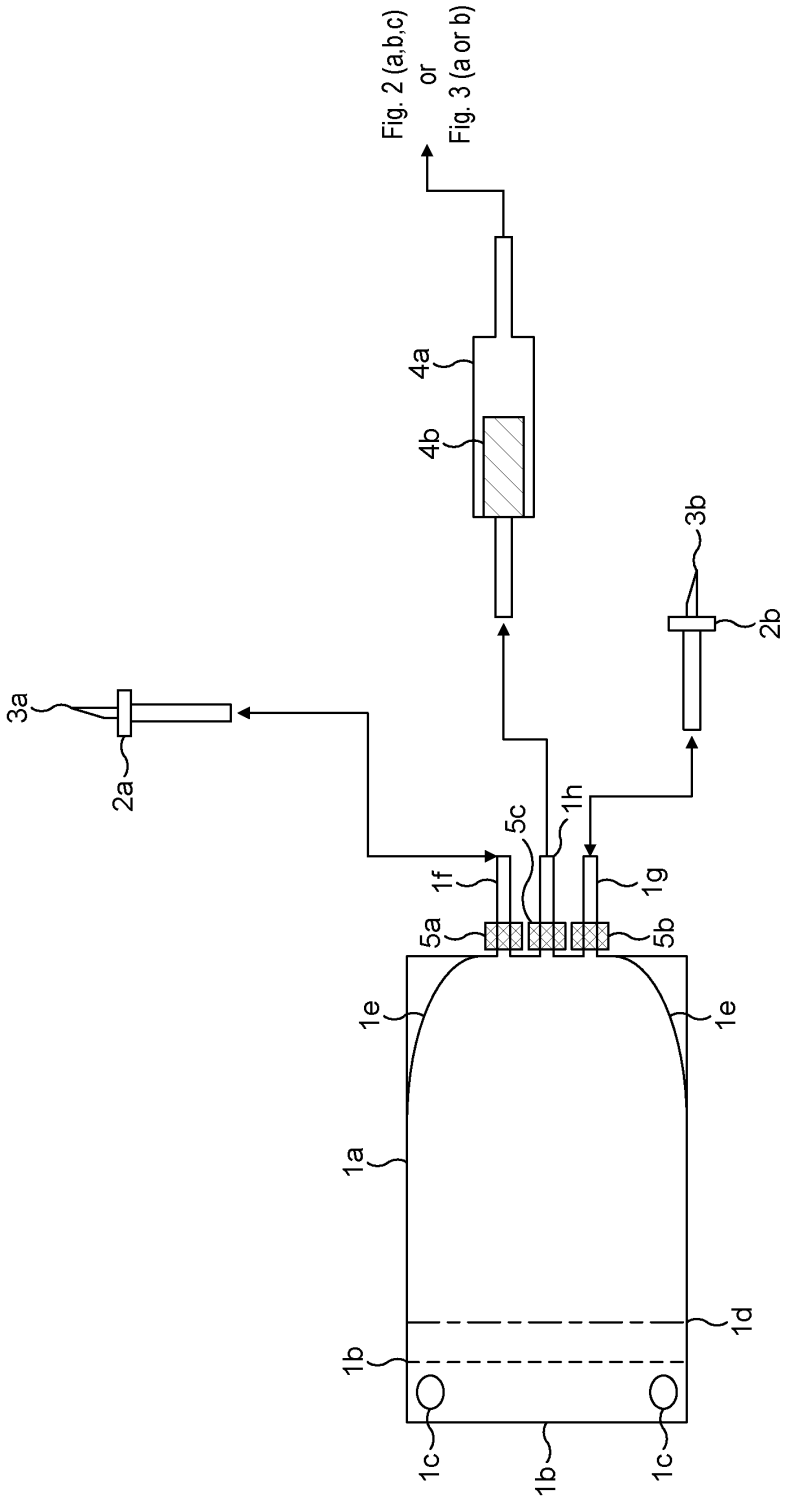


Fig. 2 (a,b,c)
or
Fig. 3 (a or b)
4a
4b
3b
2b
3a
2a
5c
1h
1f
1g
5a
5b
1e
1e
1a
1d
1b
1c
1b
1c

FIG. 1

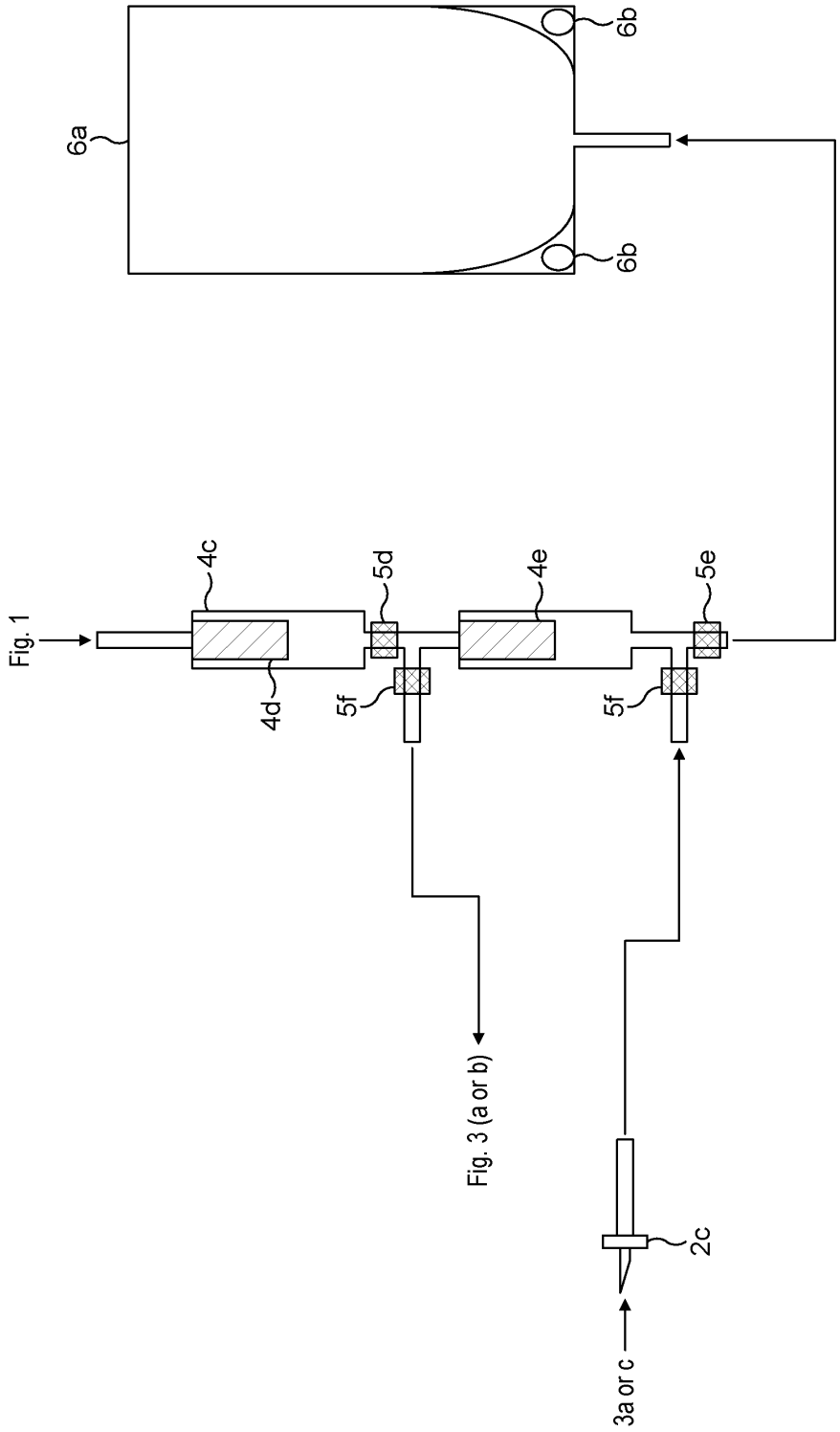


FIG. 2A

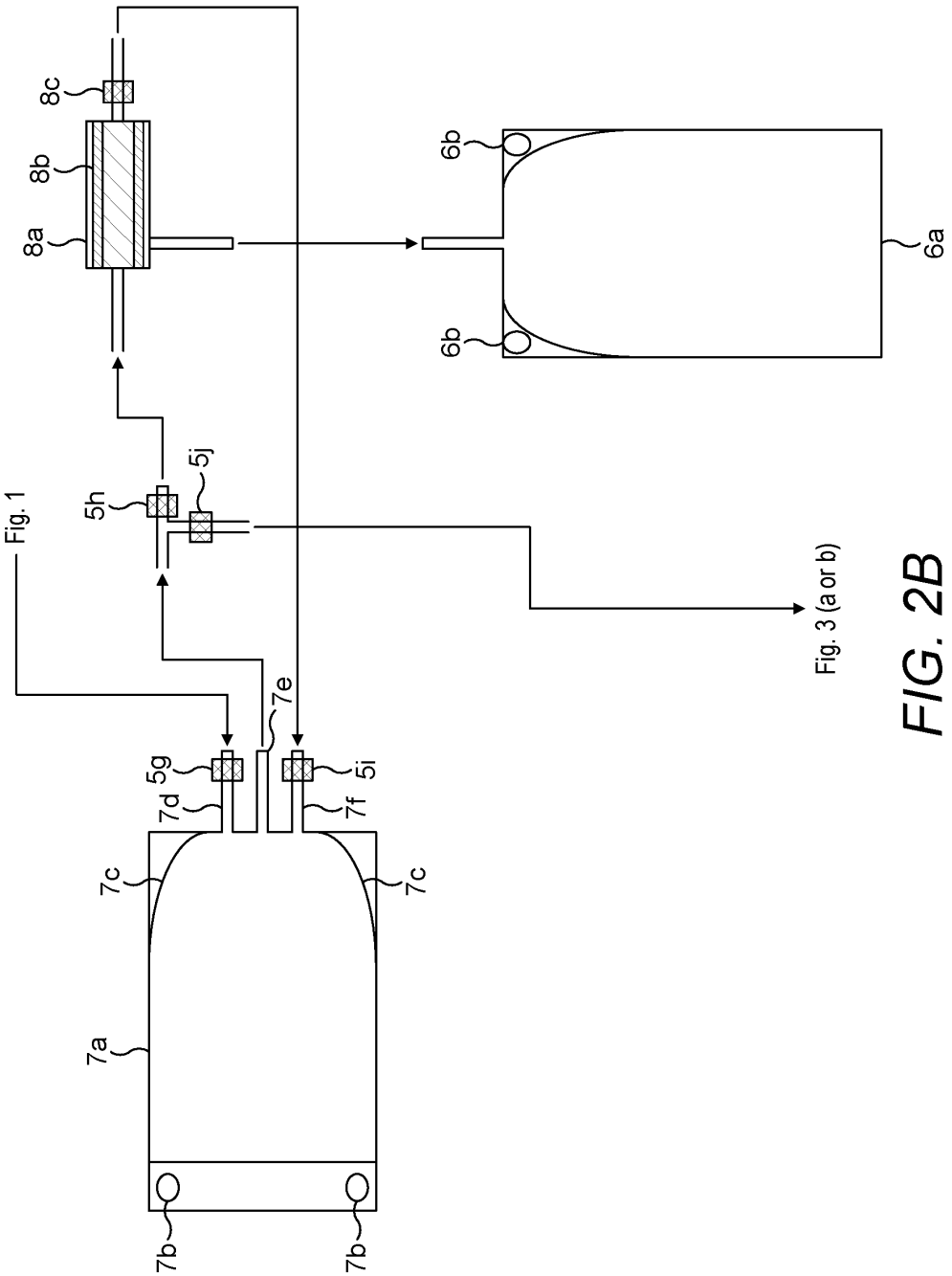


FIG. 2B

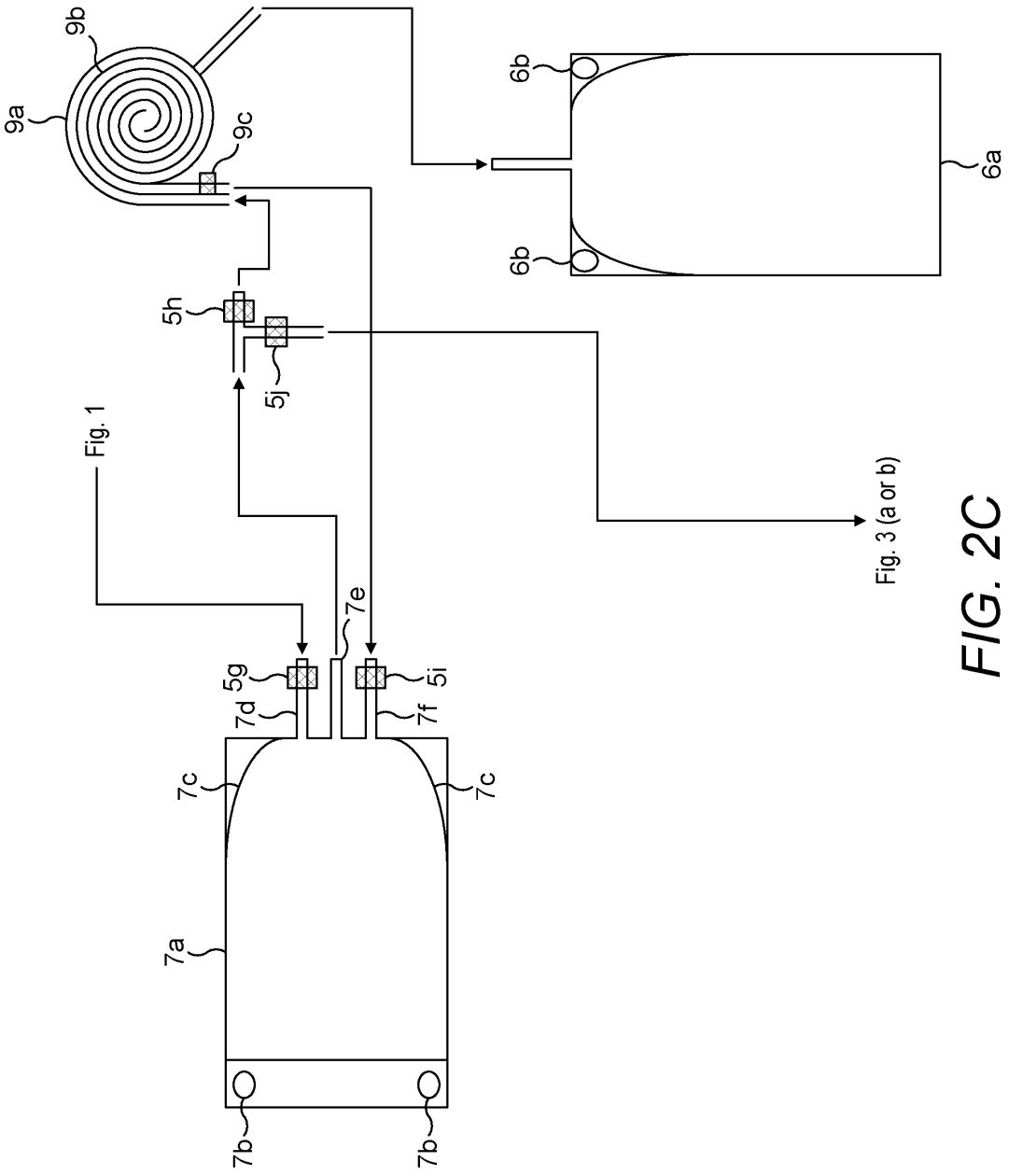


FIG. 2C

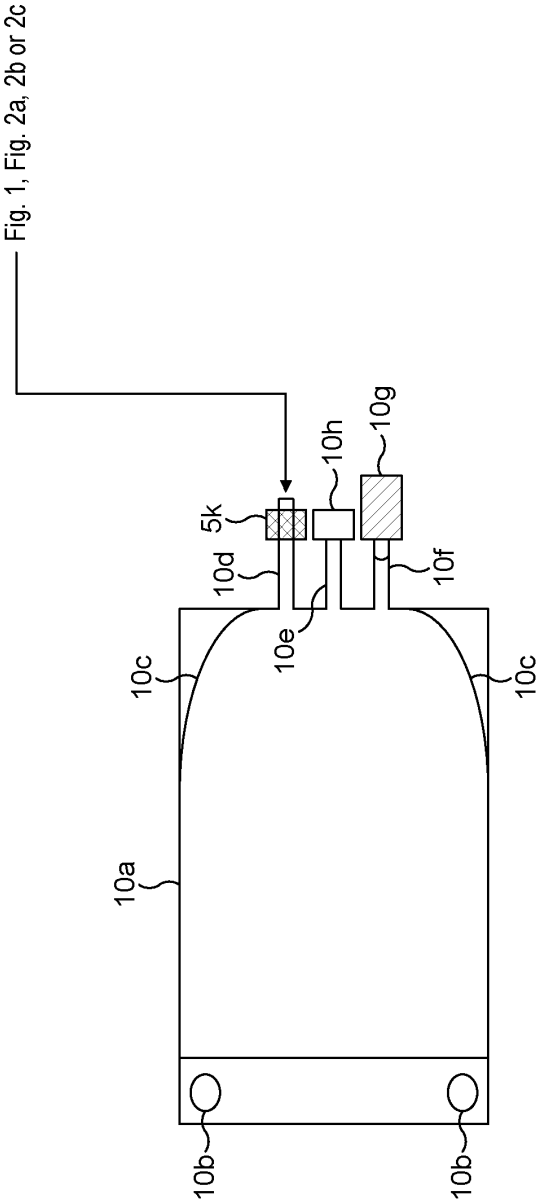


FIG. 3A

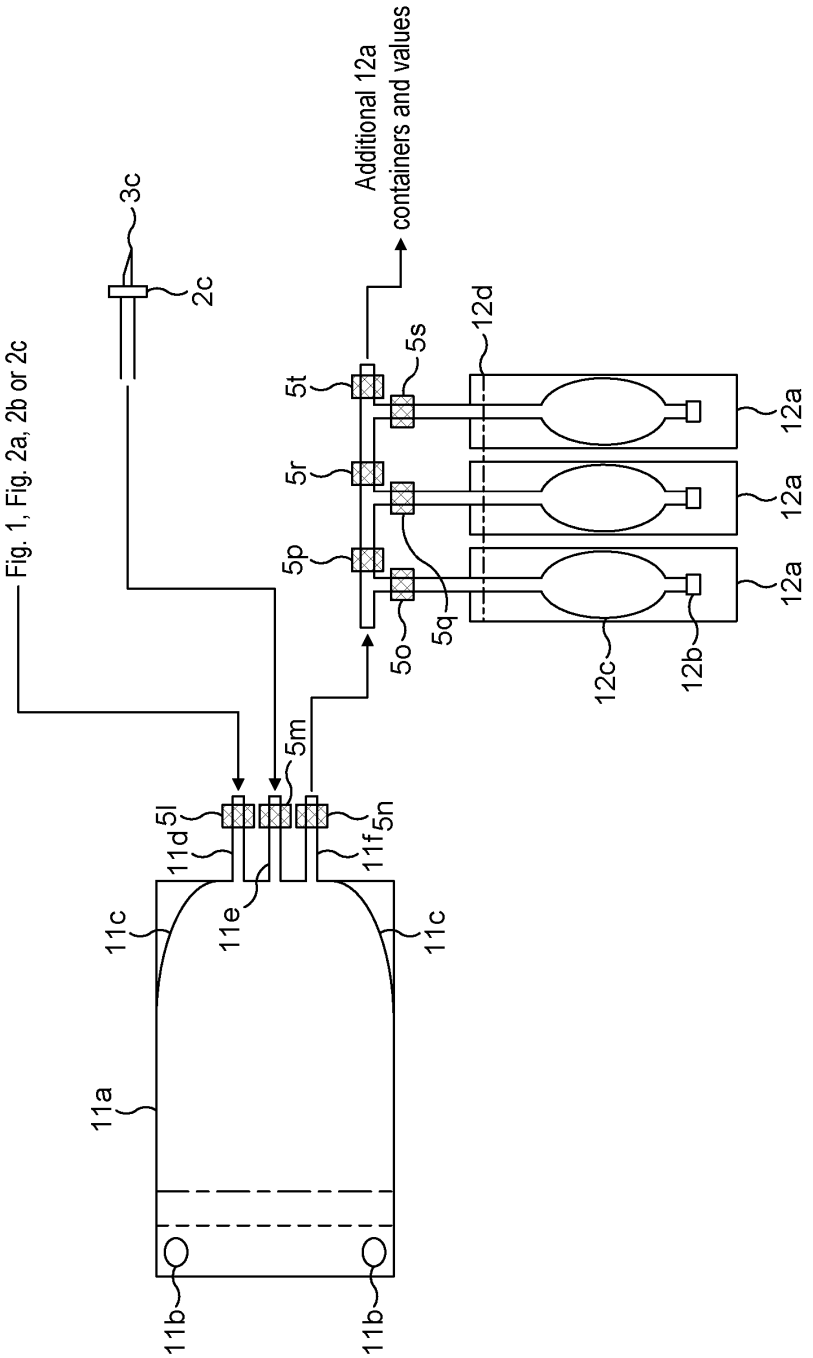


Fig. 1, Fig. 2a, 2b or 2c
3c
2c
Additional 12a containers and values
12d
5s
5t
5r
5p
5o
5q
12a
12a
12a
12c
12b
5m
5l
5n
11d
11f
11e
11c
11c
11a
11b
11b

FIG. 3B

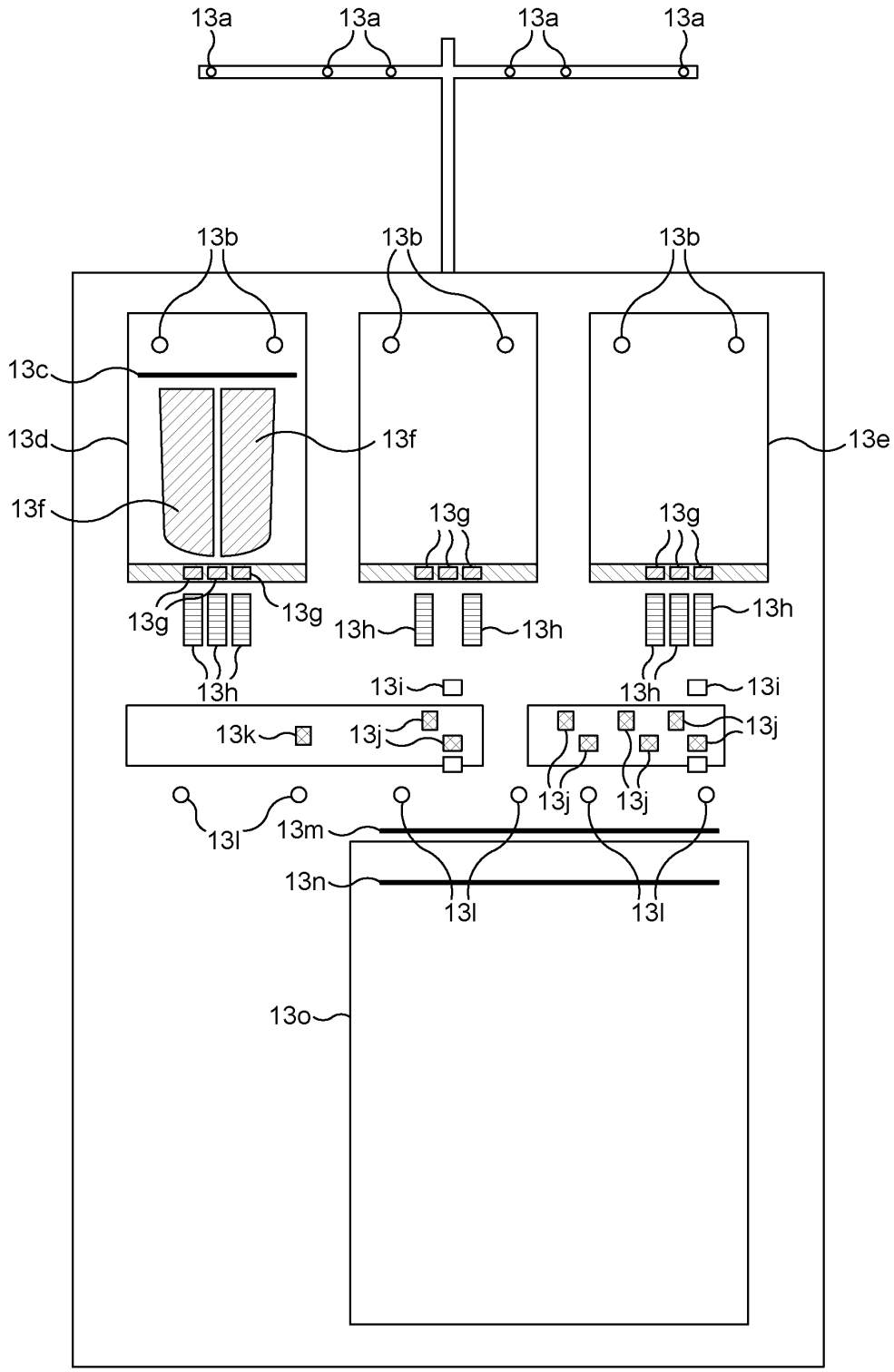

13a
13a
13a
13a
13b
13b
13b
13c
13d
13f
13e
13f
13g
13g
13g
13g
13h
13h
13h
13h
13h
13i
13i
13k
13j
13j
13j
13j
13l
13m
13n
13l
13l
13o

FIG. 4

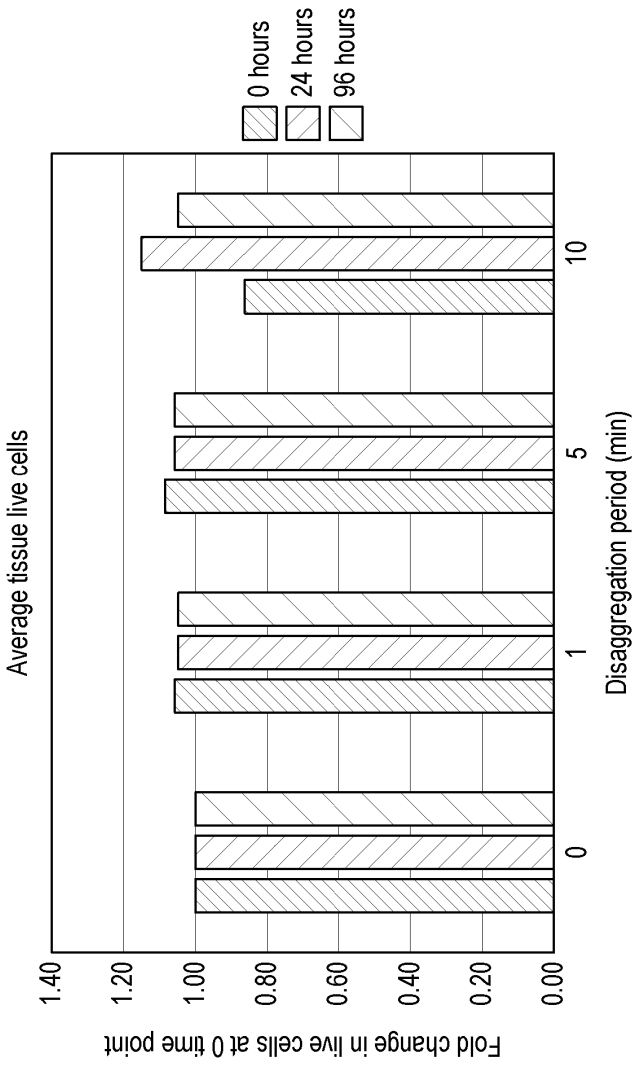

0 hours
24 hours
96 hours
Average tissue live cells
Fold change in live cells at 0 time point
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
1
5
10
Disaggregation period (min)

