Figure 1

Dependence of Cytotoxic Potency on huMov19-sulfo-SPDB-DM4 MAR

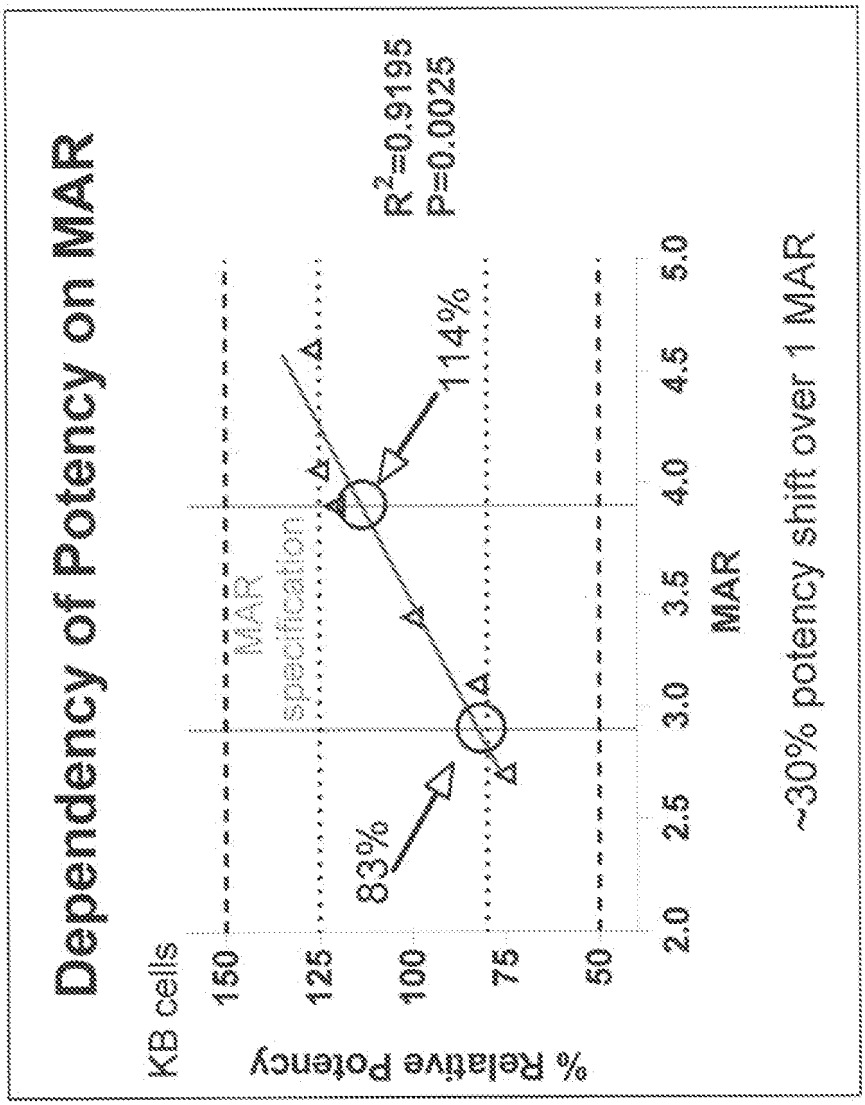


Figure 2