FIG. 5

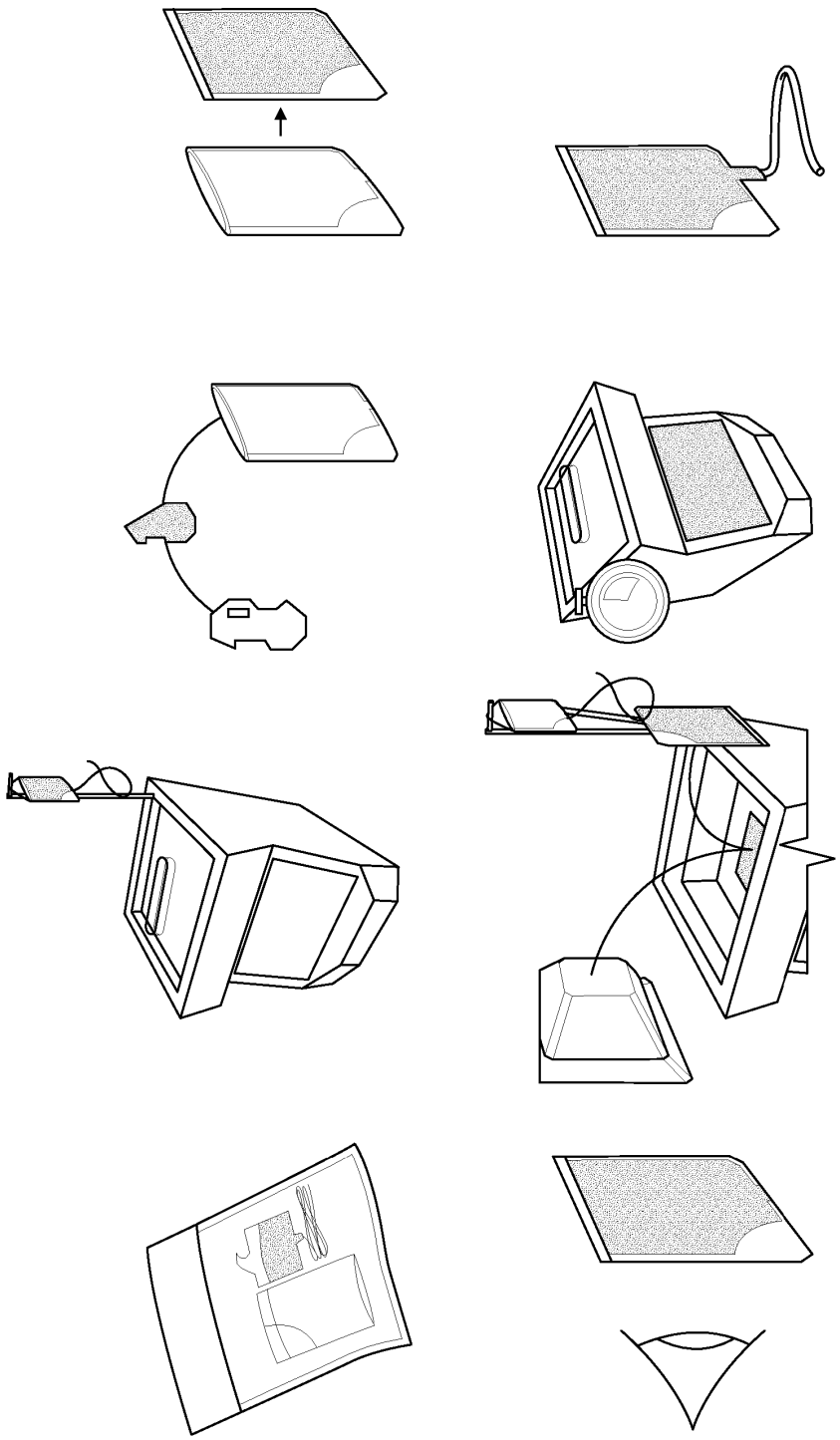


FIG. 6

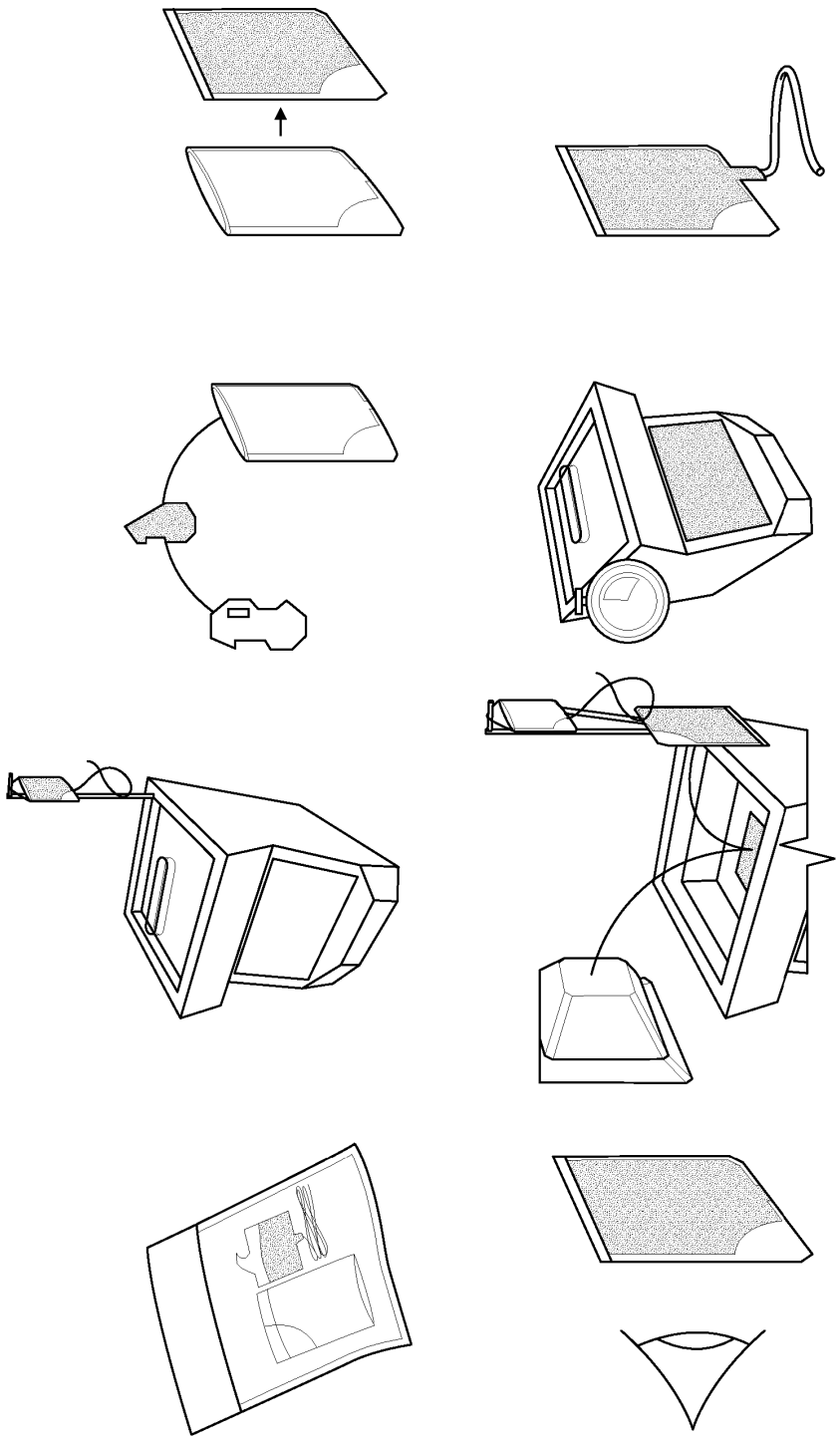


FIG. 7

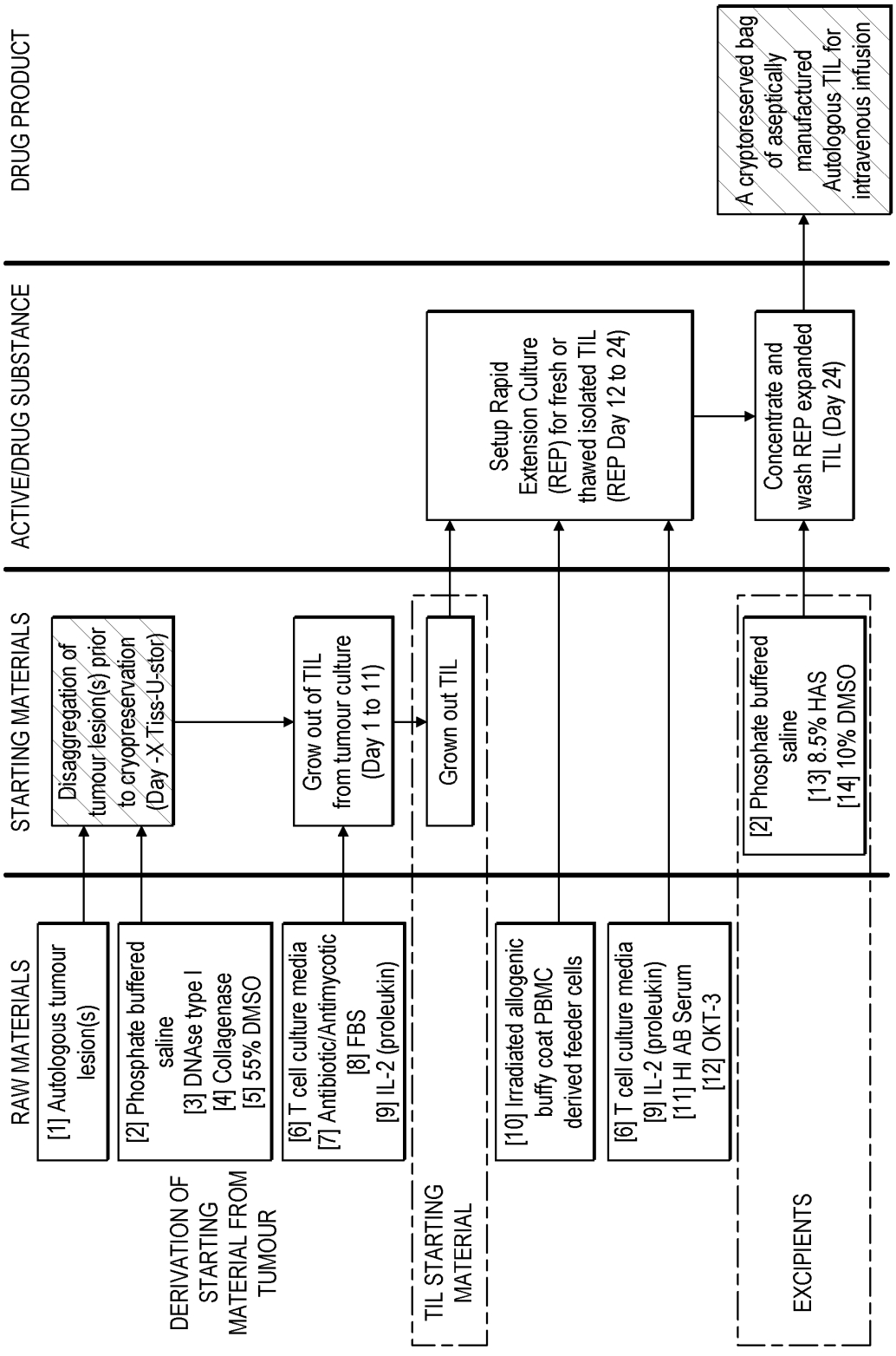

DRUG PRODUCT
ACTIVE/DRUG SUBSTANCE
STARTING MATERIALS
RAW MATERIALS
[1] Autologous tumour lesion(s)
[2] Phosphate buffered saline
[3] DNAse type I
[4] Collagenase
[5] 55% DMSO
[6] T cell culture media
[7] Antibiotic/Antimycotic
[8] FBS
[9] IL-2 (proleukin)
[10] Irradiated allogenic buffy coat PBMC derived feeder cells
[6] T cell culture media
[9] IL-2 (proleukin)
[11] HI AB Serum
[12] OKT-3
[2] Phosphate buffered saline
[13] 8.5% HAS
[14] 10% DMSO
Disaggregation of tumour lesion(s) prior to cryopreservation (Day -X Tiss-U-stor)
Grow out of TIL from tumour culture (Day 1 to 11)
Grown out TIL
Setup Rapid Extension Culture (REP) for fresh or thawed isolated TIL (REP Day 12 to 24)
Concentrate and wash REP expanded TIL (Day 24)
A cryptoreserved bag of aseptically manufactured Autologous TIL for intravenous infusion
DERIVATION OF STARTING MATERIAL FROM TUMOUR
TIL STARTING MATERIAL
EXCIPIENTS

FIG. 8

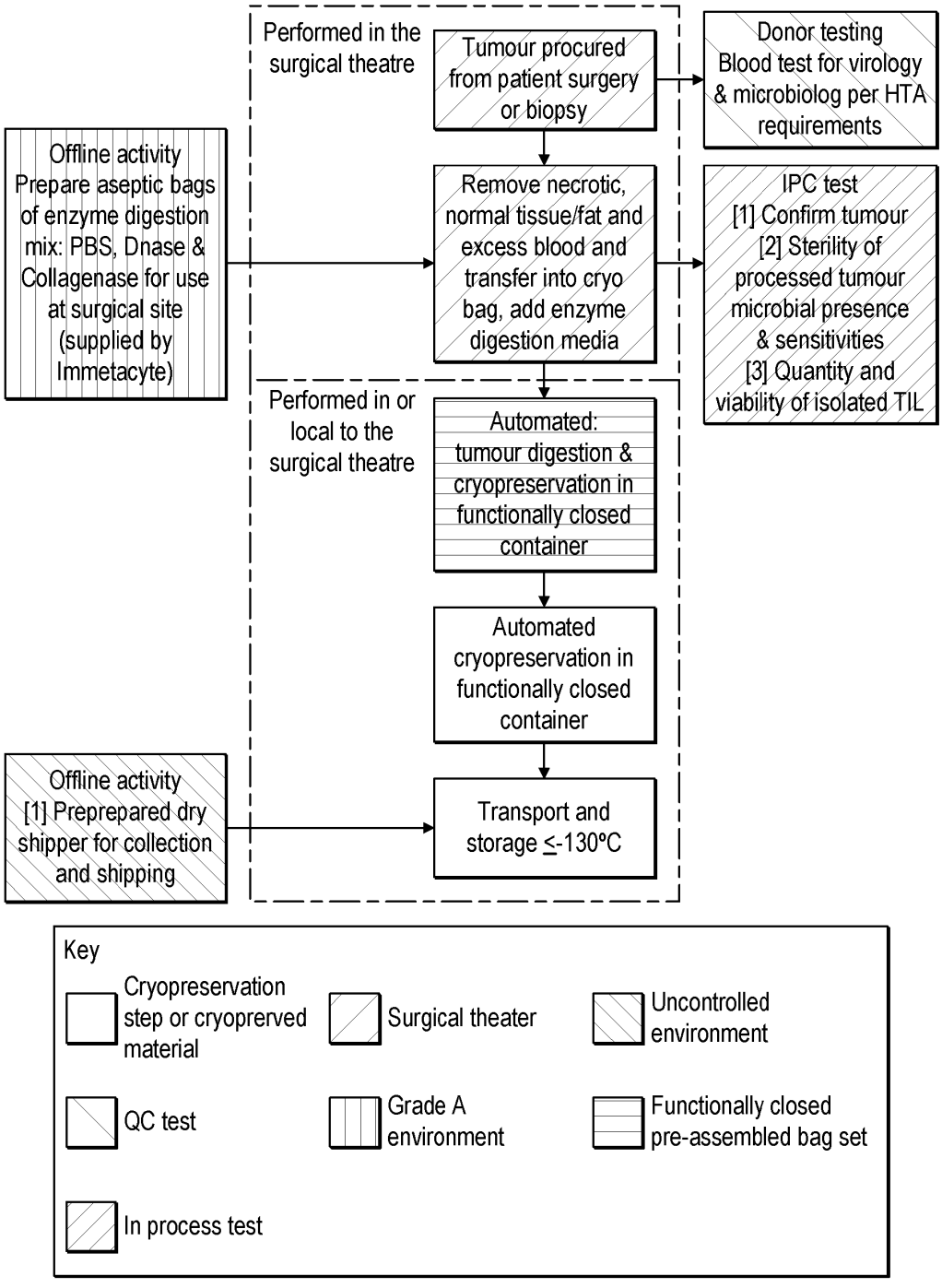

Performed in the surgical theatre
Tumour procured from patient surgery or biopsy
Donor testing Blood test for virology & microbiolog per HTA requirements
Offline activity Prepare aseptic bags of enzyme digestion mix: PBS, Dnase & Collagenase for use at surgical site (supplied by Immetacyte)
Remove necrotic, normal tissue/fat and excess blood and transfer into cryo bag, add enzyme digestion media
IPC test [1] Confirm tumour [2] Sterility of processed tumour microbial presence & sensitivities [3] Quantity and viability of isolated TIL
Performed in or local to the surgical theatre
Automated: tumour digestion & cryopreservation in functionally closed container
Automated cryopreservation in functionally closed container
Offline activity [1] Preprepared dry shipper for collection and shipping
Transport and storage ≤-130°C
Key
Cryopreservation step or cryoprerved material
Surgical theater
Uncontrolled environment
QC test
Grade A environment
Functionally closed pre-assembled bag set
In process test

FIG. 9

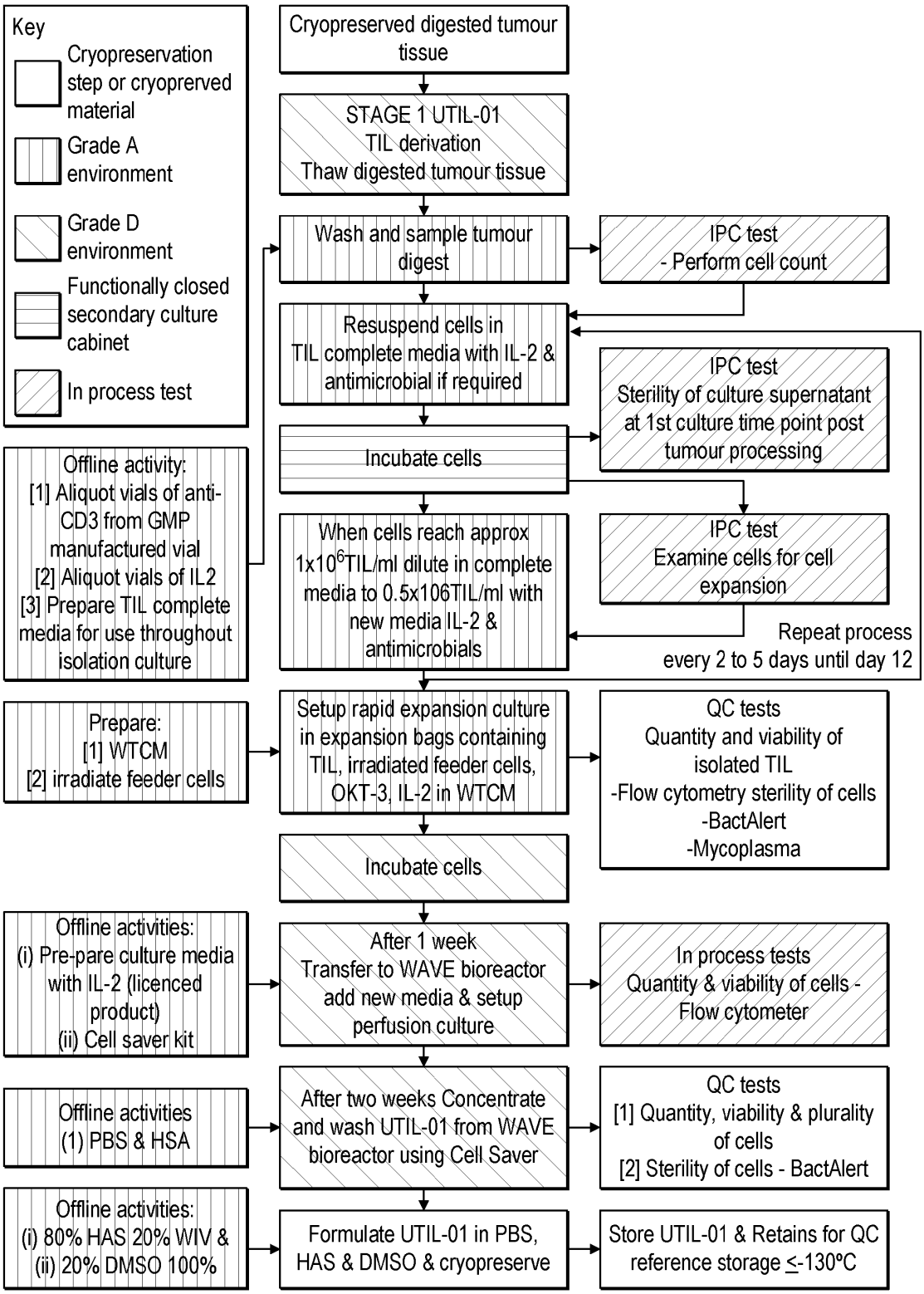

Key
Cryopreservation step or cryoprerved material
Grade A environment
Grade D environment
Functionally closed secondary culture cabinet
In process test
Cryopreserved digested tumour tissue
STAGE 1 UTIL-01 TIL derivation Thaw digested tumour tissue
Wash and sample tumour digest
IPC test - Perform cell count
Resuspend cells in TIL complete media with IL-2 & antimicrobial if required
IPC test Sterility of culture supernatant at 1st culture time point post tumour processing
Incubate cells
Offline activity: [1] Aliquot vials of anti-CD3 from GMP manufactured vial [2] Aliquot vials of IL2 [3] Prepare TIL complete media for use throughout isolation culture
When cells reach approx 1x10^6TIL/ml dilute in complete media to 0.5x106TIL/ml with new media IL-2 & antimicrobials
IPC test Examine cells for cell expansion
Repeat process every 2 to 5 days until day 12
Prepare: [1] WTCM [2] irradiate feeder cells
Setup rapid expansion culture in expansion bags containing TIL, irradiated feeder cells, OKT-3, IL-2 in WTCM
QC tests Quantity and viability of isolated TIL -Flow cytometry sterility of cells -BactAlert -Mycoplasma
Incubate cells
Offline activities: (i) Pre-pare culture media with IL-2 (licenced product) (ii) Cell saver kit
After 1 week Transfer to WAVE bioreactor add new media & setup perfusion culture
In process tests Quantity & viability of cells - Flow cytometer
Offline activities (1) PBS & HSA
After two weeks Concentrate and wash UTIL-01 from WAVE bioreactor using Cell Saver
QC tests [1] Quantity, viability & plurality of cells [2] Sterility of cells - BactAlert
Offline activities: (i) 80% HAS 20% WIV & (ii) 20% DMSO 100%
Formulate UTIL-01 in PBS, HAS & DMSO & cryopreserve
Store UTIL-01 & Retains for QC reference storage ≤-130°C

FIG. 10

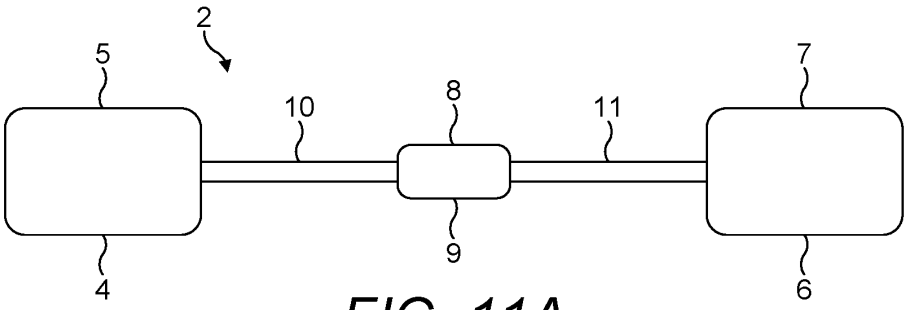


FIG. 11A

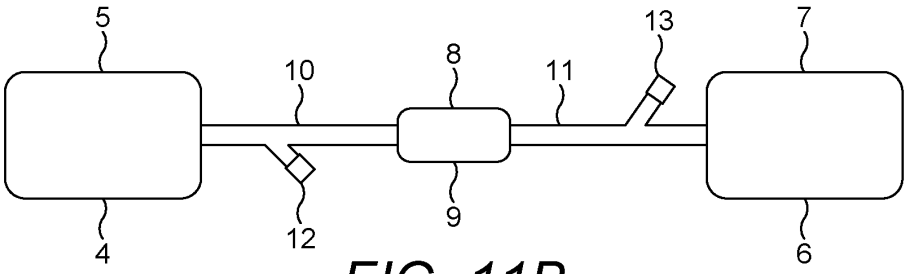


FIG. 11B

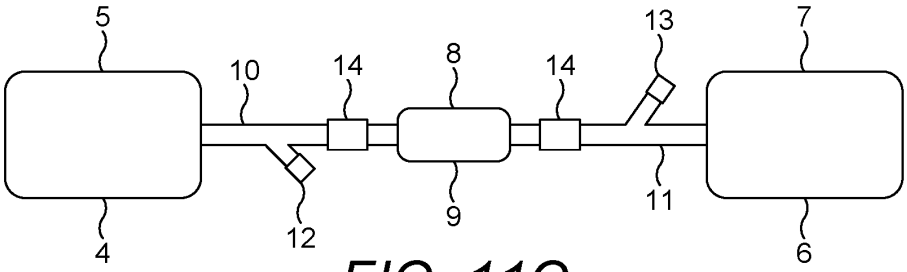


FIG. 11C

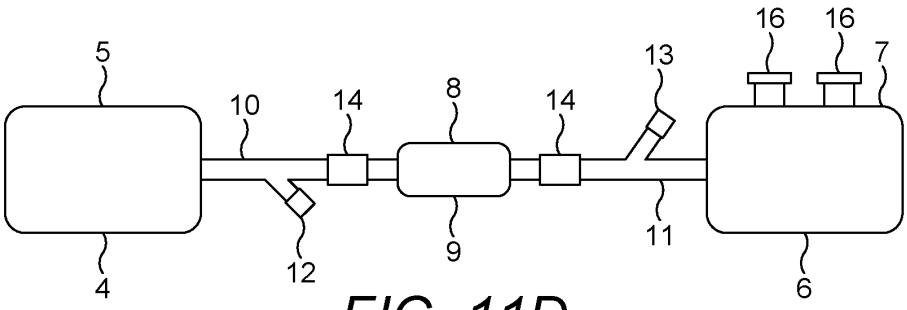


FIG. 11D

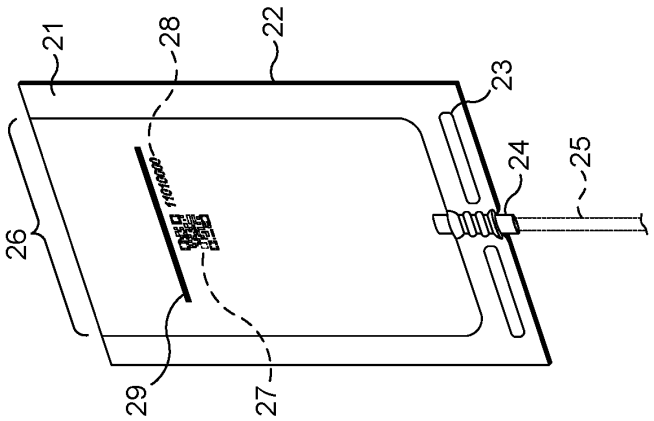


FIG. 12C

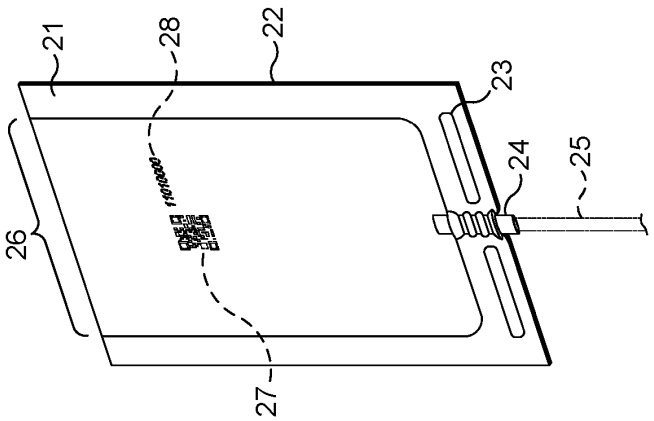


FIG. 12B

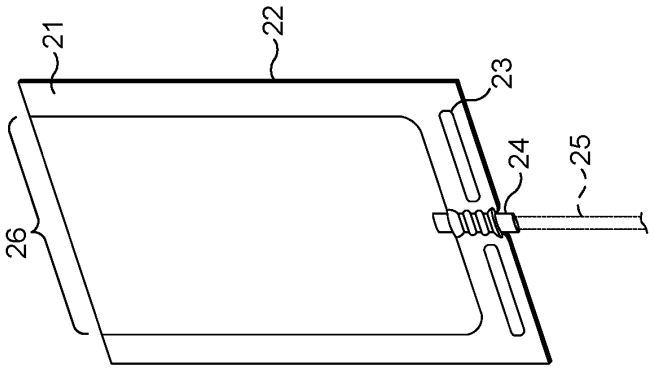


FIG. 12A

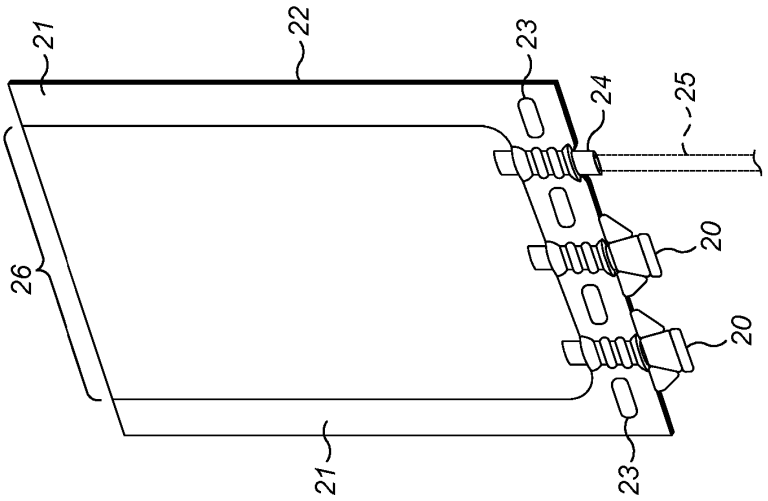


FIG. 12E

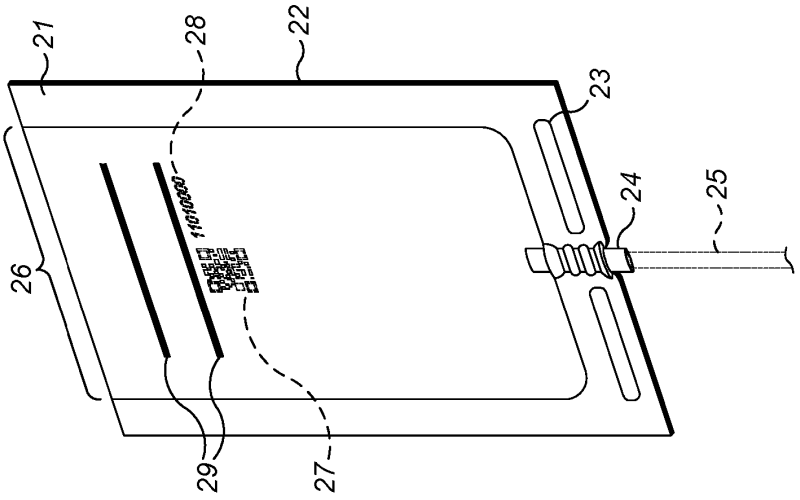


FIG. 12D

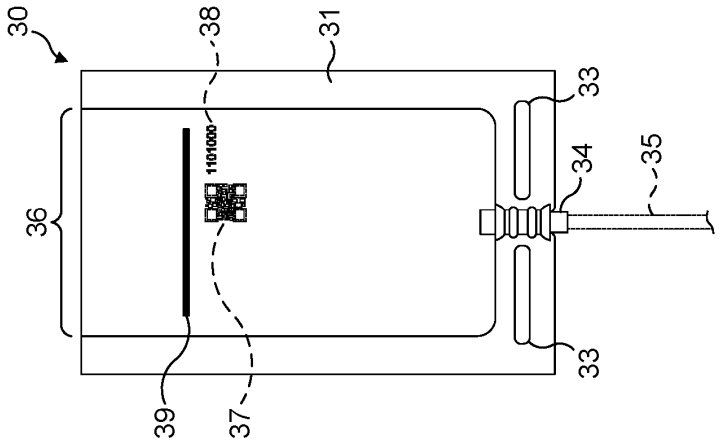


FIG. 13C

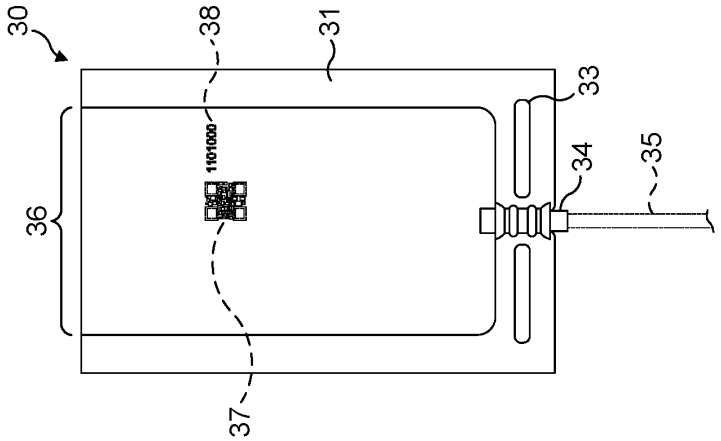


FIG. 13B

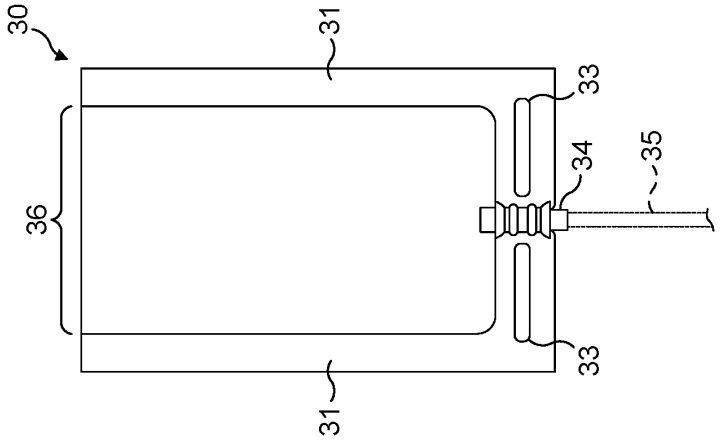


FIG. 13A

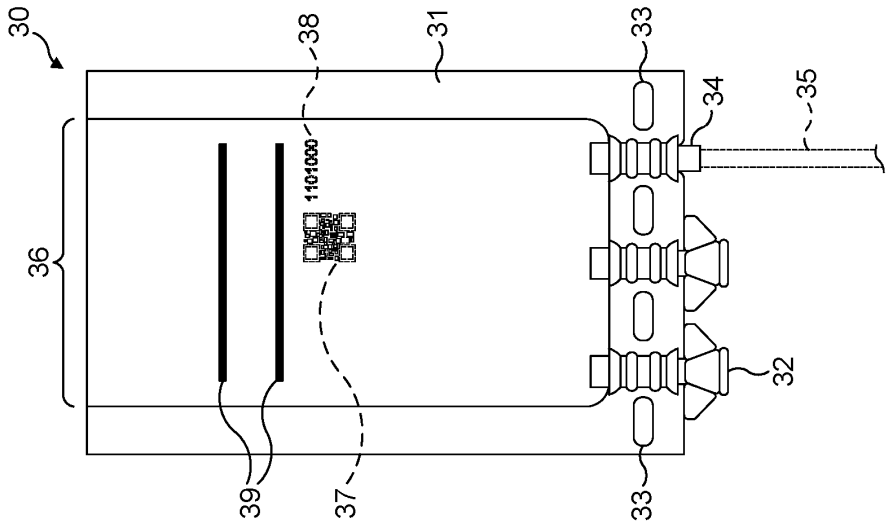


FIG. 13E

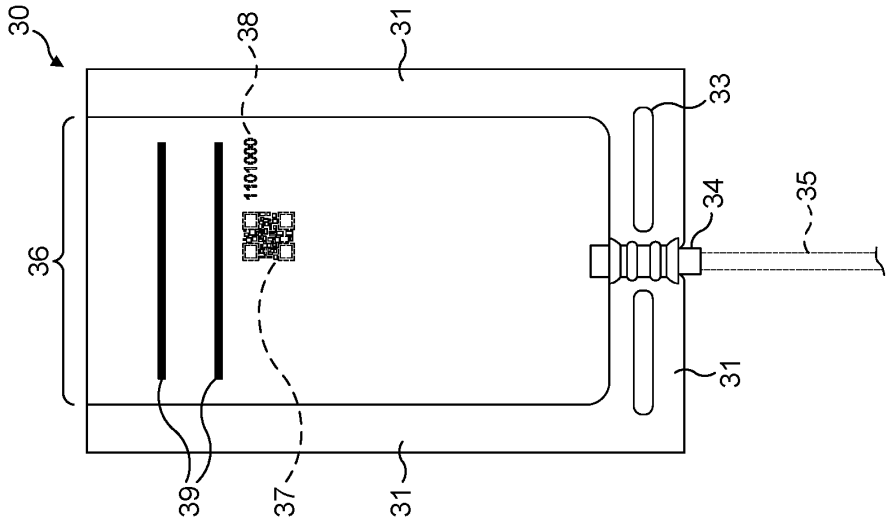


FIG. 13D

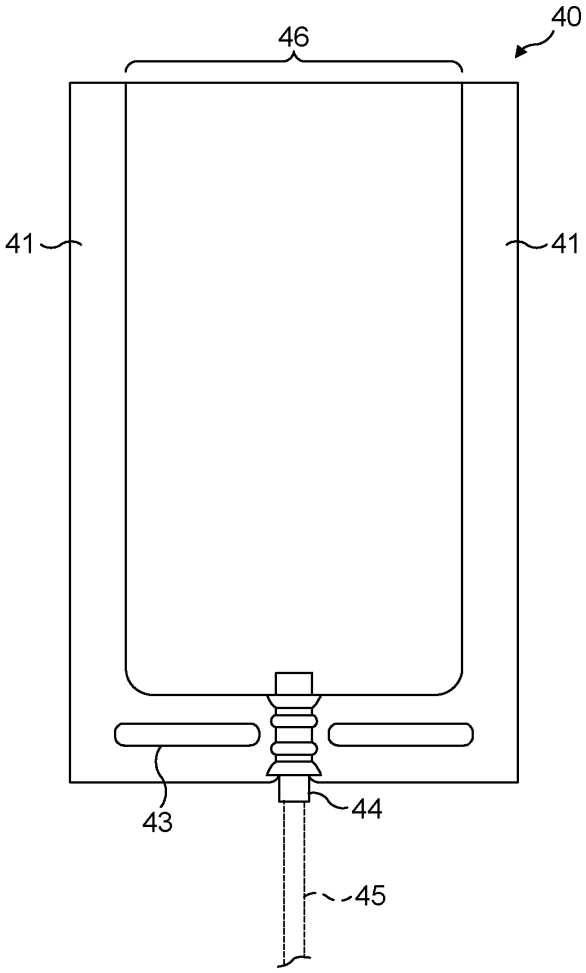


FIG. 14

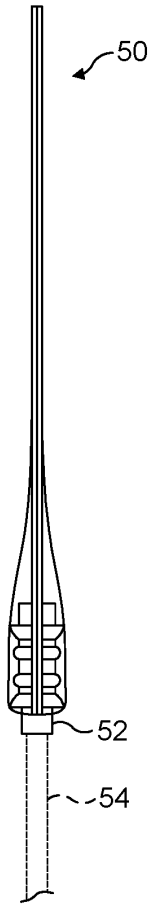


FIG. 15

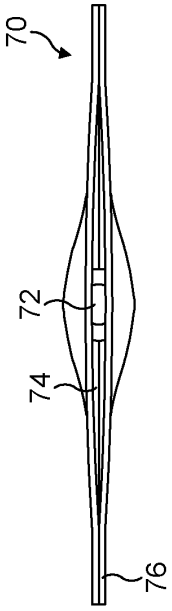


FIG. 17A

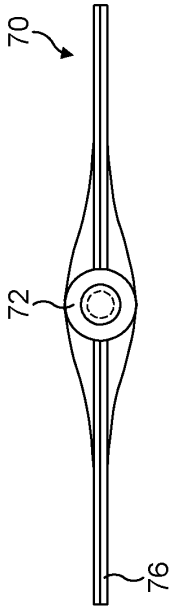


FIG. 17B

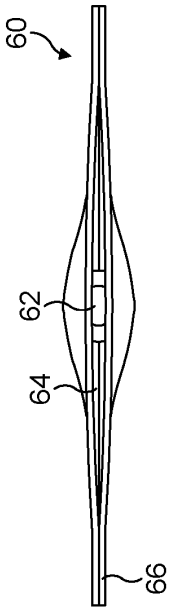


FIG. 16A

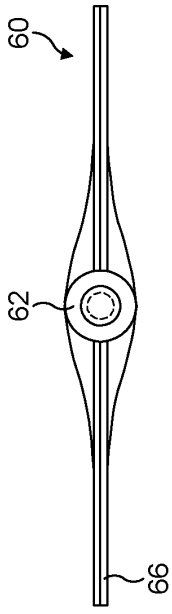


FIG. 16B

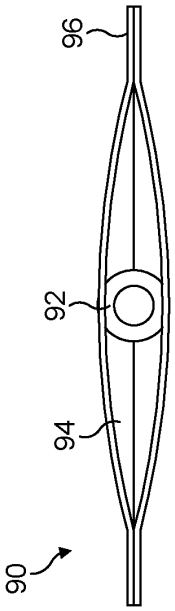


FIG. 19A

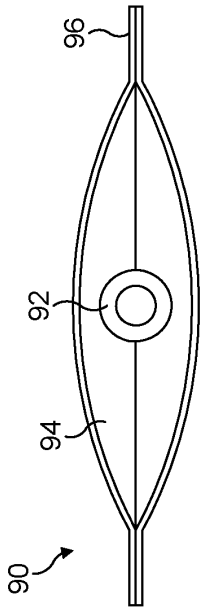


FIG. 19B

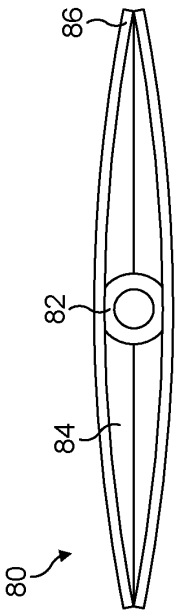


FIG. 18A

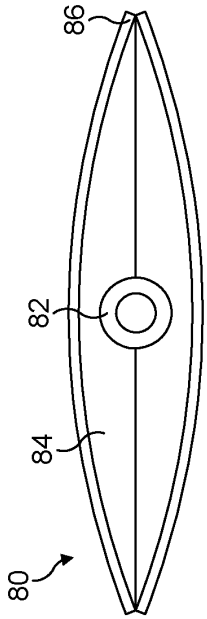


FIG. 18B

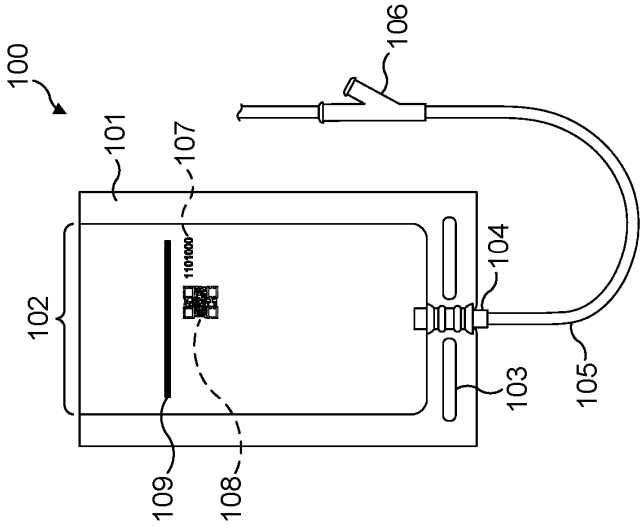


FIG. 20C

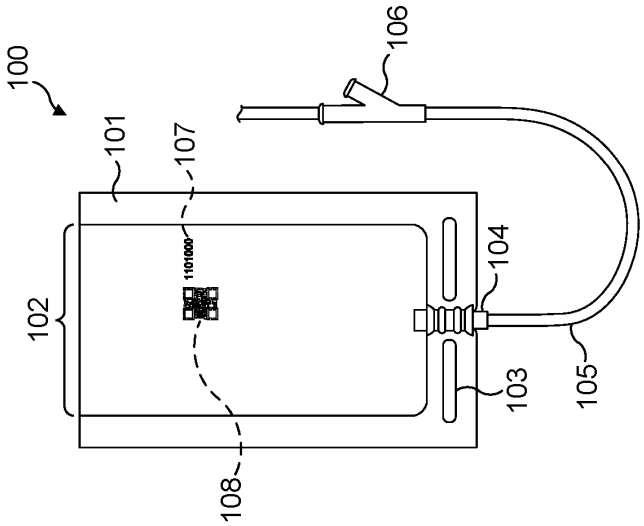


FIG. 20B

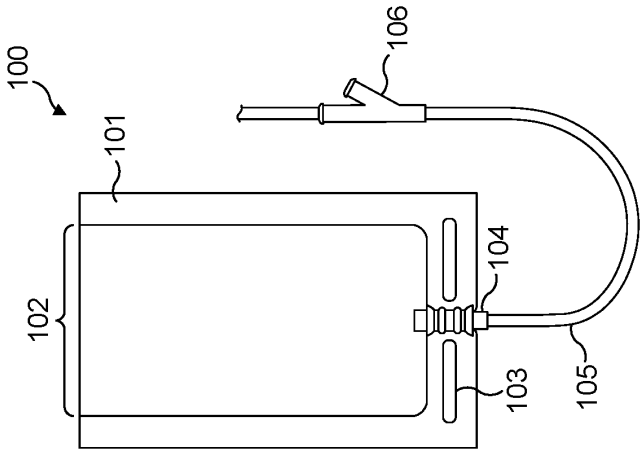


FIG. 20A

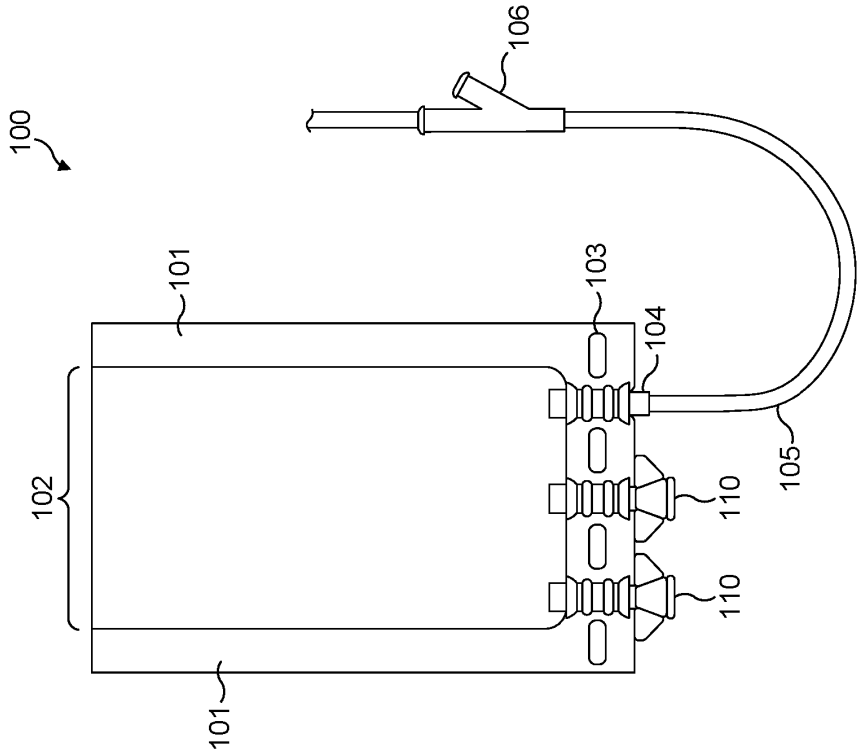


FIG. 20E

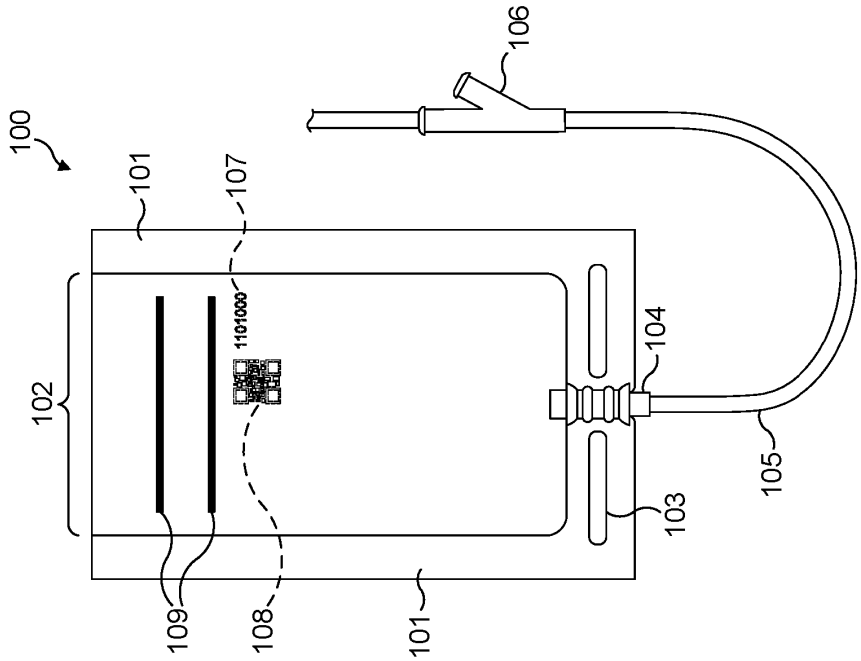


FIG. 20D

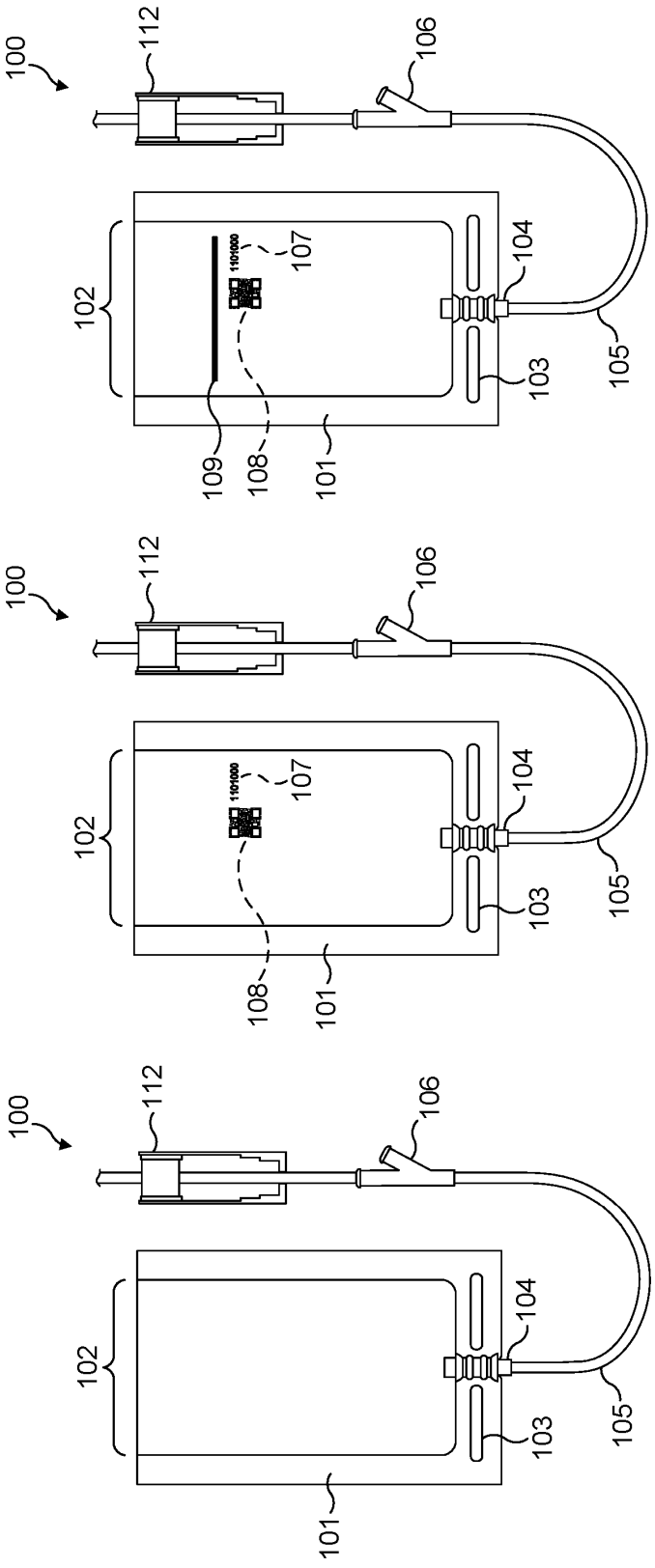


FIG. 21C

FIG. 21B

FIG. 21A

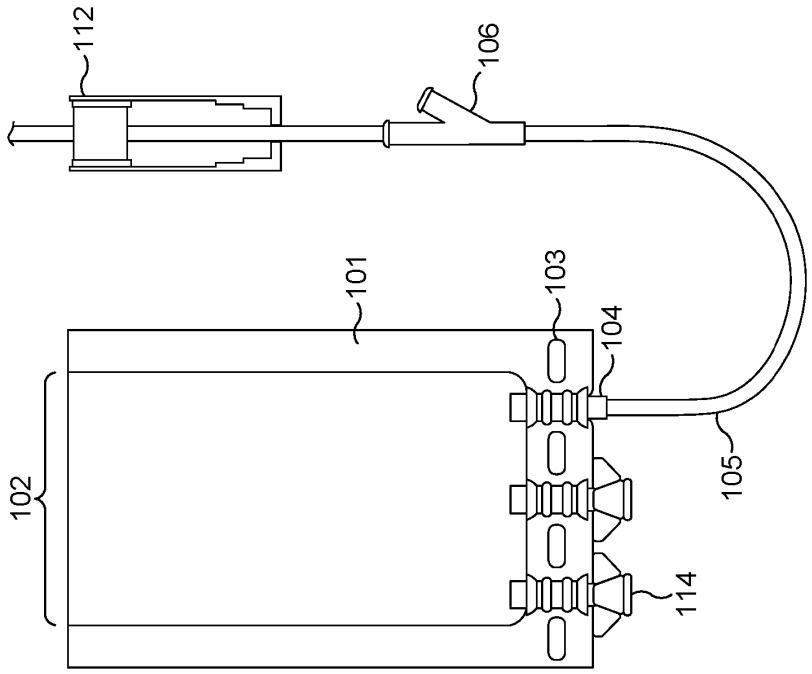


FIG. 21E

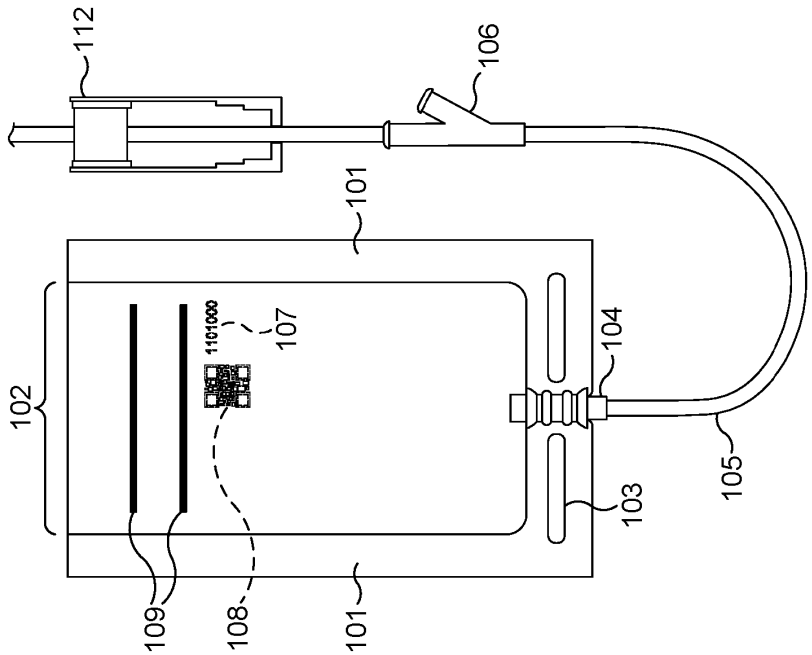


FIG. 21D

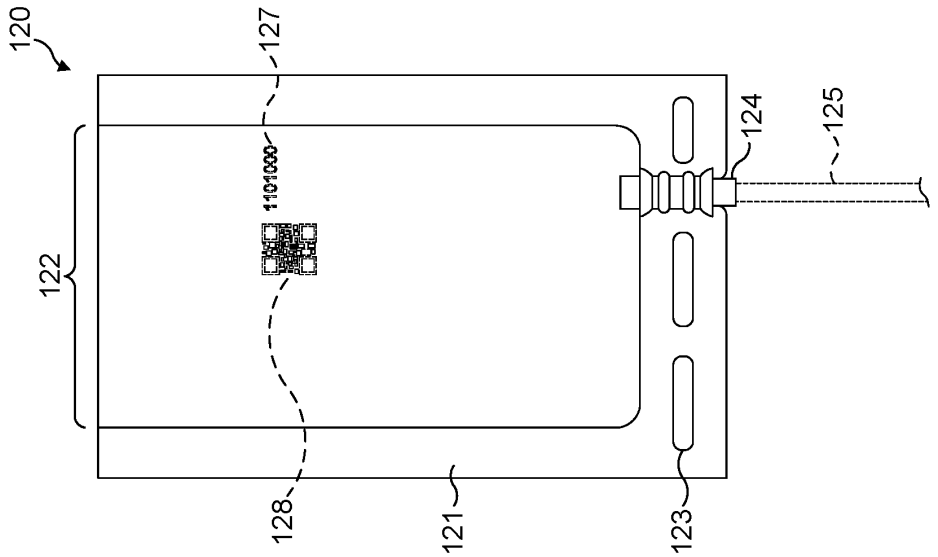


FIG. 22B

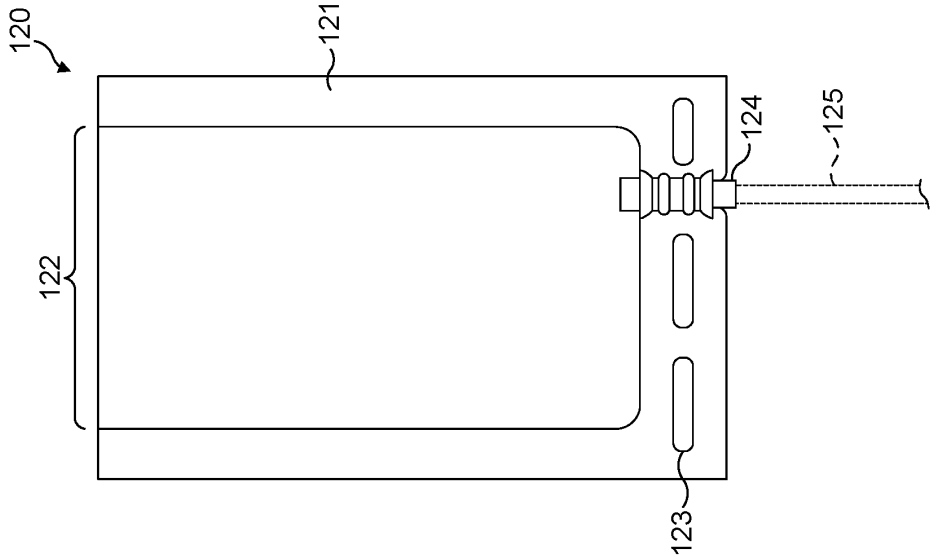


FIG. 22A

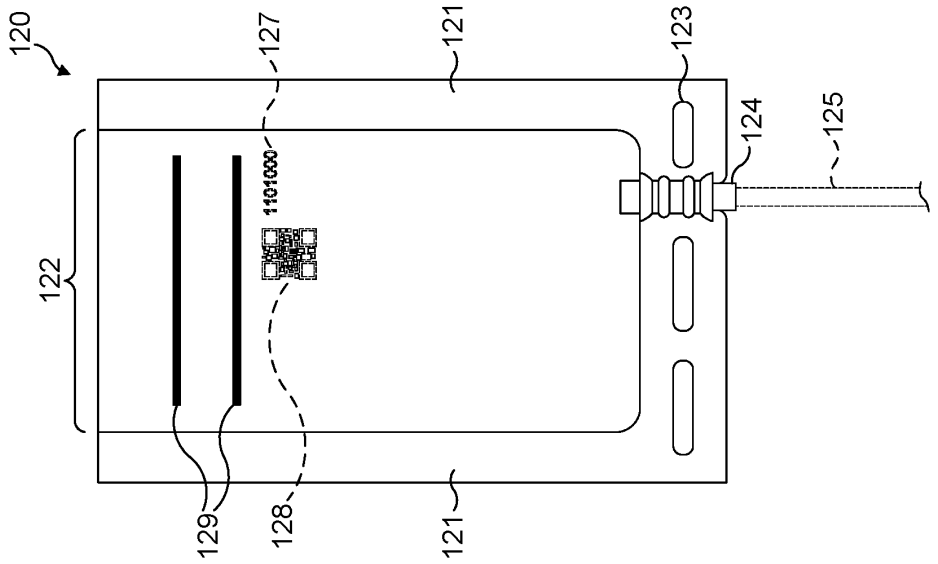


FIG. 22D

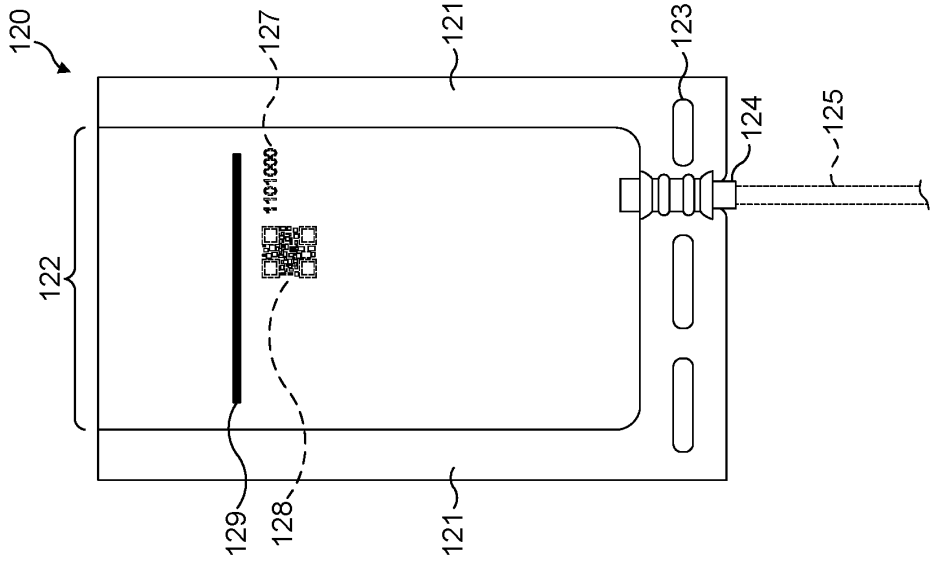


FIG. 22C

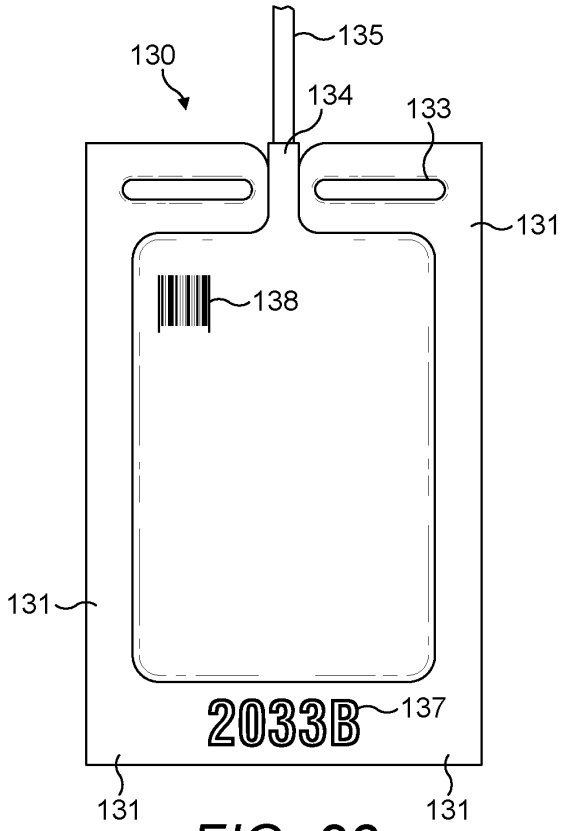

135
130
134
133
131
138
131
2033B
137
131
131

FIG. 23

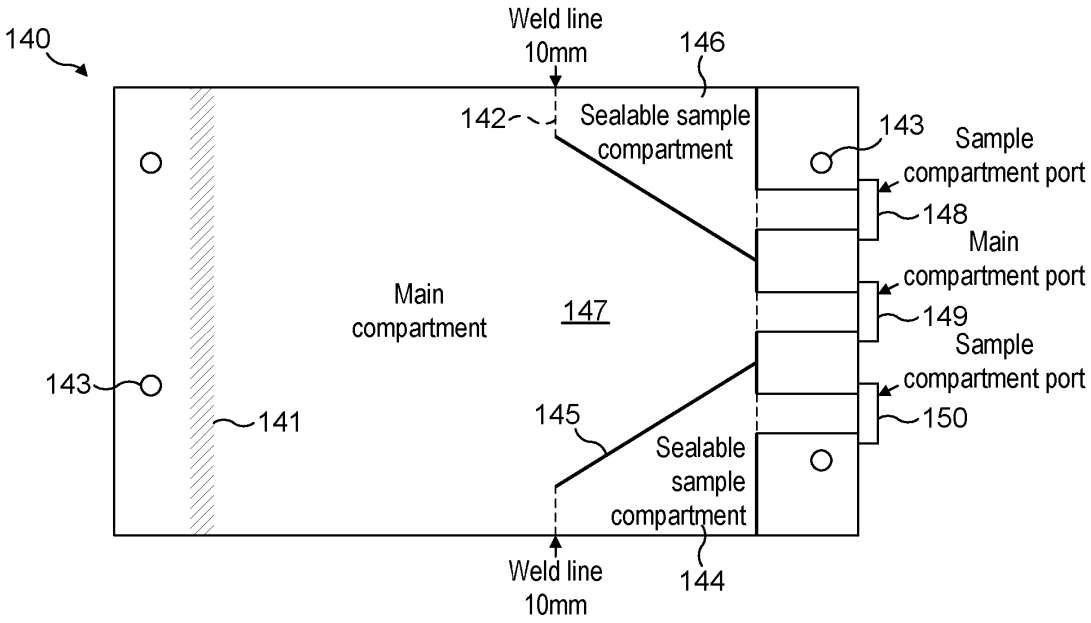

140
Weld line
10mm
146
142
Sealable sample
compartment
143
Sample
compartment port
148
Main
compartment port
149
Main
compartment
147
Sample
compartment port
150
143
141
145
Sealable
sample
compartment
Weld line
10mm
144

FIG. 24

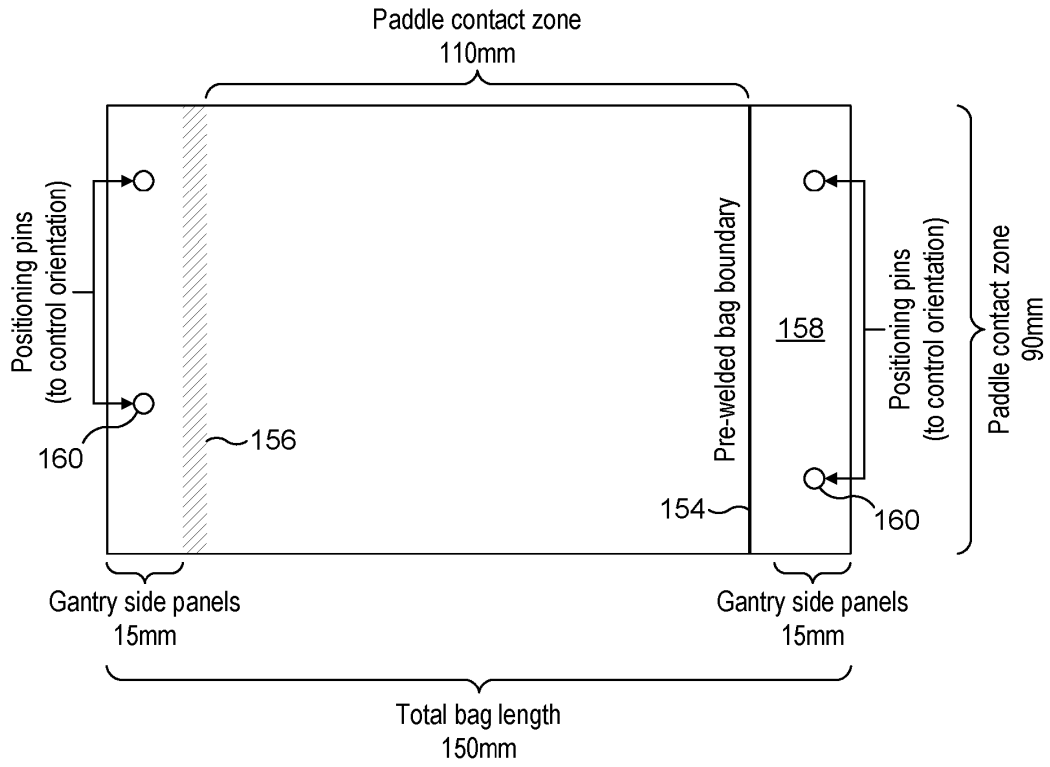

Paddle contact zone
110mm
Positioning pins
(to control orientation)
160
156
Pre-welded bag boundary
158
154
Positioning pins
(to control orientation)
160
Paddle contact zone
90mm
Gantry side panels
15mm
Gantry side panels
15mm
Total bag length
150mm

FIG. 25

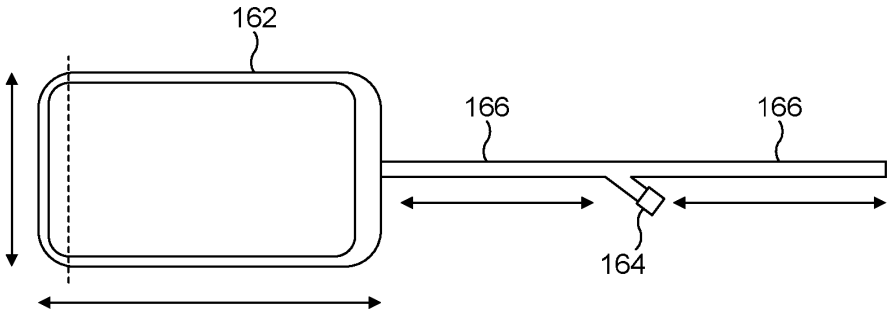

162
166
166
164

FIG. 26

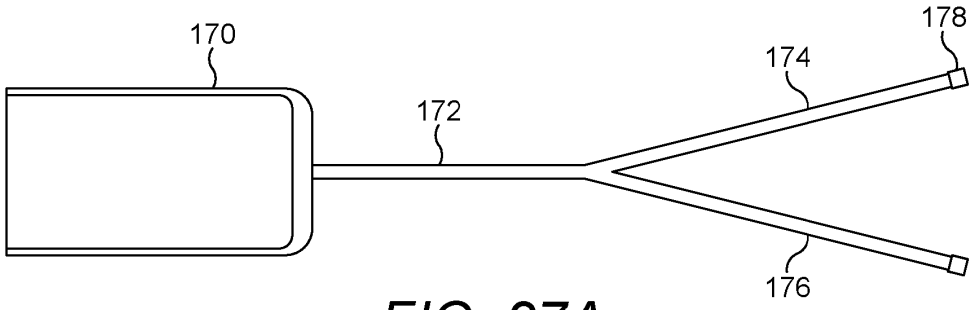


FIG. 27A

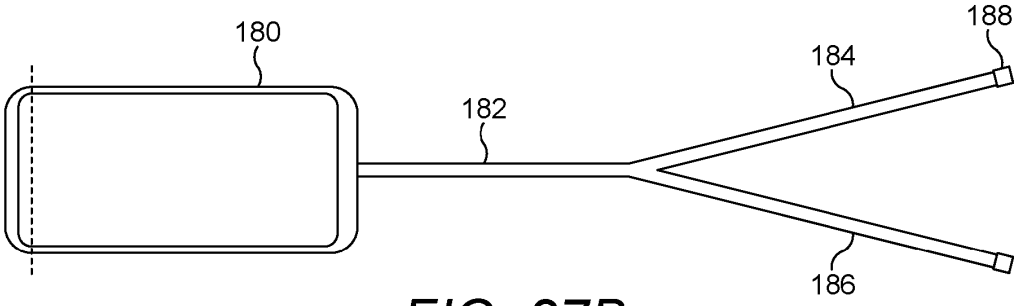


FIG. 27B

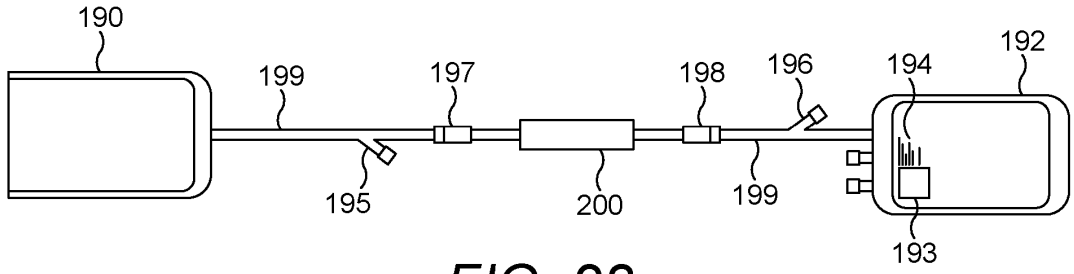


FIG. 28

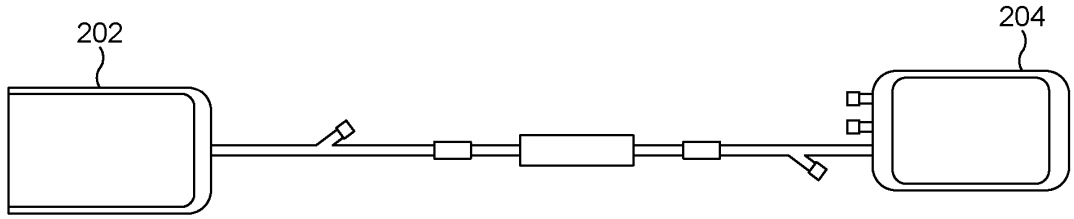


FIG. 29

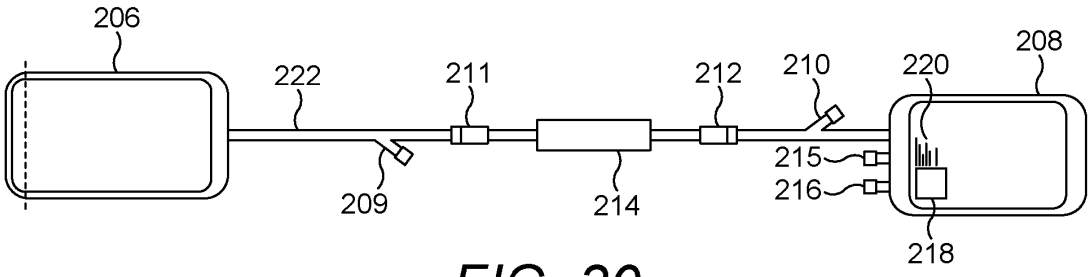


FIG. 30

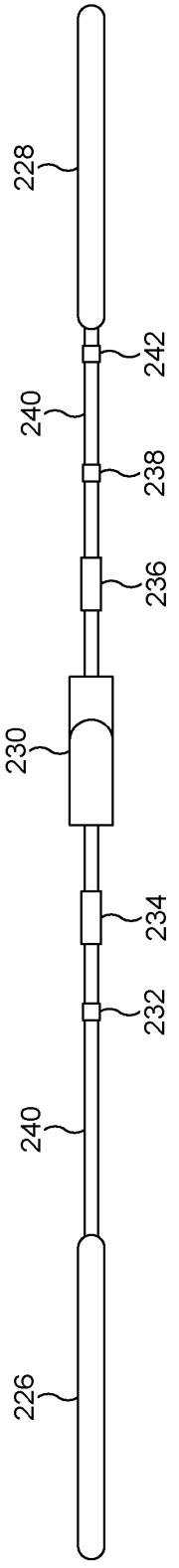


FIG. 31

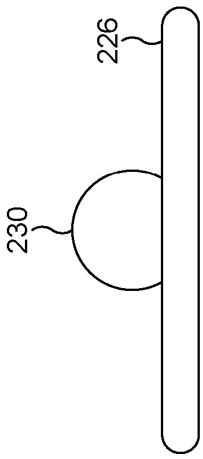


FIG. 32

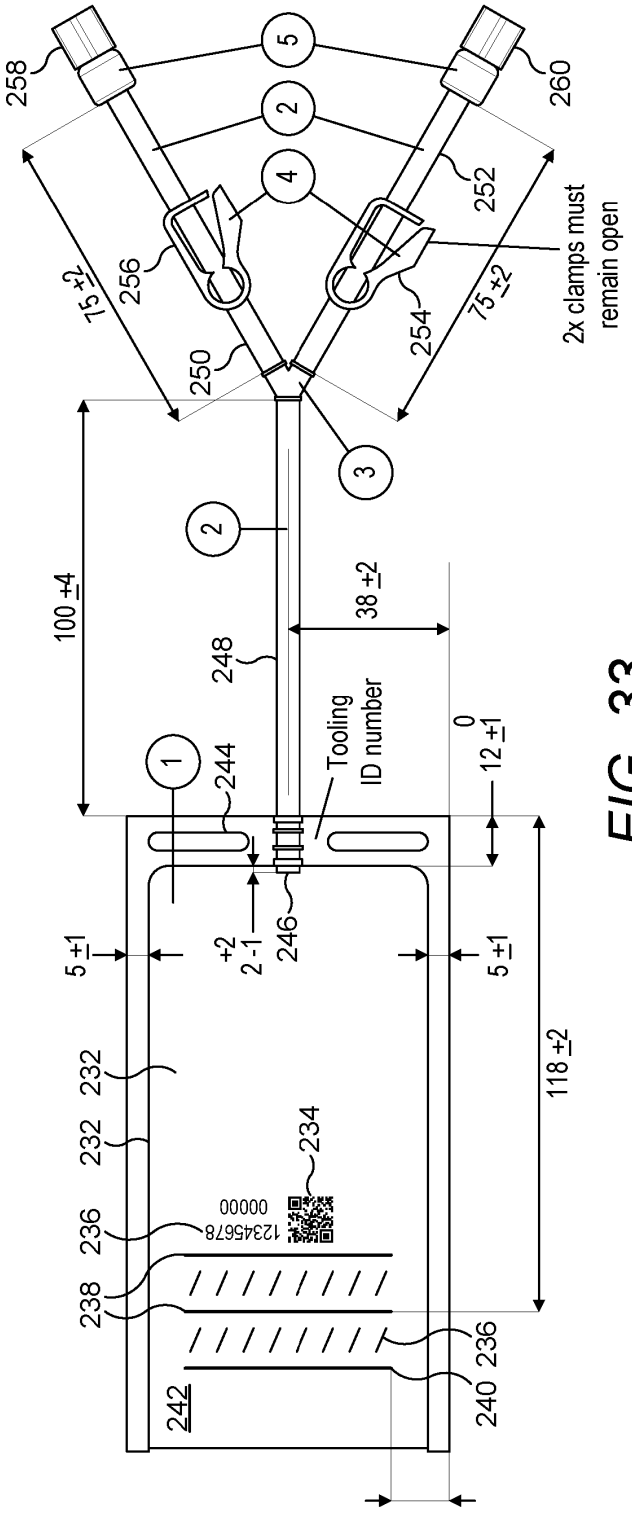

258
260
5
2
4
252
256
254
250
75 ±2
75 ±2
2x clamps must remain open
3
2
100 ±4
38 ±2
248
Tooling ID number
1
244
0
12 -1
246
+2
2 -1
5 ±1
5 ±1
118 ±2
232
232
234
00000
12345678
236
238
236
240
242

FIG. 33

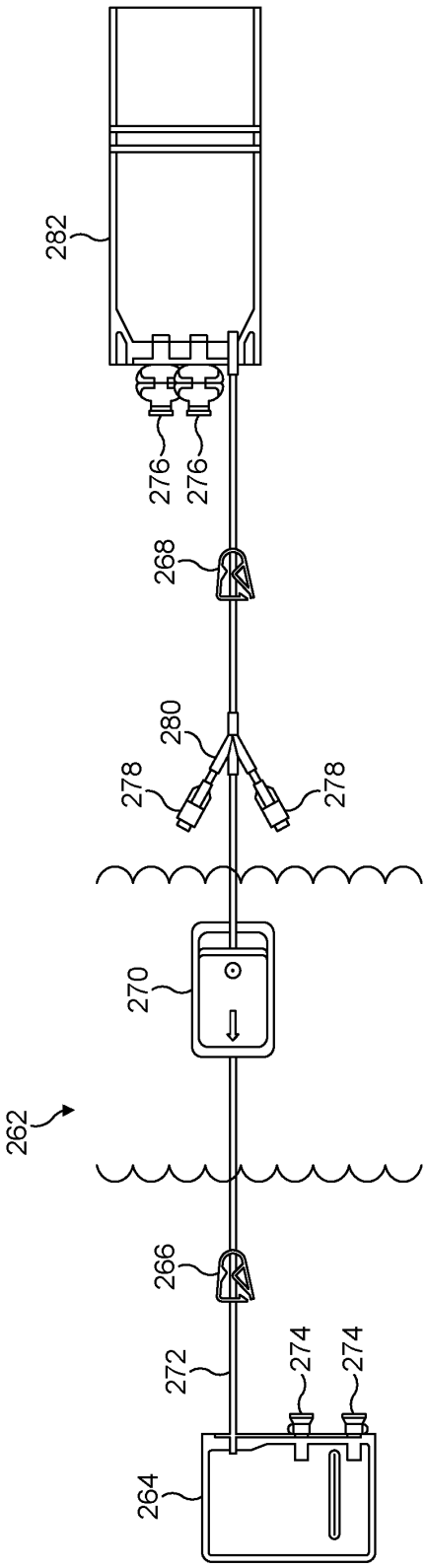


FIG. 34

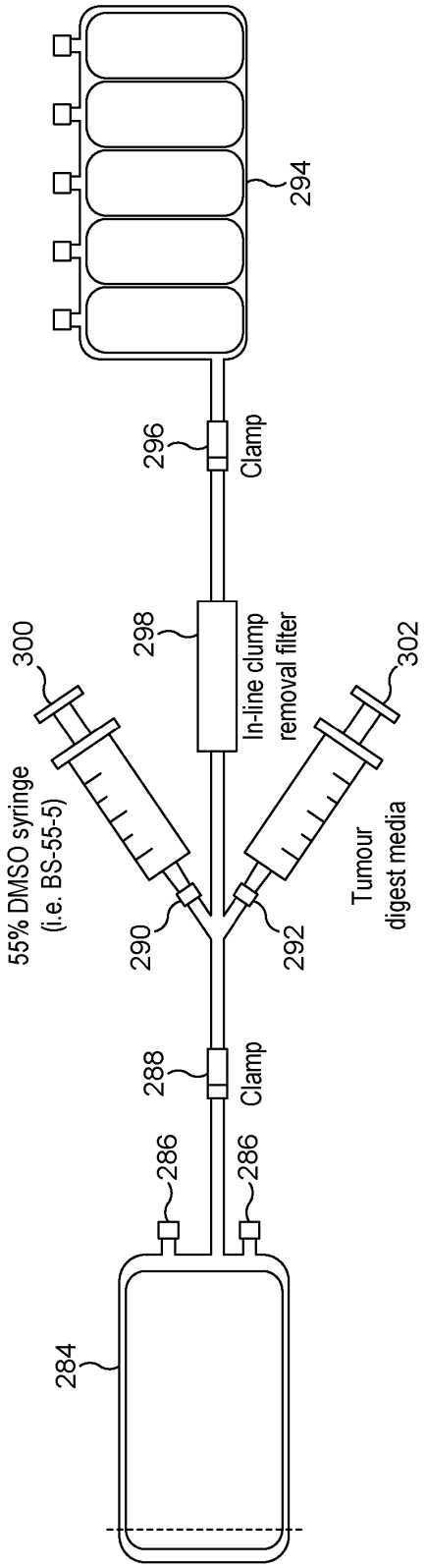

294
296
Clamp
298
In-line clump removal filter
300
302
55% DMSO syringe (i.e. BS-55-5)
Tumour digest media
290
292
288
Clamp
286
286
284

FIG. 35

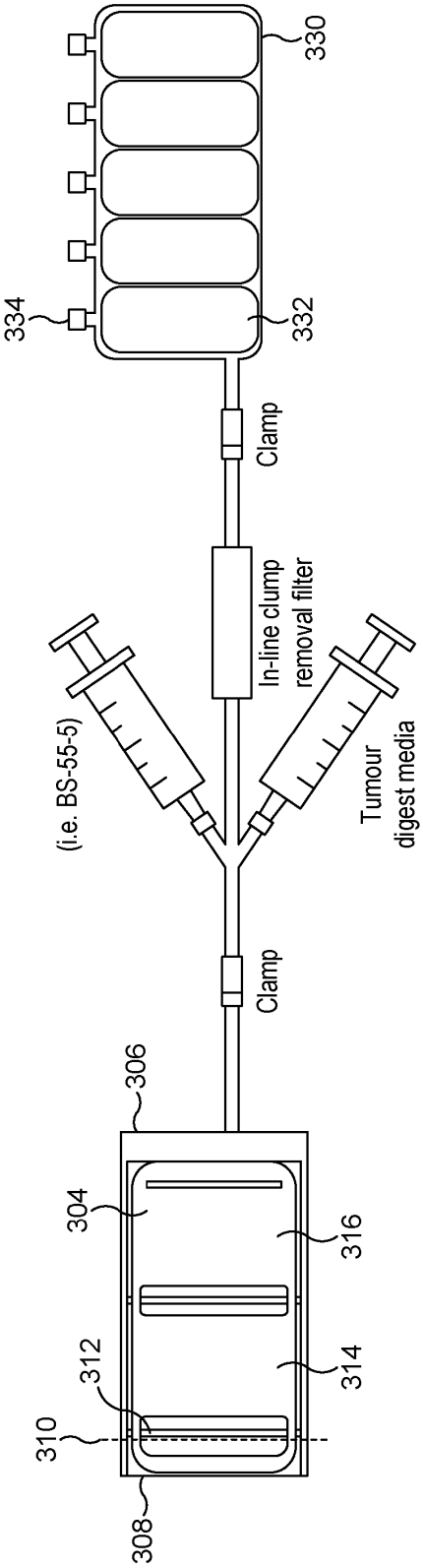


FIG. 36A

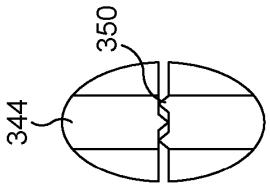


FIG. 36C

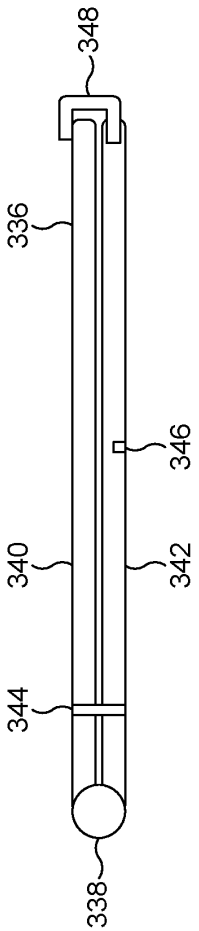


FIG. 36B

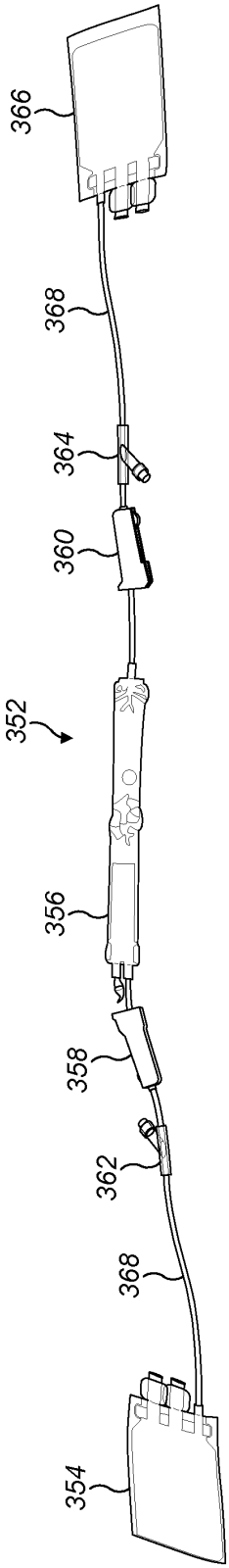

366
368
364
360
352
356
358
362
368
354

FIG. 37

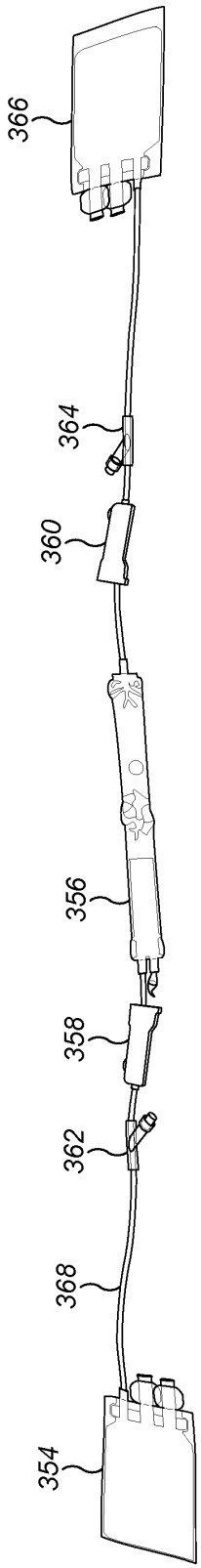

366
364
360
356
358
362
368
354

FIG. 38

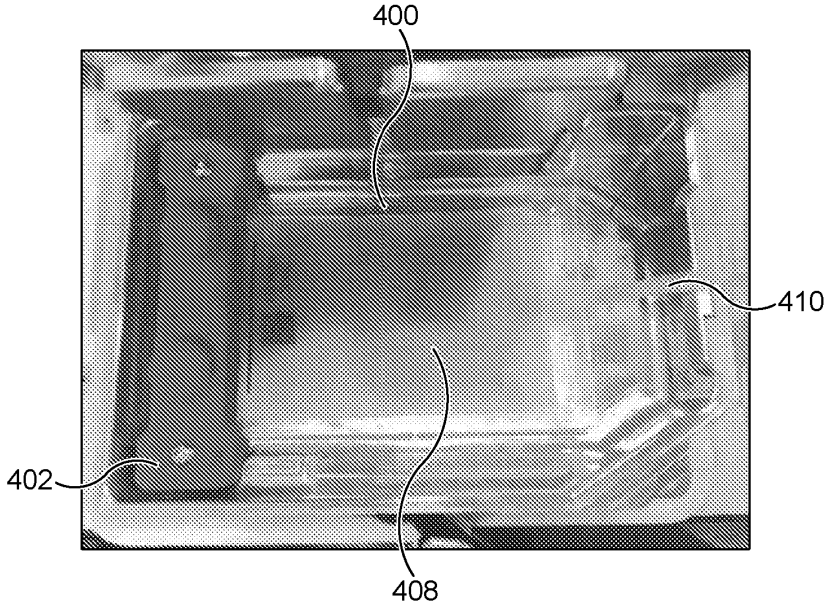


FIG. 39

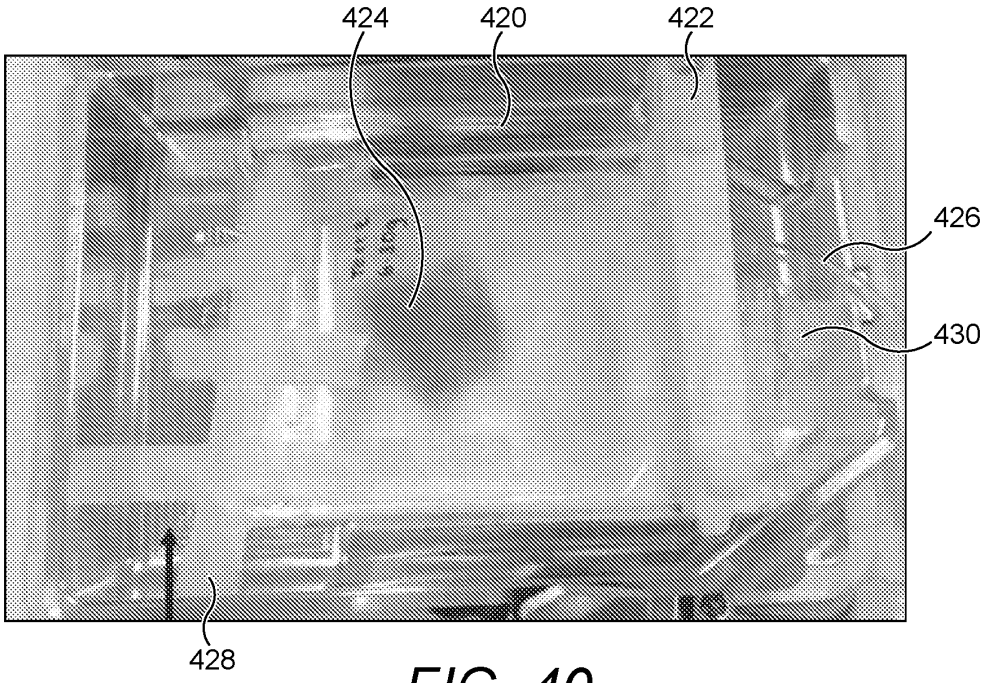


FIG. 40

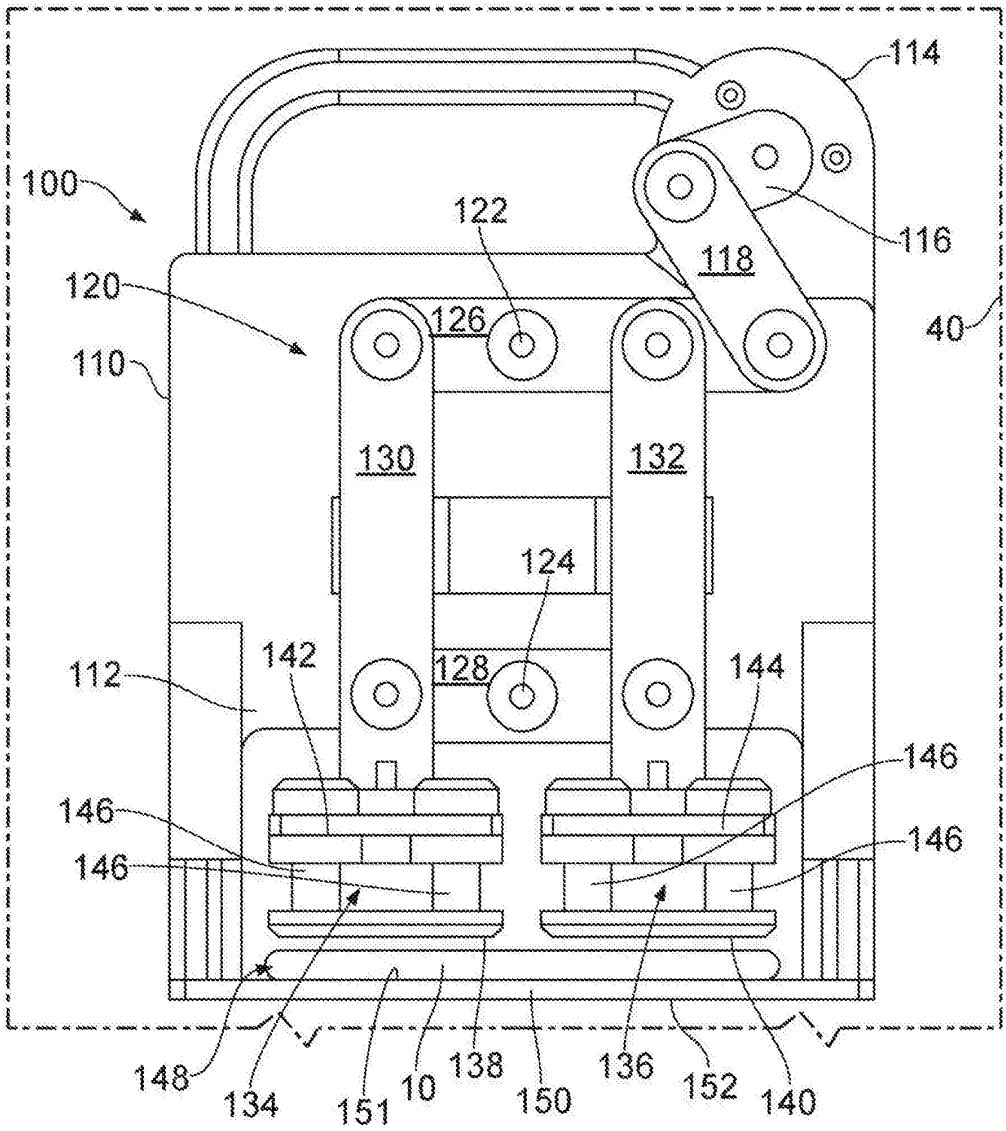

114
100
122
116
118
120
126
40
110
130
132
124
112
142
128
144
146
146
146
146
148
134
151
10
138
150
136
152
140

FIG. 41

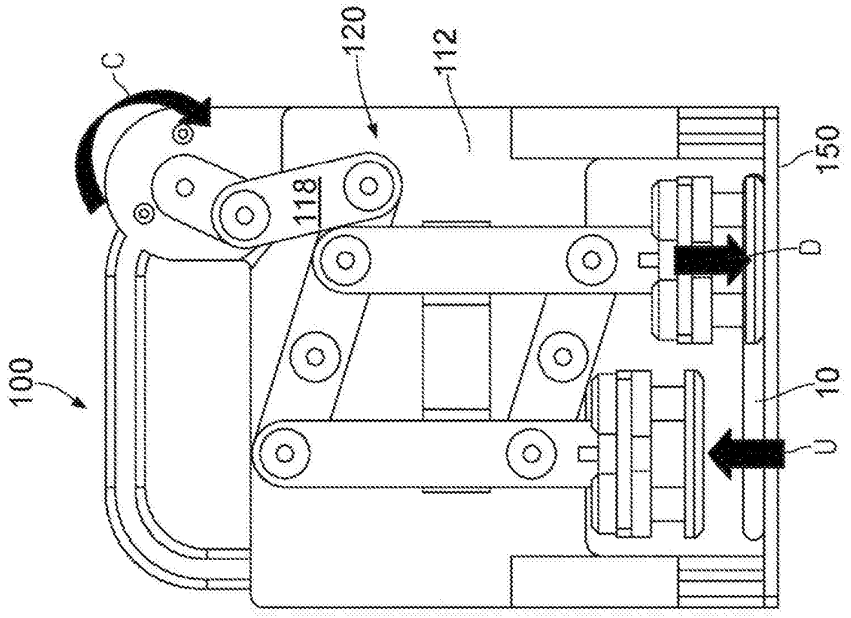


FIG. 43

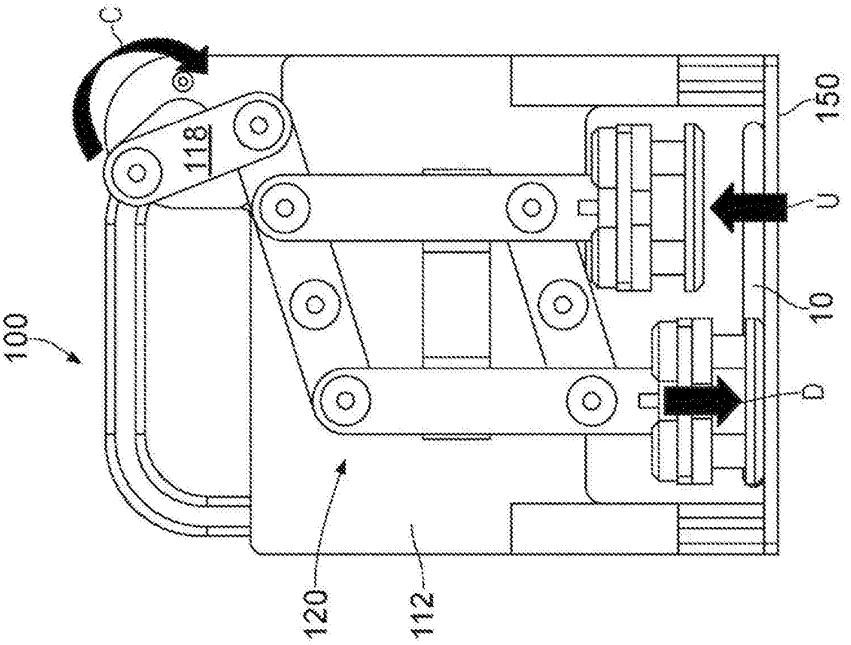


FIG. 42

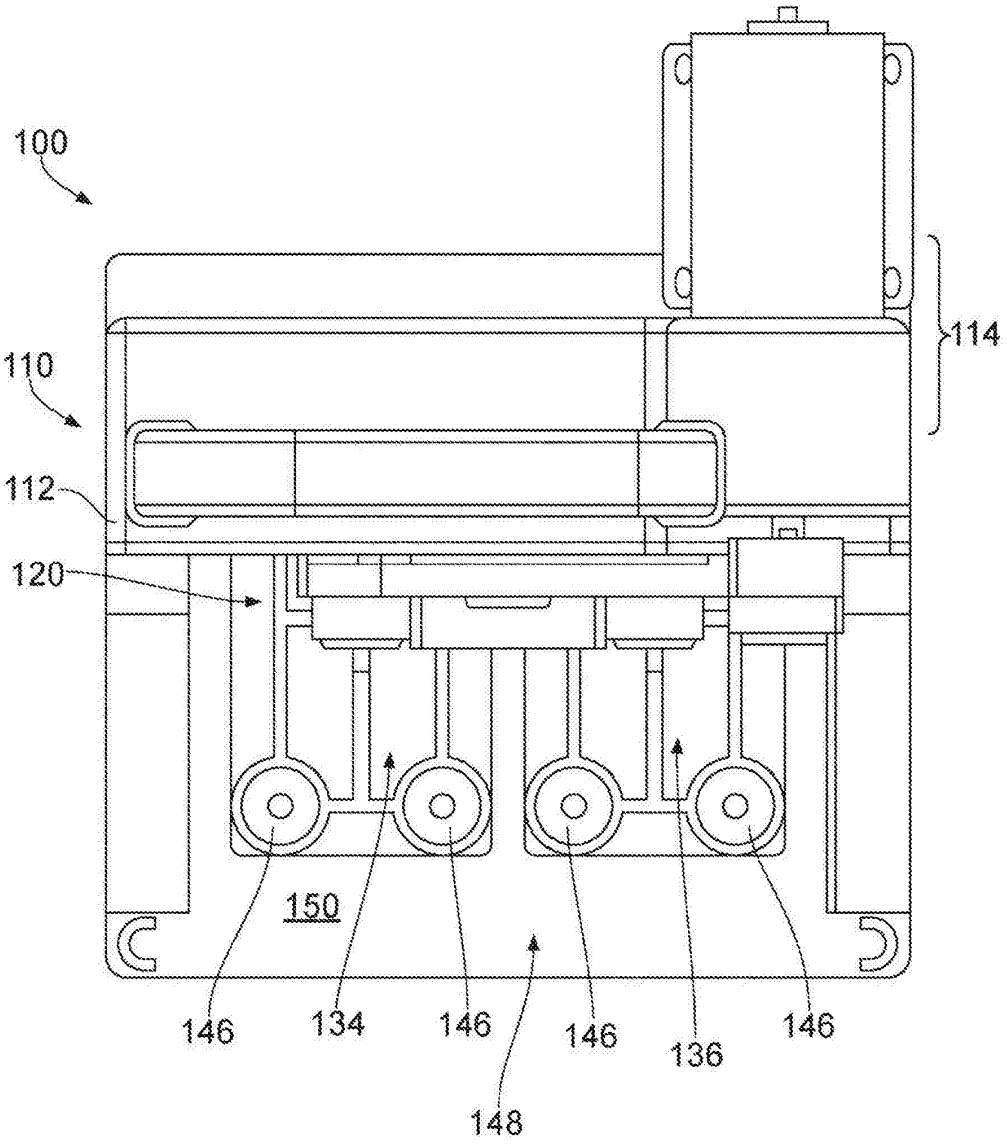


FIG. 44

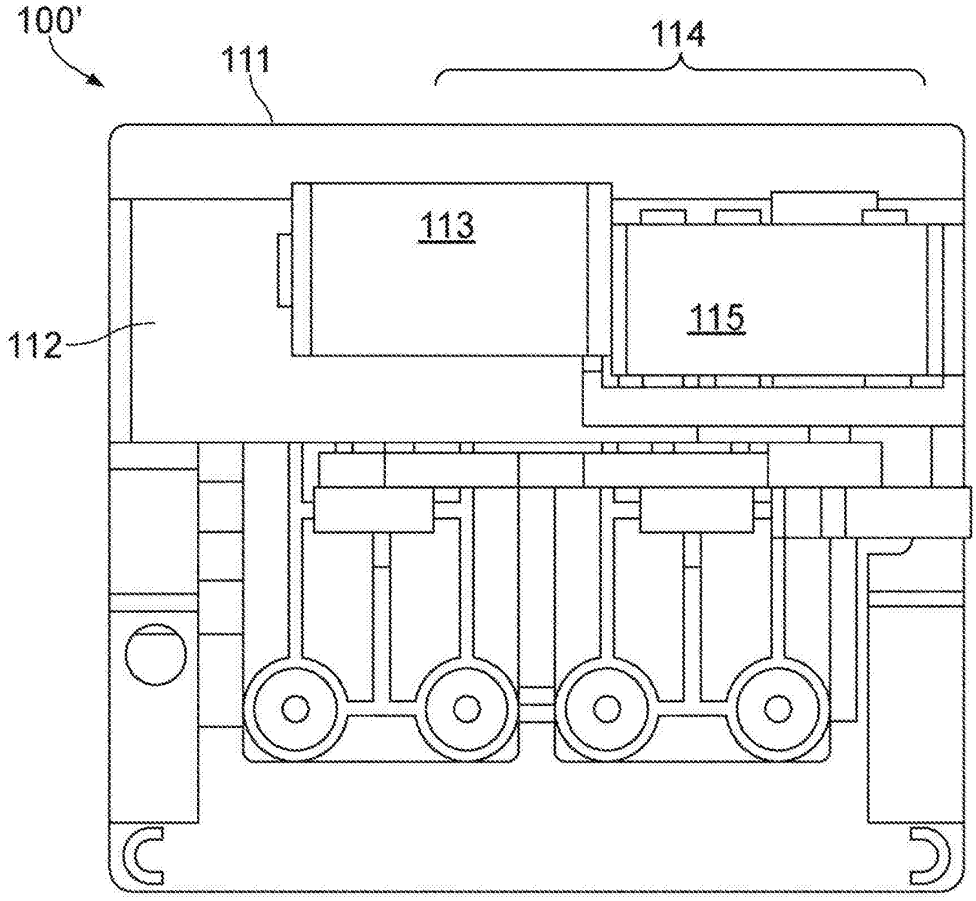


FIG. 45

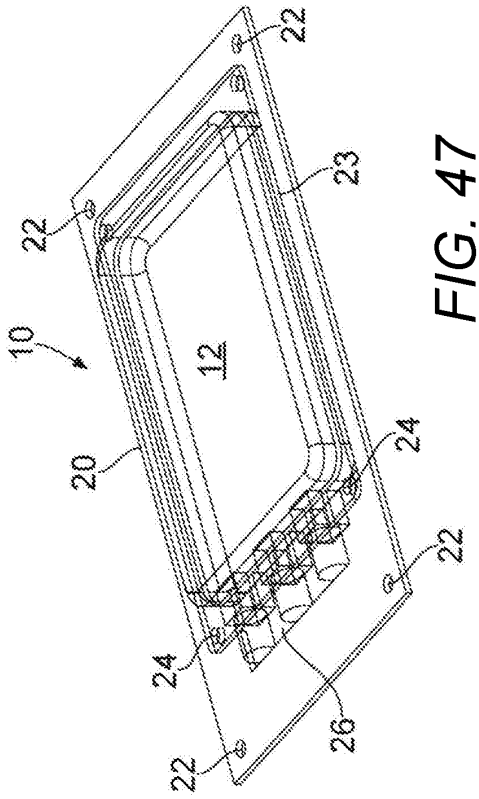


FIG. 47

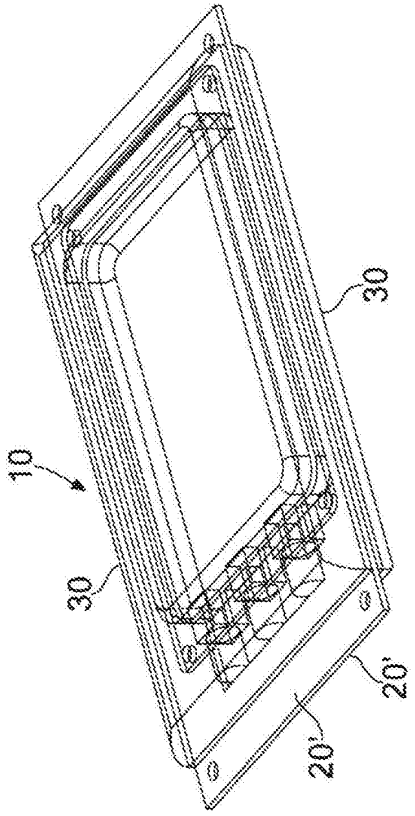


FIG. 48

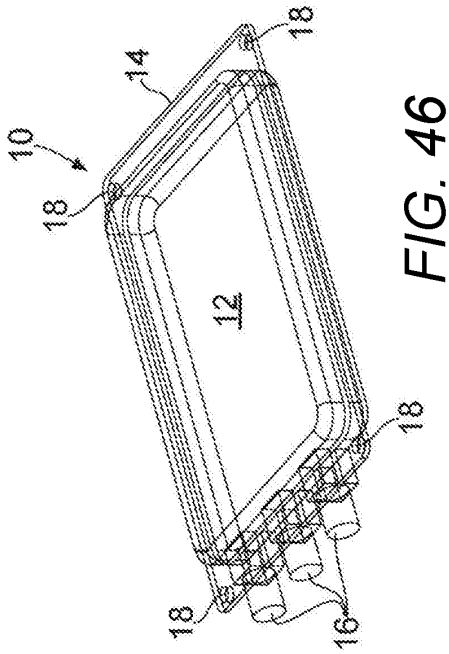


FIG. 46

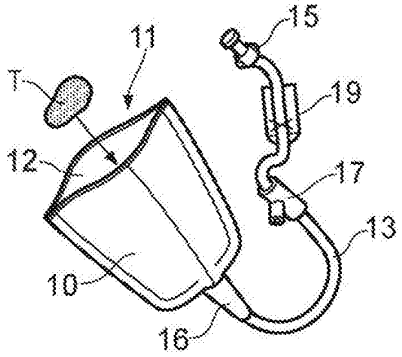


FIG. 49

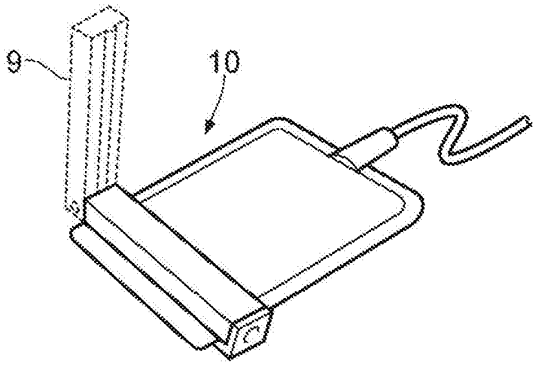


FIG. 50

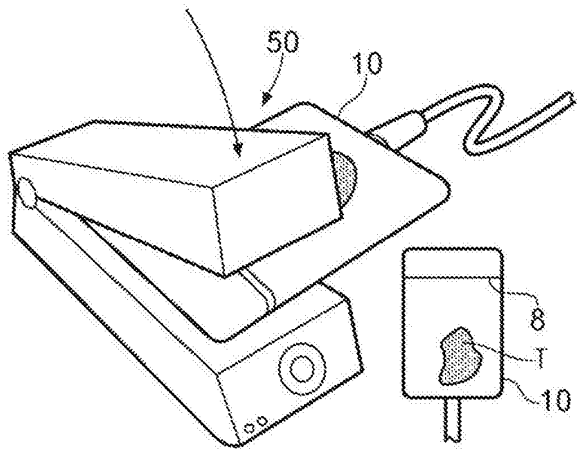


FIG. 51A

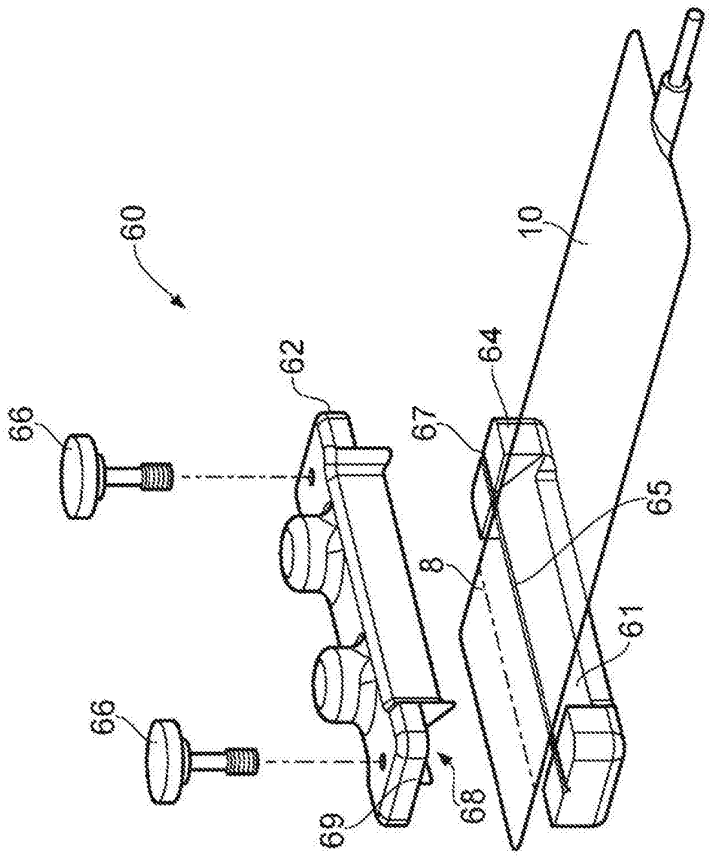


FIG. 51C

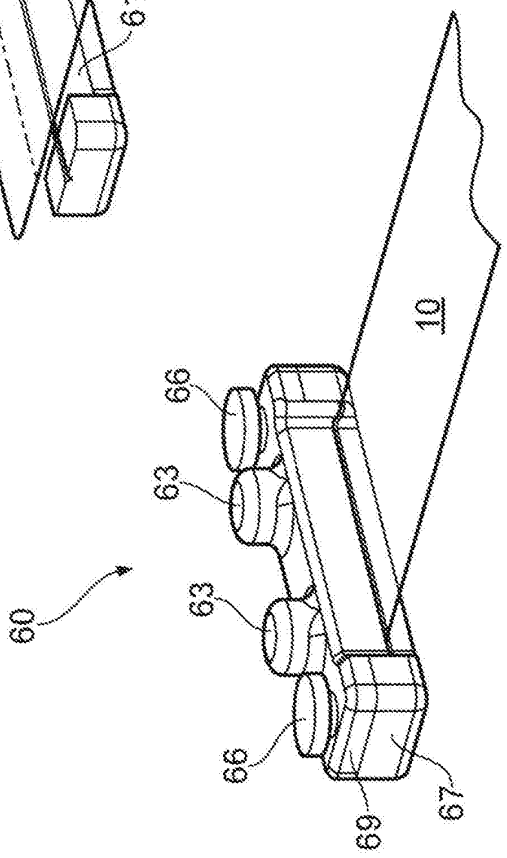


FIG. 51B

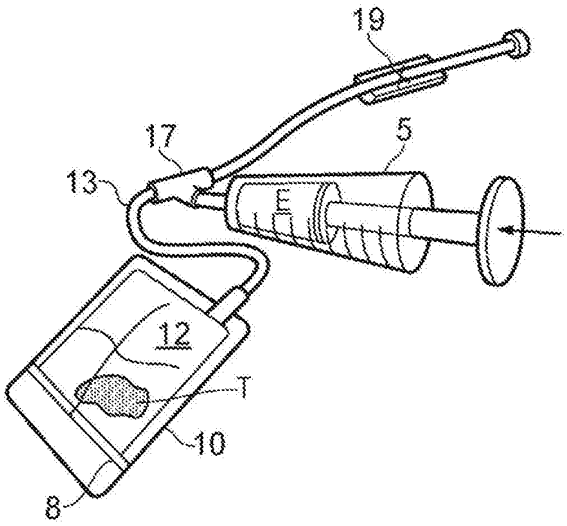


FIG. 52

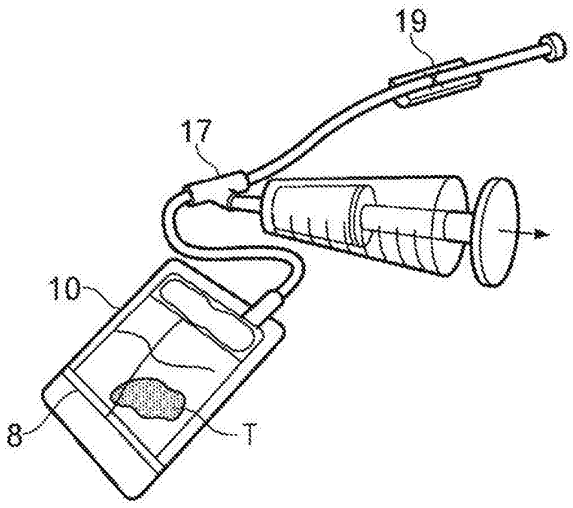


FIG. 53

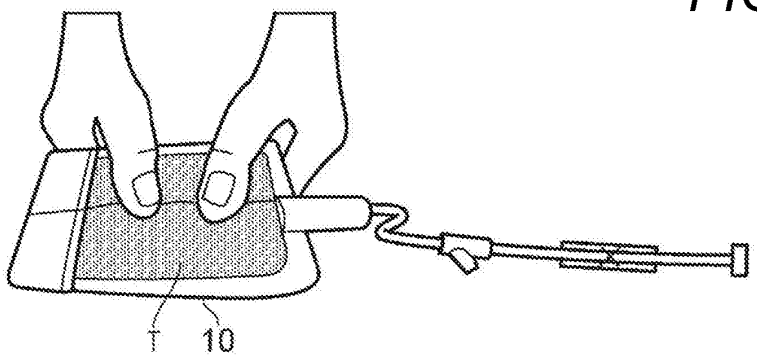


FIG. 54

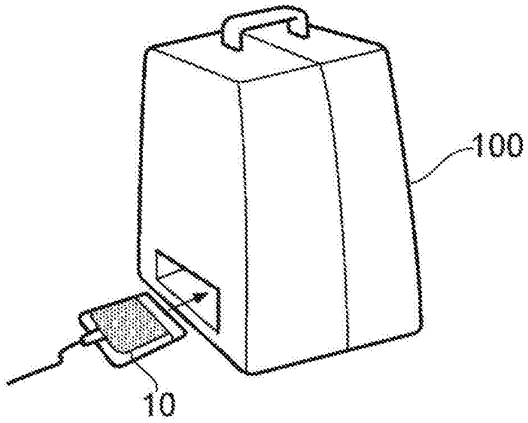


FIG. 55

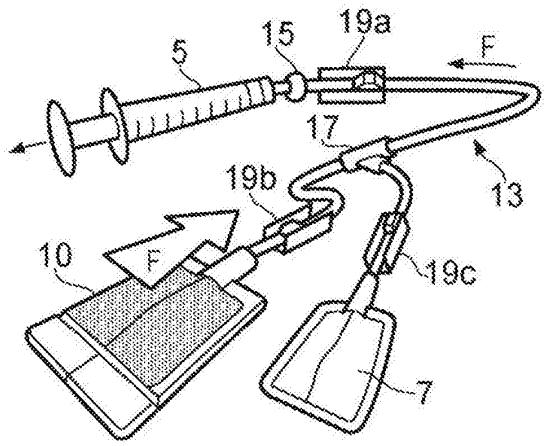


FIG. 56

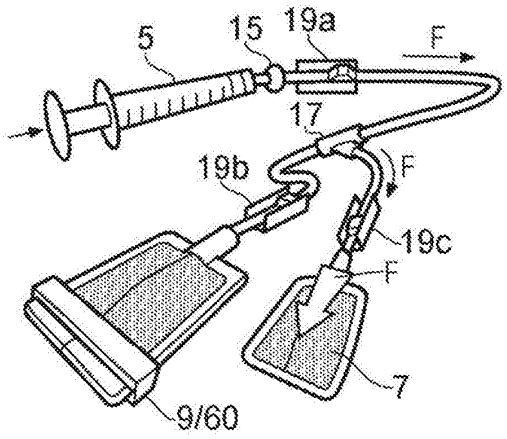


FIG. 57

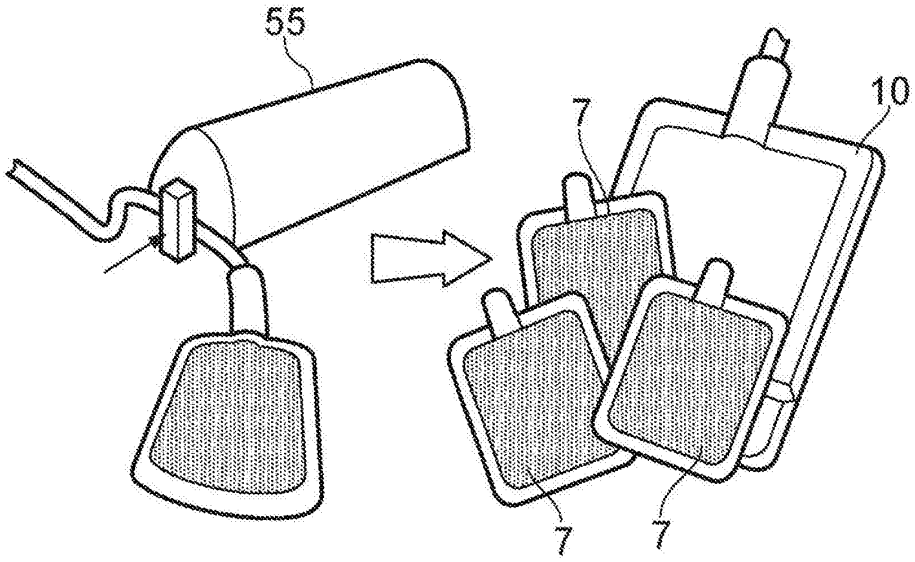


FIG. 58

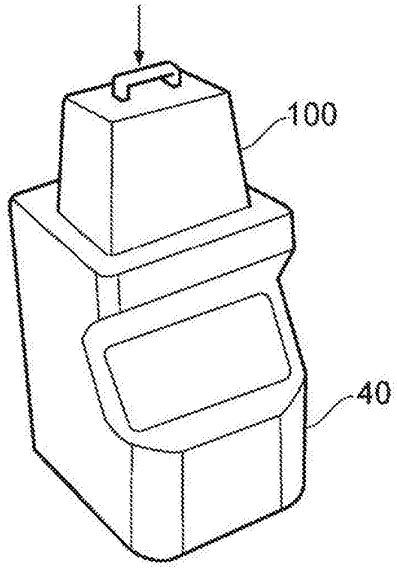


FIG. 59

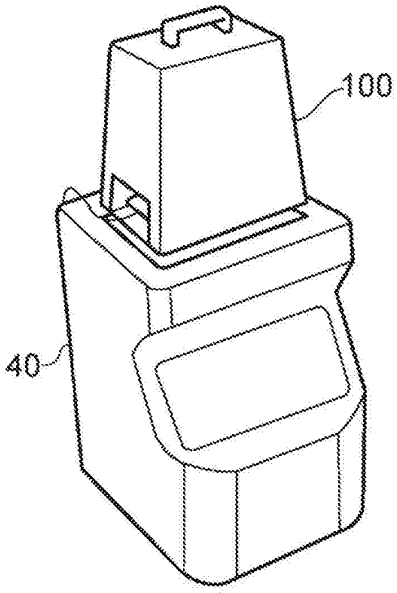


FIG. 60

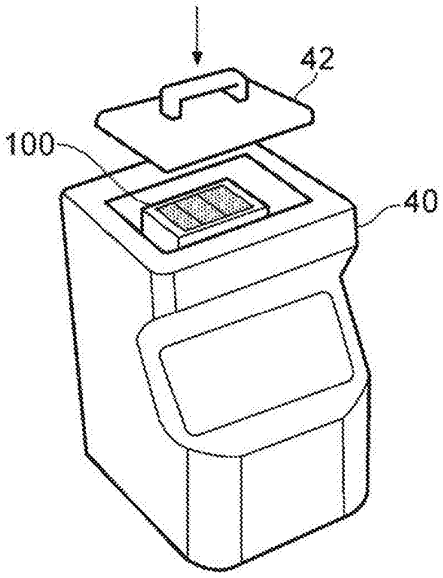


FIG. 61

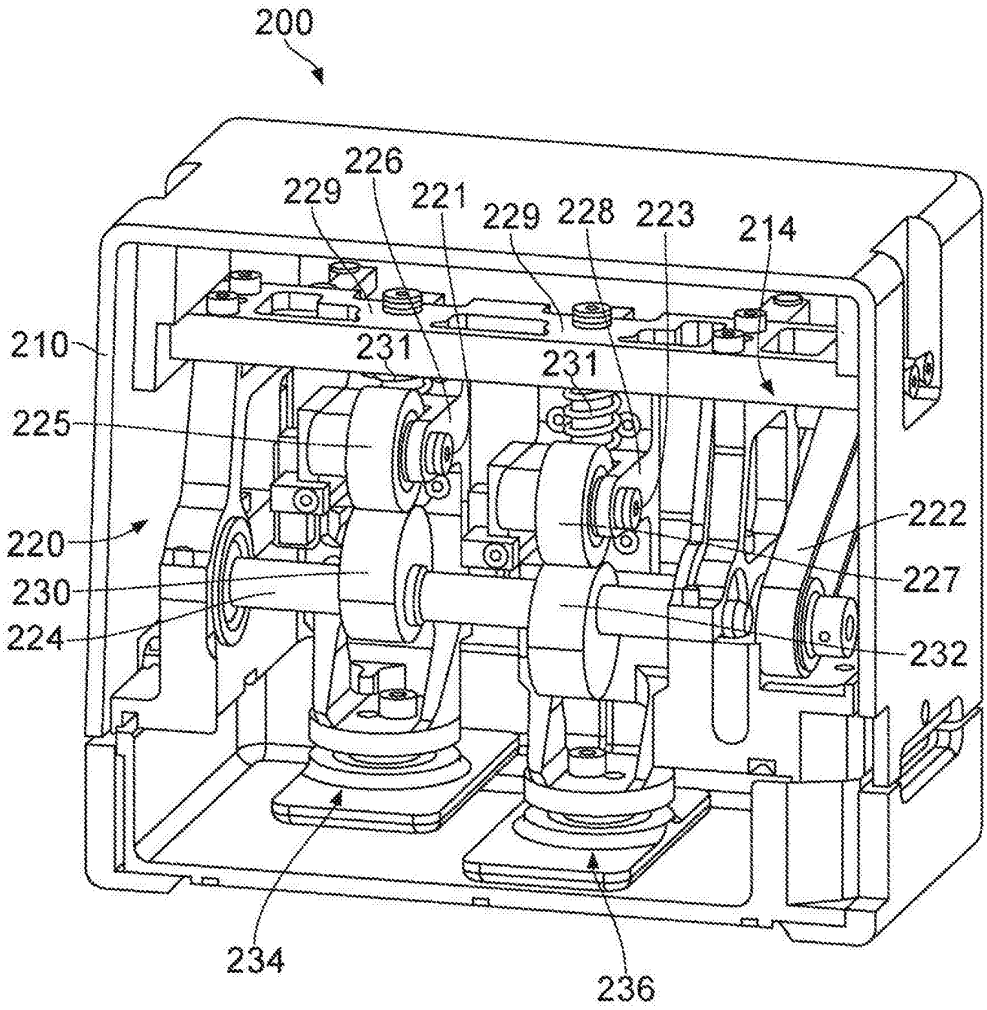

200
226
229
221
229
228
223
214
210
231
231
225
222
220
227
230
232
224
234
236

FIG. 62

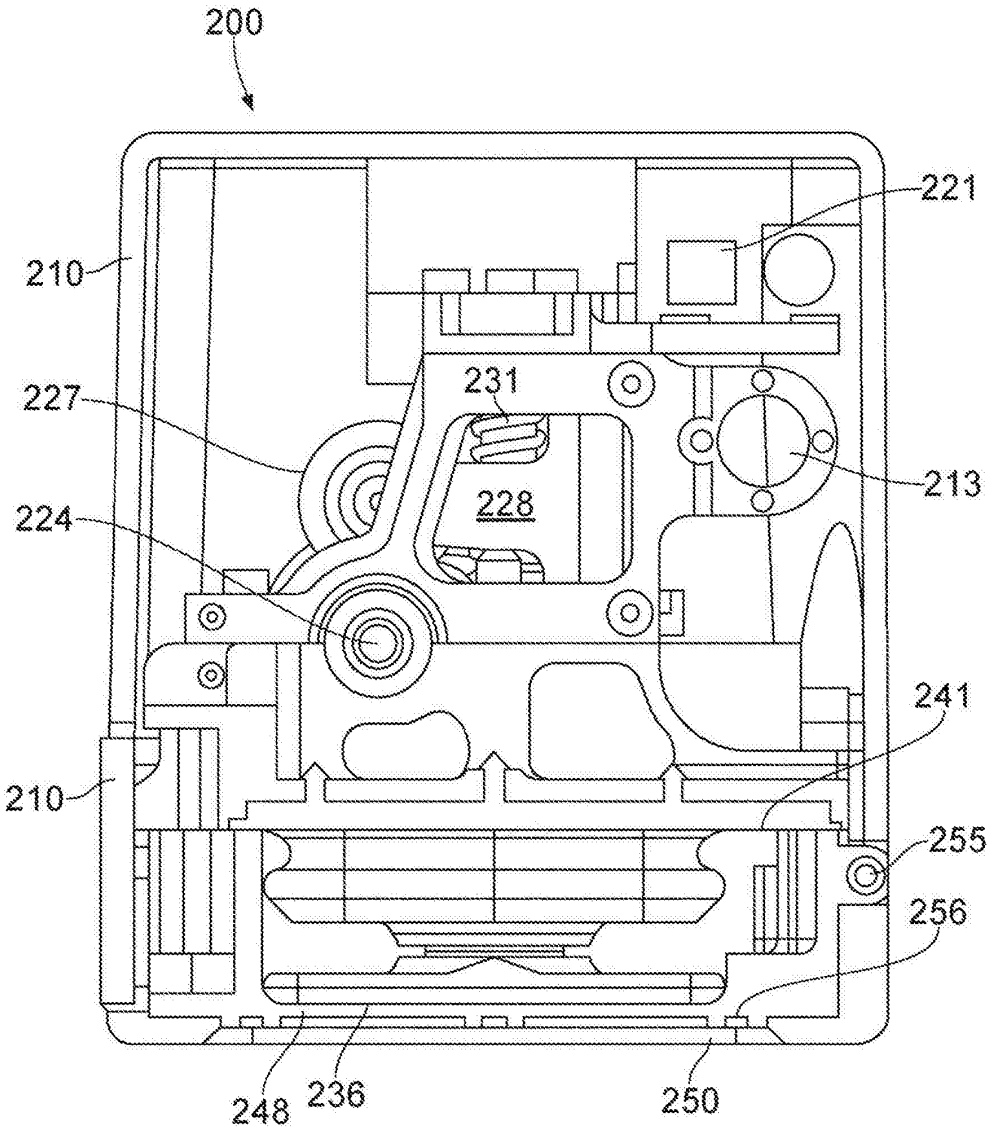


FIG. 63

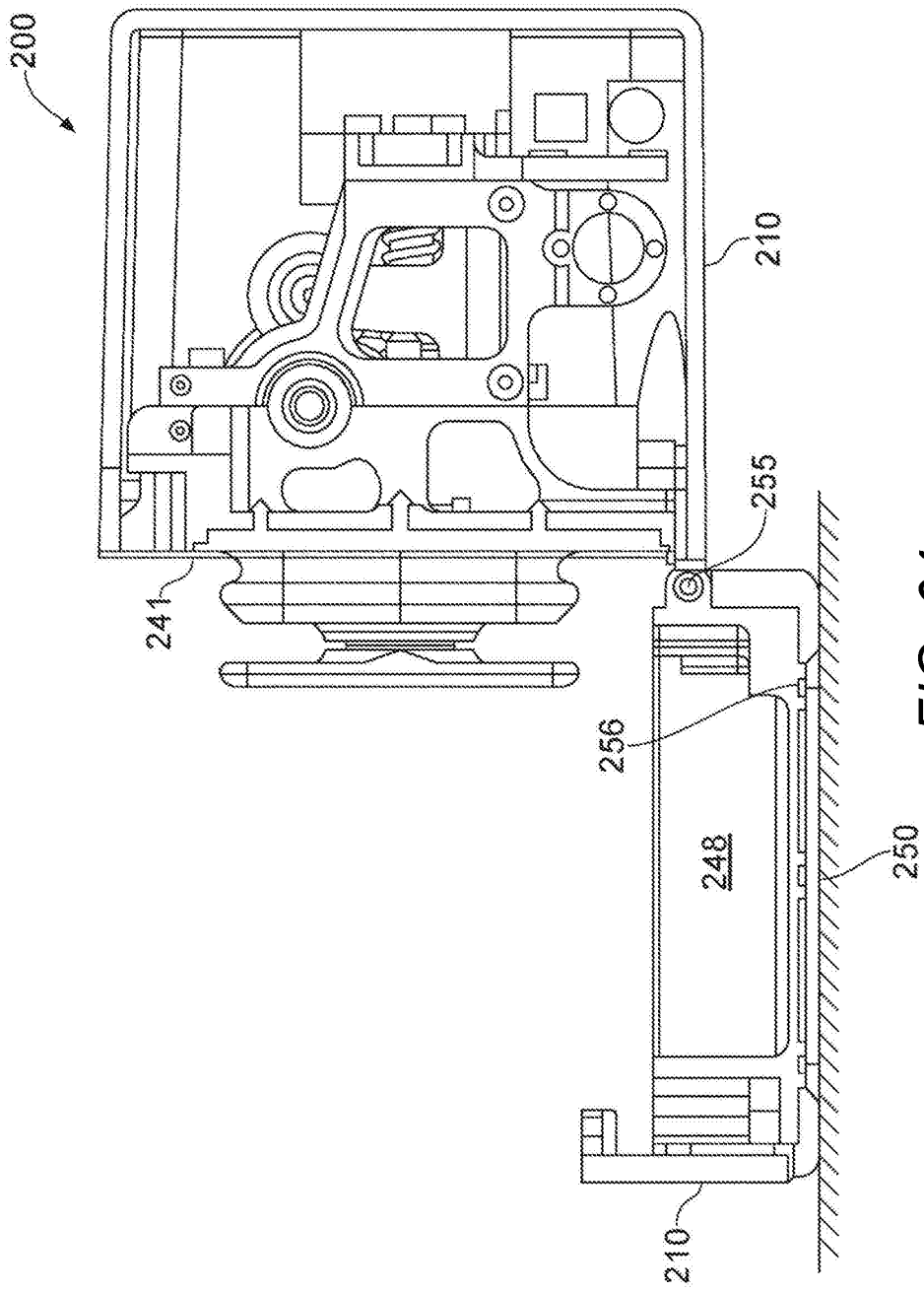


FIG. 64

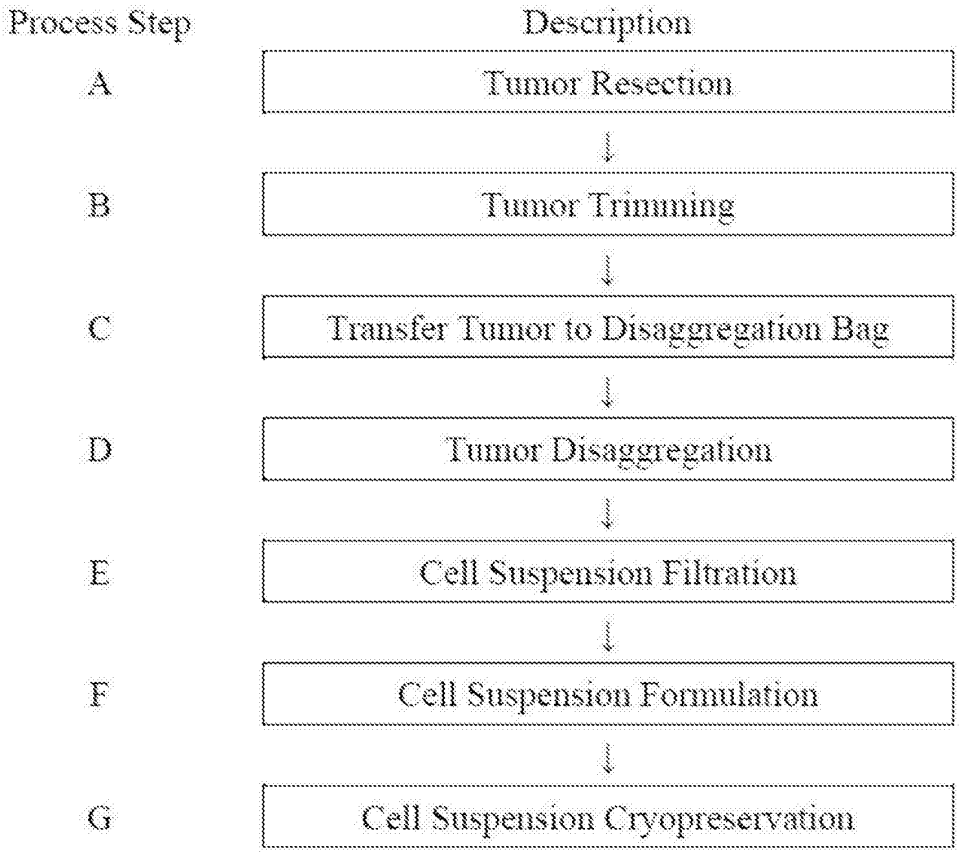

Process Step
Description
A
Tumor Resection
B
Tumor Trimming
C
Transfer Tumor to Disaggregation Bag
D
Tumor Disaggregation
E
Cell Suspension Filtration
F
Cell Suspension Formulation
G
Cell Suspension Cryopreservation

FIG. 65

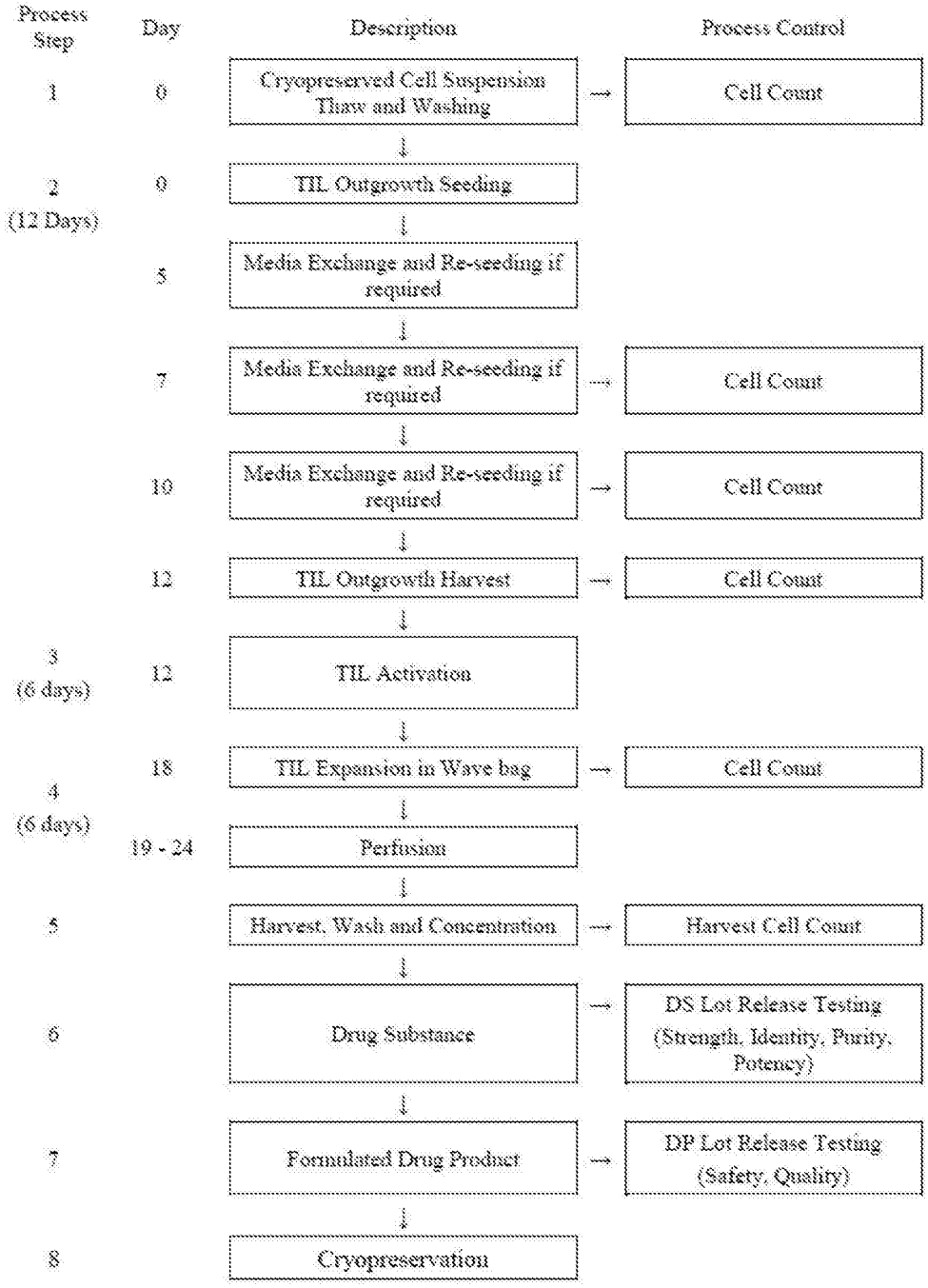

Process Step
Day
Description
Process Control
1
0
Cryopreserved Cell Suspension Thaw and Washing
Cell Count
2 (12 Days)
0
TIL Outgrowth Seeding
5
Media Exchange and Re-seeding if required
7
Media Exchange and Re-seeding if required
Cell Count
10
Media Exchange and Re-seeding if required
Cell Count
12
TIL Outgrowth Harvest
Cell Count
3 (6 days)
12
TIL Activation
18
TIL Expansion in Wave bag
Cell Count
4 (6 days)
19 - 24
Perfusion
5
Harvest, Wash and Concentration
Harvest Cell Count
6
Drug Substance
DS Lot Release Testing (Strength, Identity, Purity, Potency)
7
Formulated Drug Product
DP Lot Release Testing (Safety, Quality)
8
Cryopreservation

FIG. 66

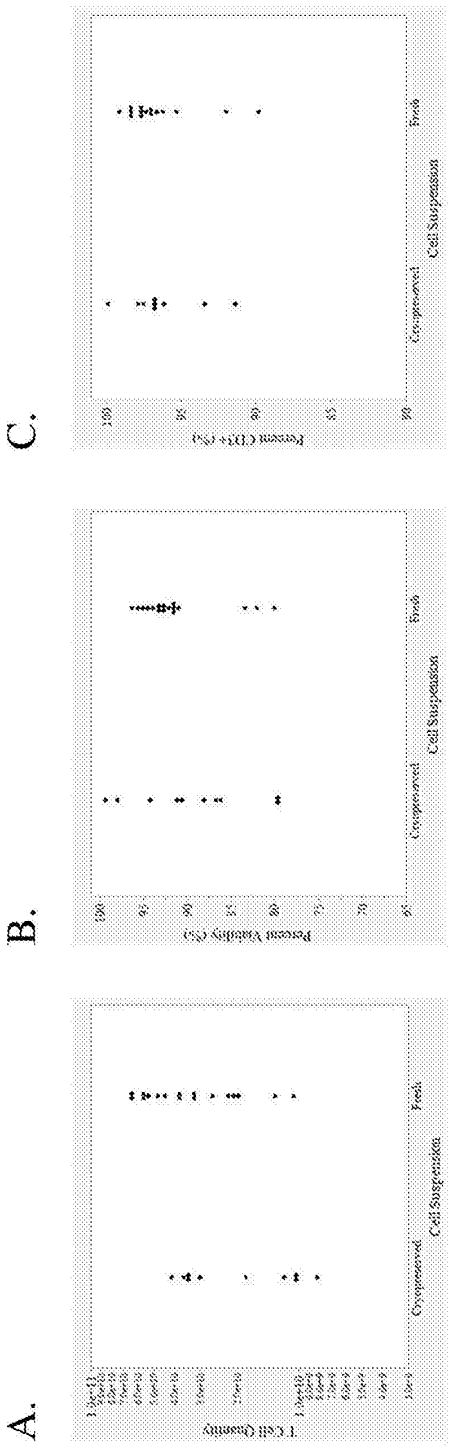

A.
T Cell Quantity
Cryopreserved
Fresh
Cell Suspension
B.
Percent Viability (%)
Cryopreserved
Fresh
Cell Suspension
C.
Percent CD3+ (%)
Cryopreserved
Fresh
Cell Suspension

FIG. 67

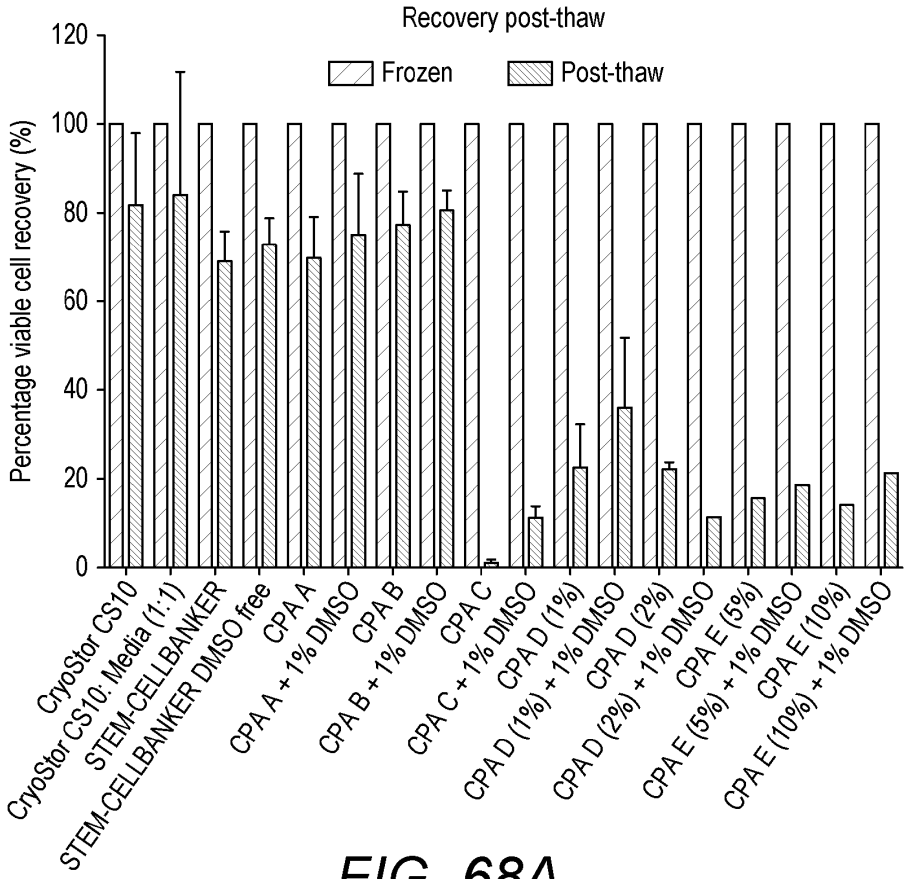


FIG. 68A

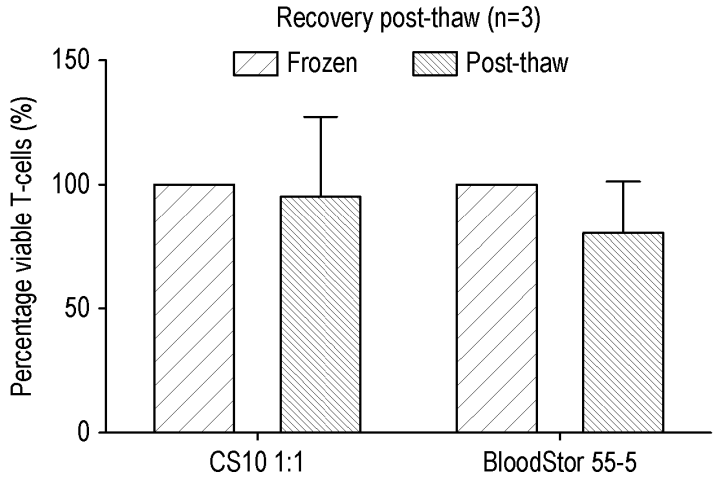


FIG. 68B

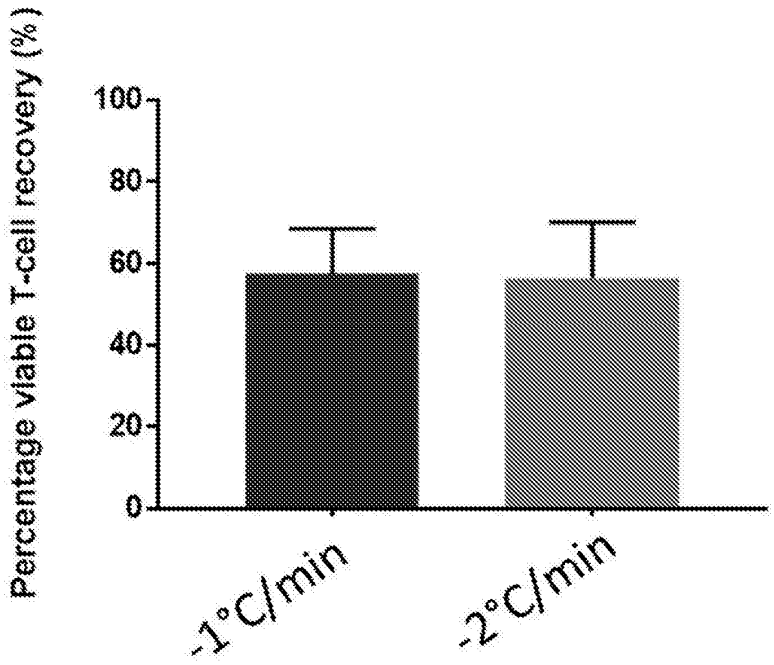

Percentage viable T-cell recovery (%)
100
80
60
40
20
0
-1°C/min
-2°C/min

FIG. 69

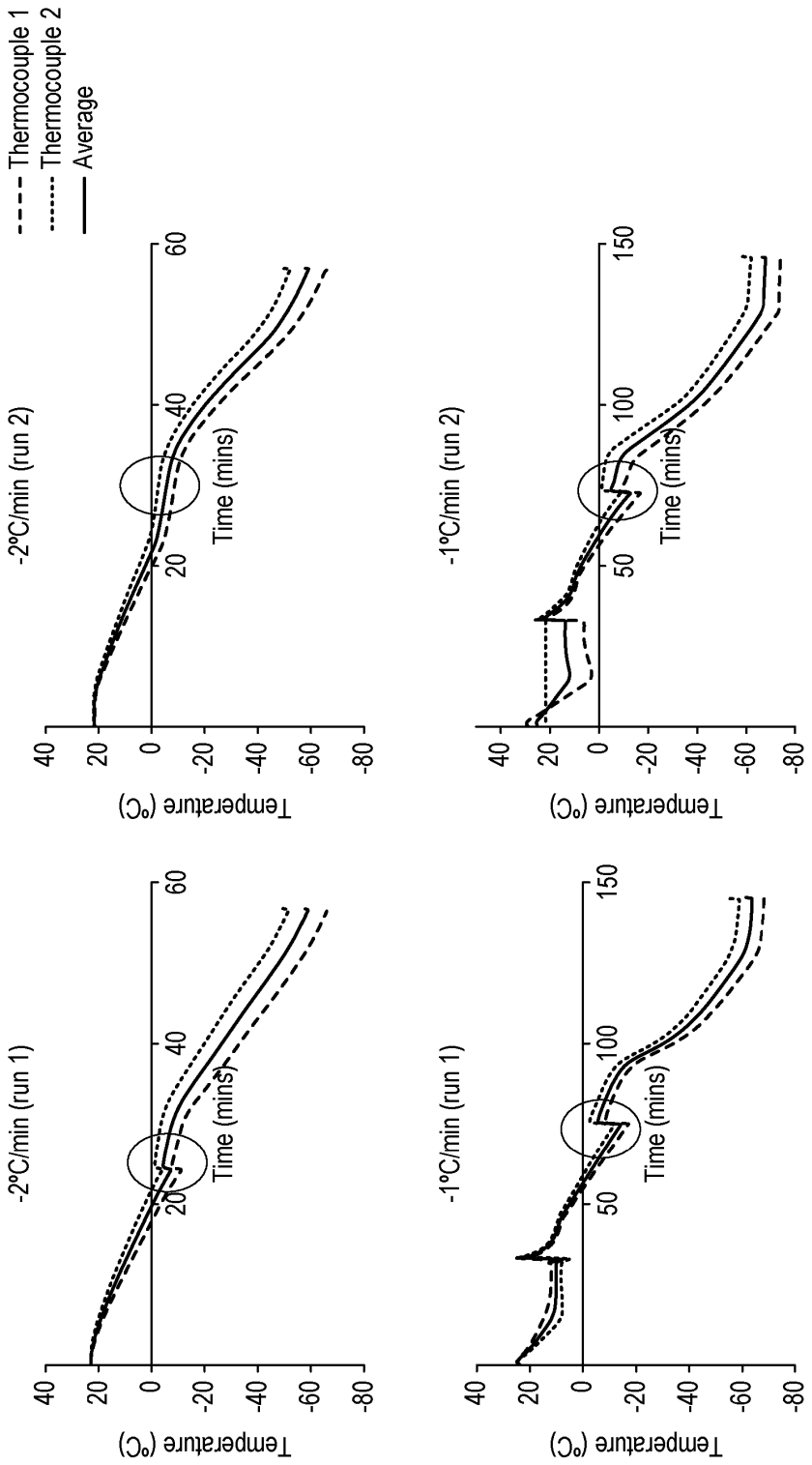
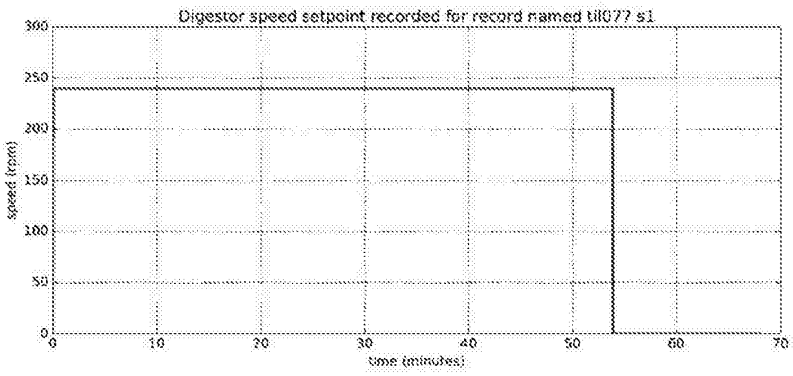
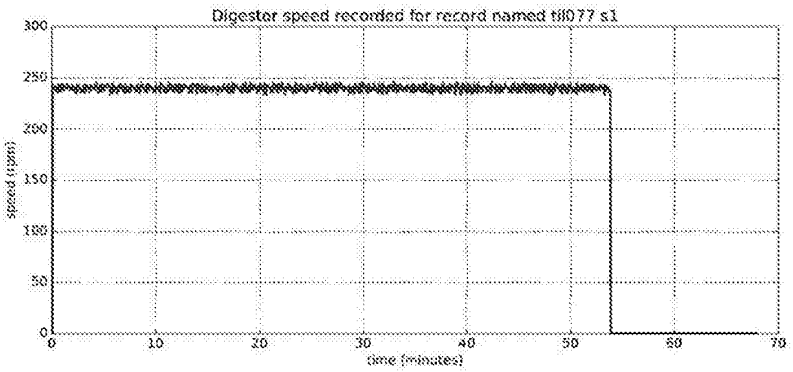

Thermocouple 1
Thermocouple 2
Average
-2ºC/min (run 2)
-1ºC/min (run 2)
-2ºC/min (run 1)
-1ºC/min (run 1)
Time (mins)
Temperature (ºC)

FIG. 70

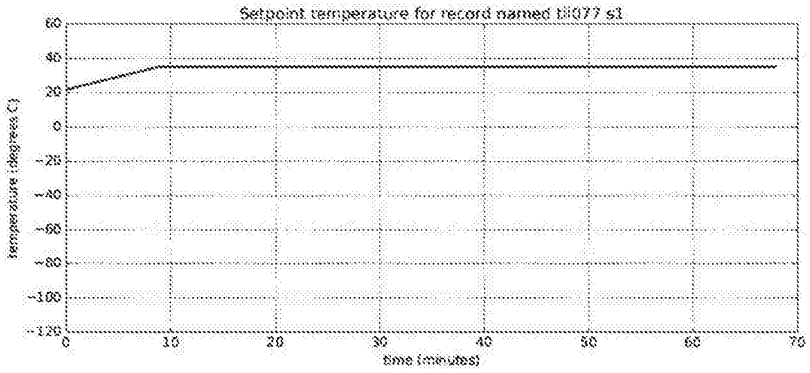
A.



B.



C.



D.

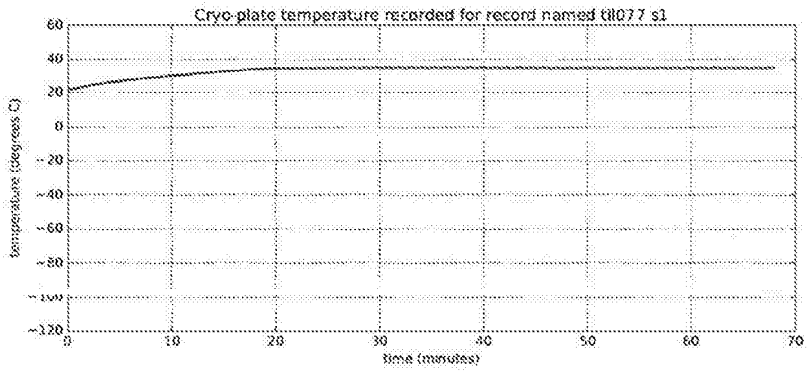
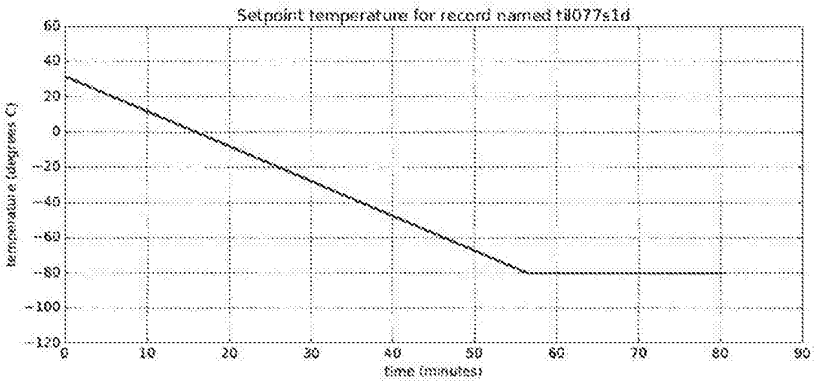
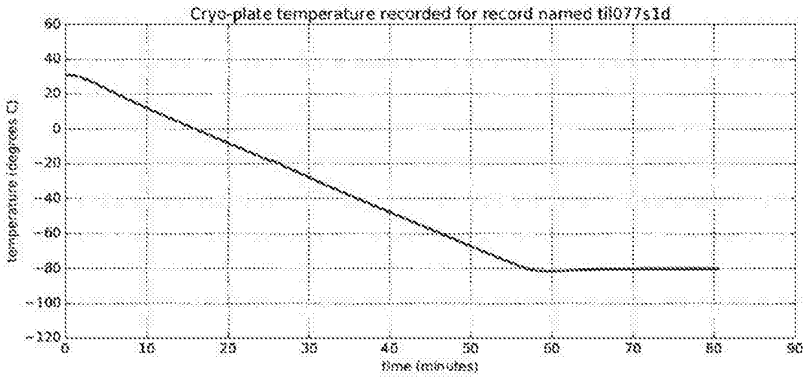


FIG. 71A-71D

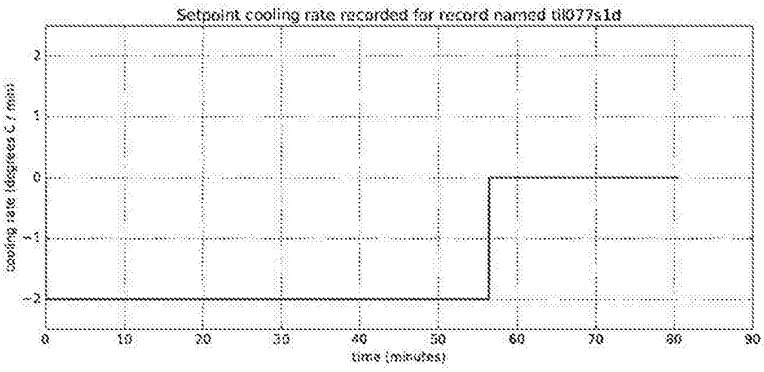
E.



F.



G.



H.

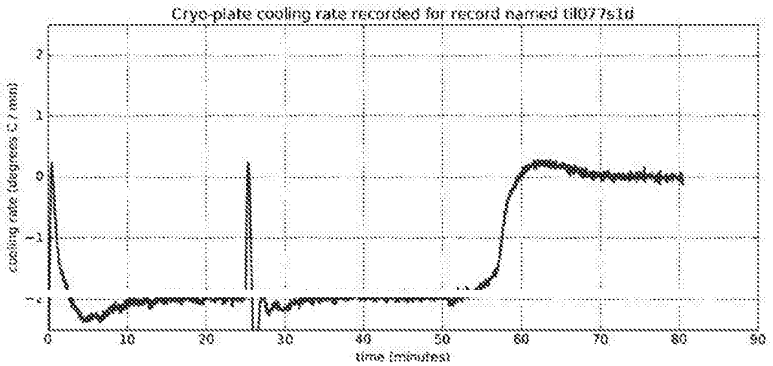
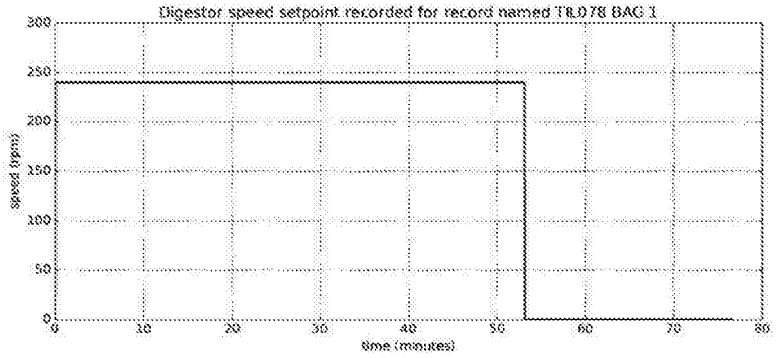
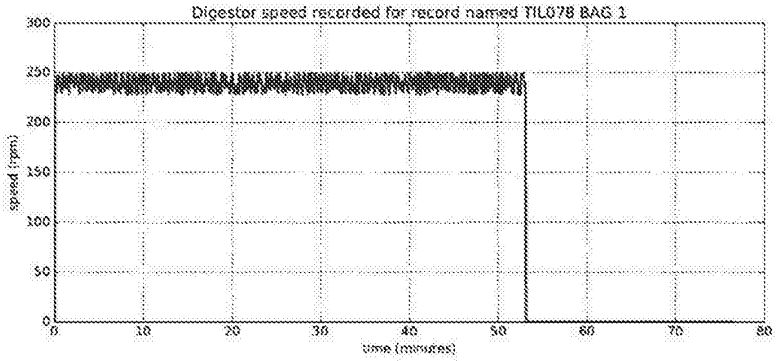


FIG. 71E-71H

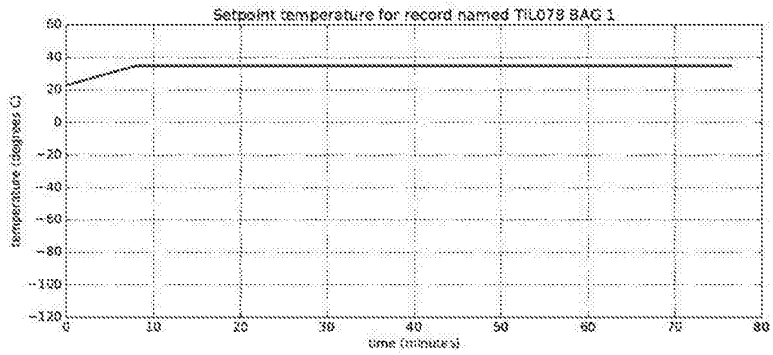
A.



B.



C.



D.

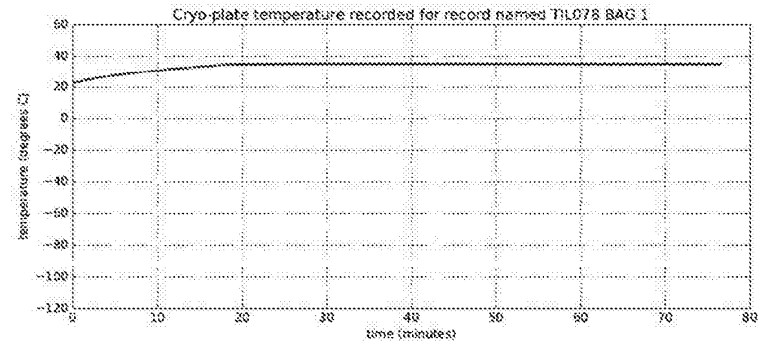
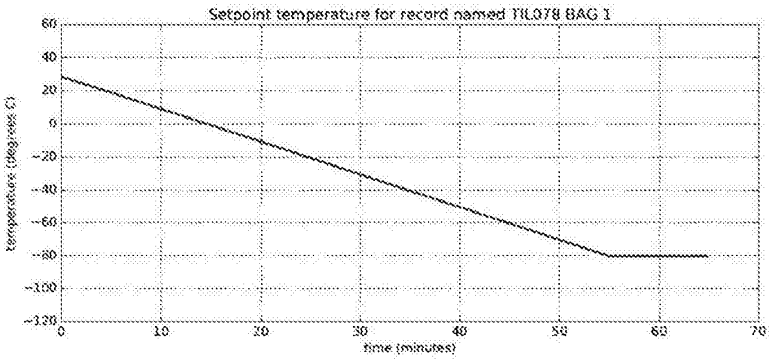
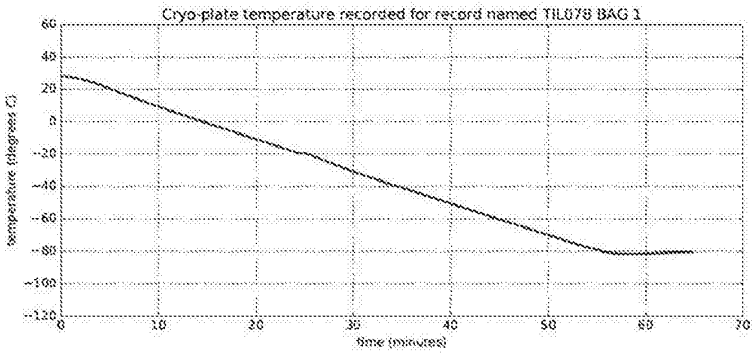


FIG. 72A-72D

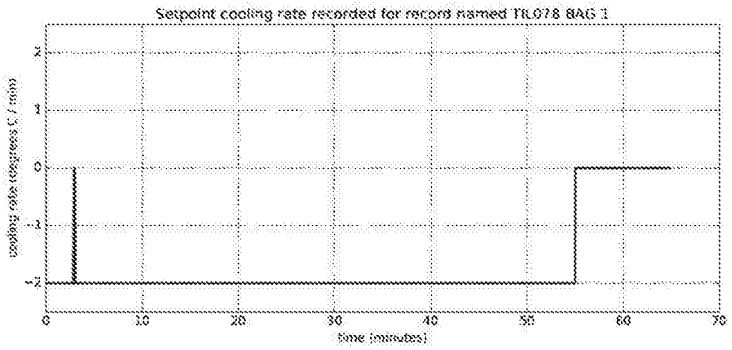
E.



F.



G.



H.

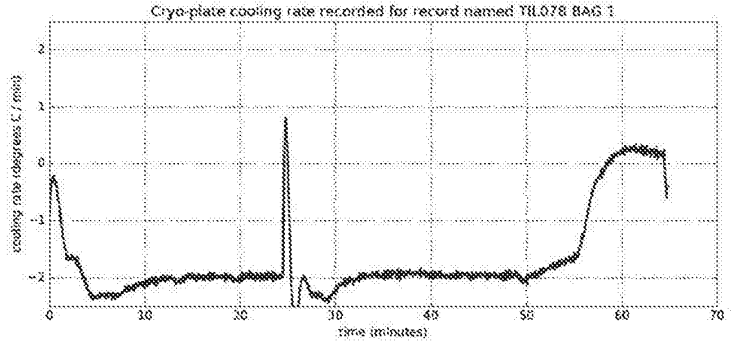
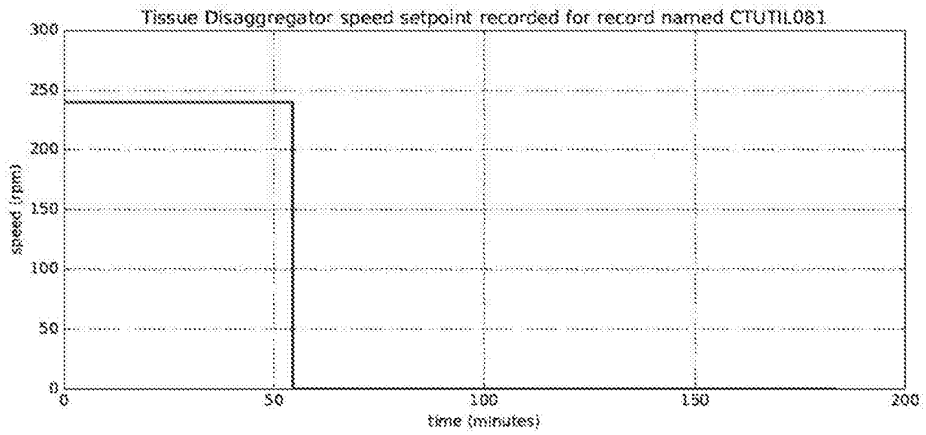
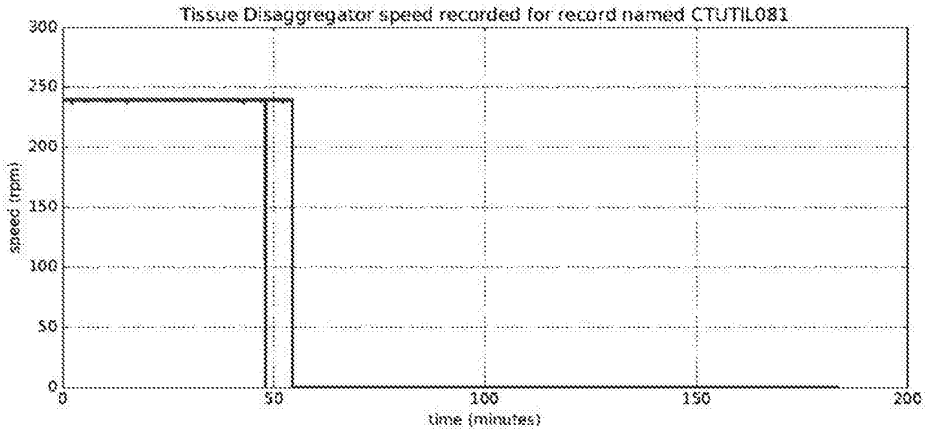


FIG. 72E-72H

A.



B.



C.

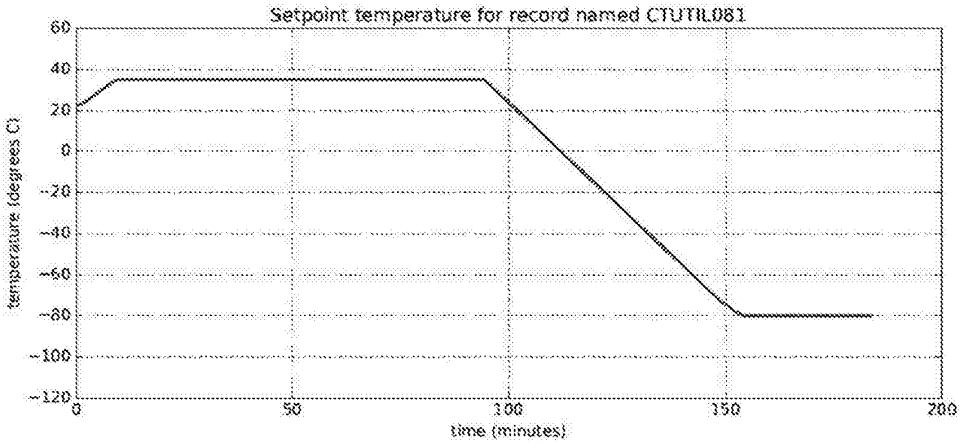
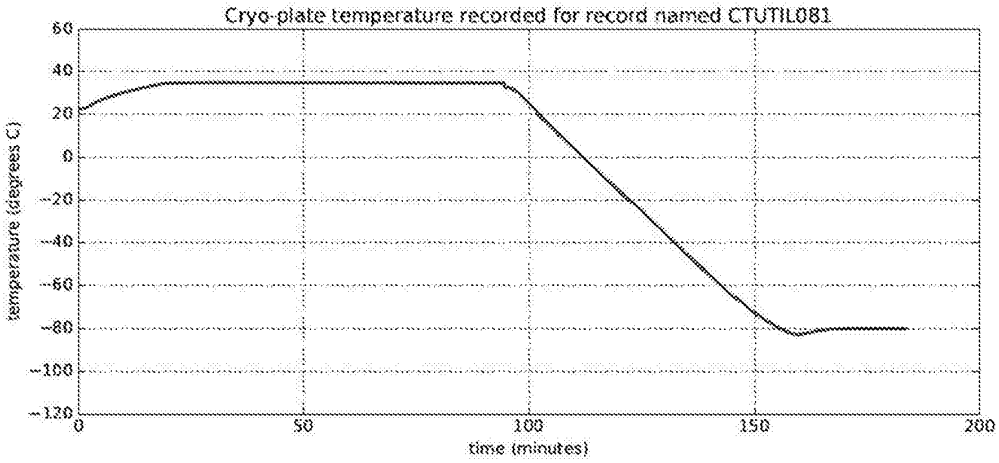
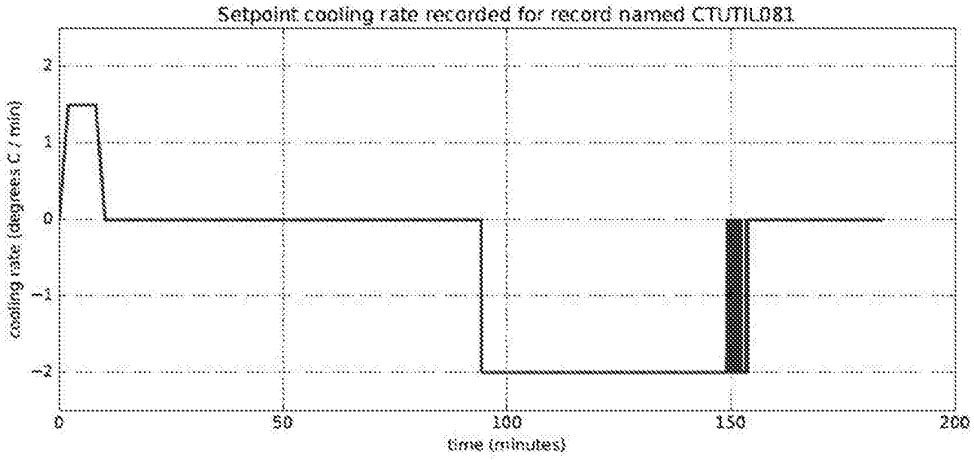


FIG. 73A-73C

D.



E.



F.

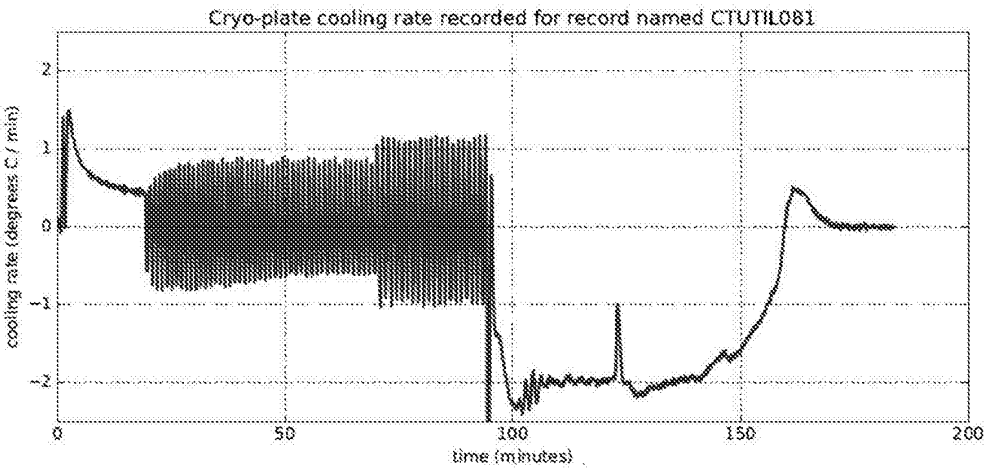


FIG. 73D-73F

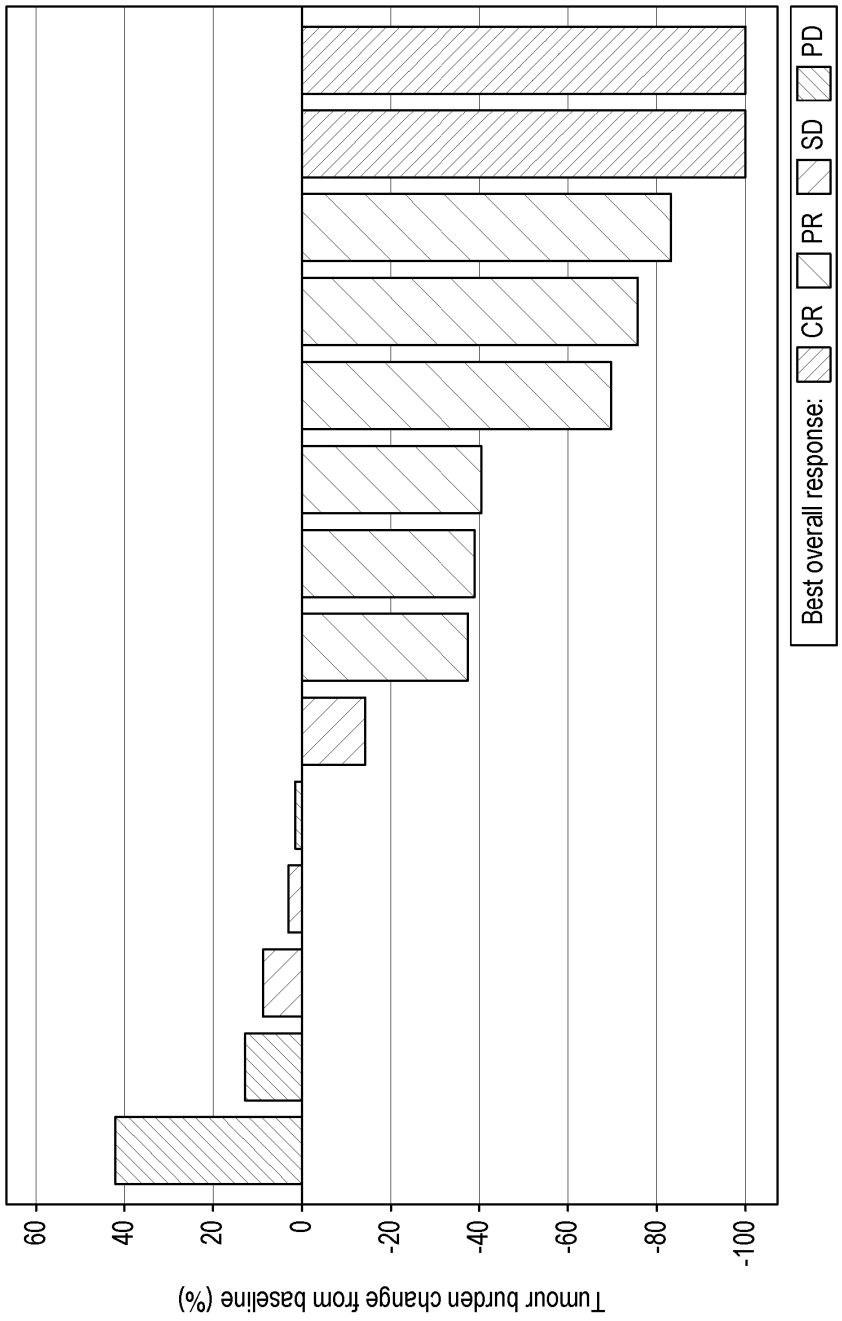
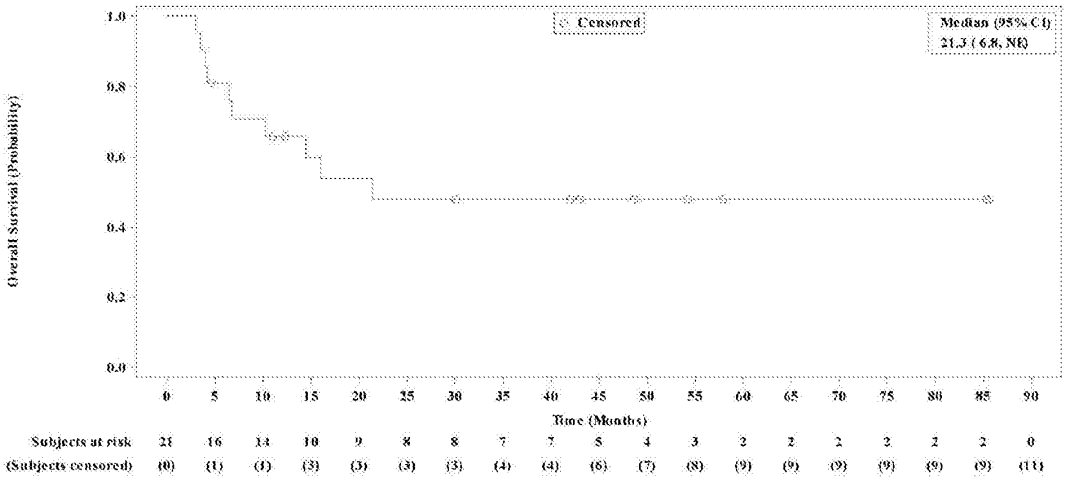
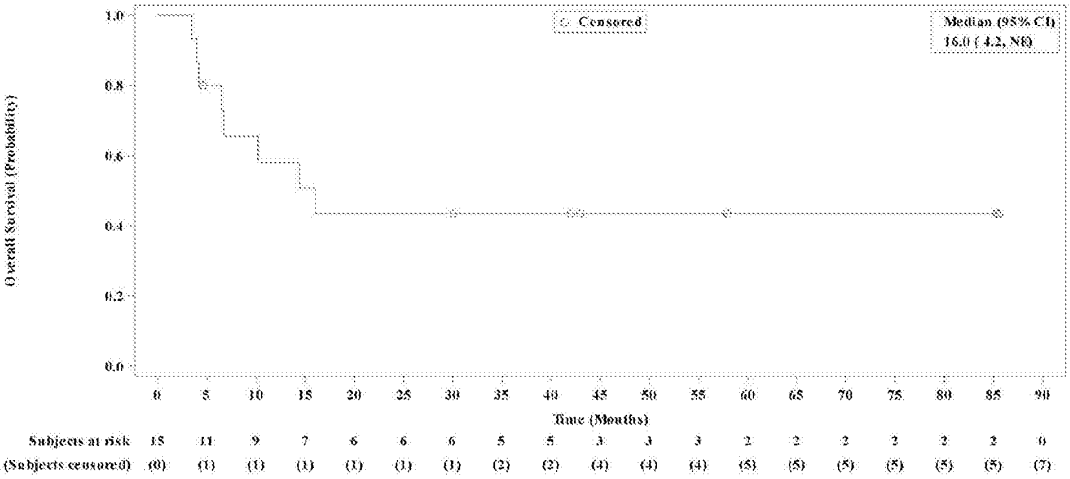

Best overall response:
CR
PR
SD
PD
60
40
20
0
-20
-40
-60
-80
-100
Tumour burden change from baseline (%)

FIG. 74

A.



B.



C.

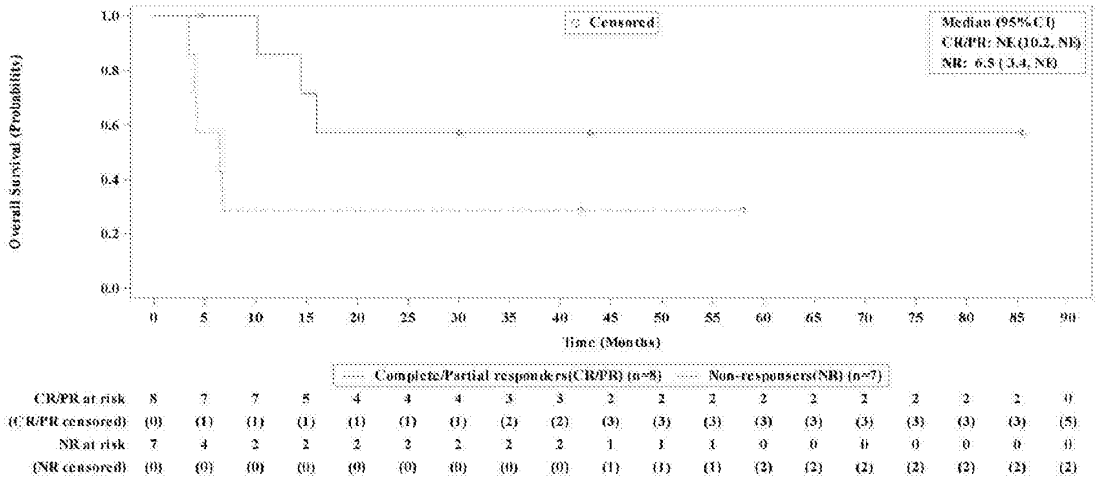


FIG. 75A-75C

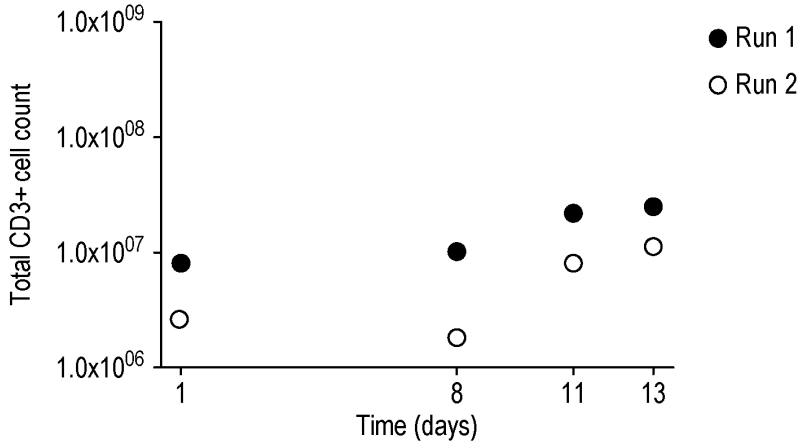


FIG. 76A

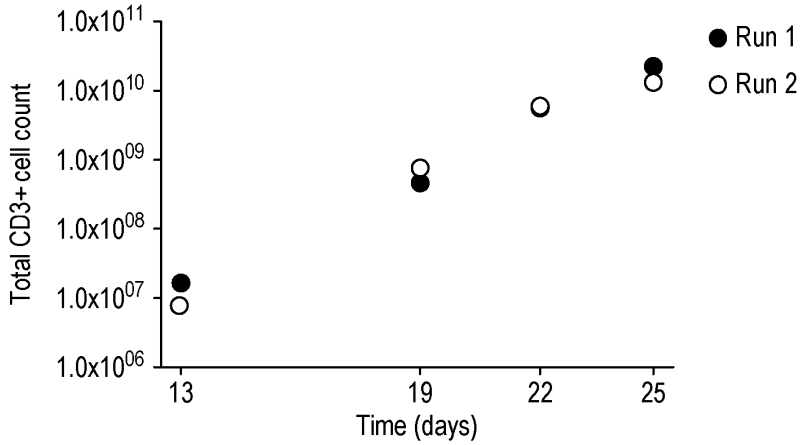


FIG. 76B

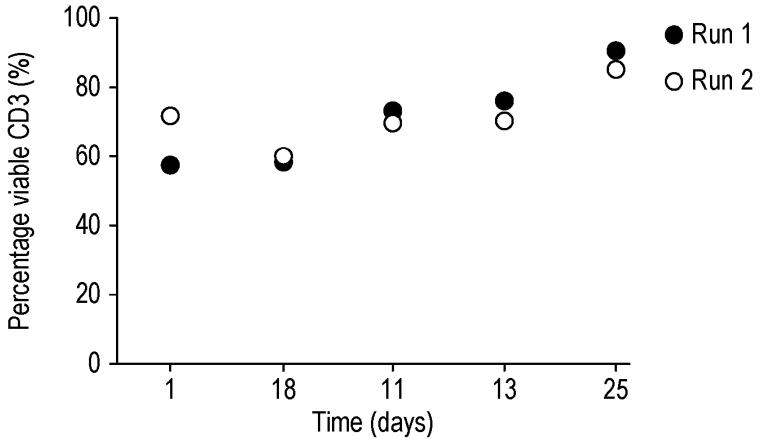


FIG. 76C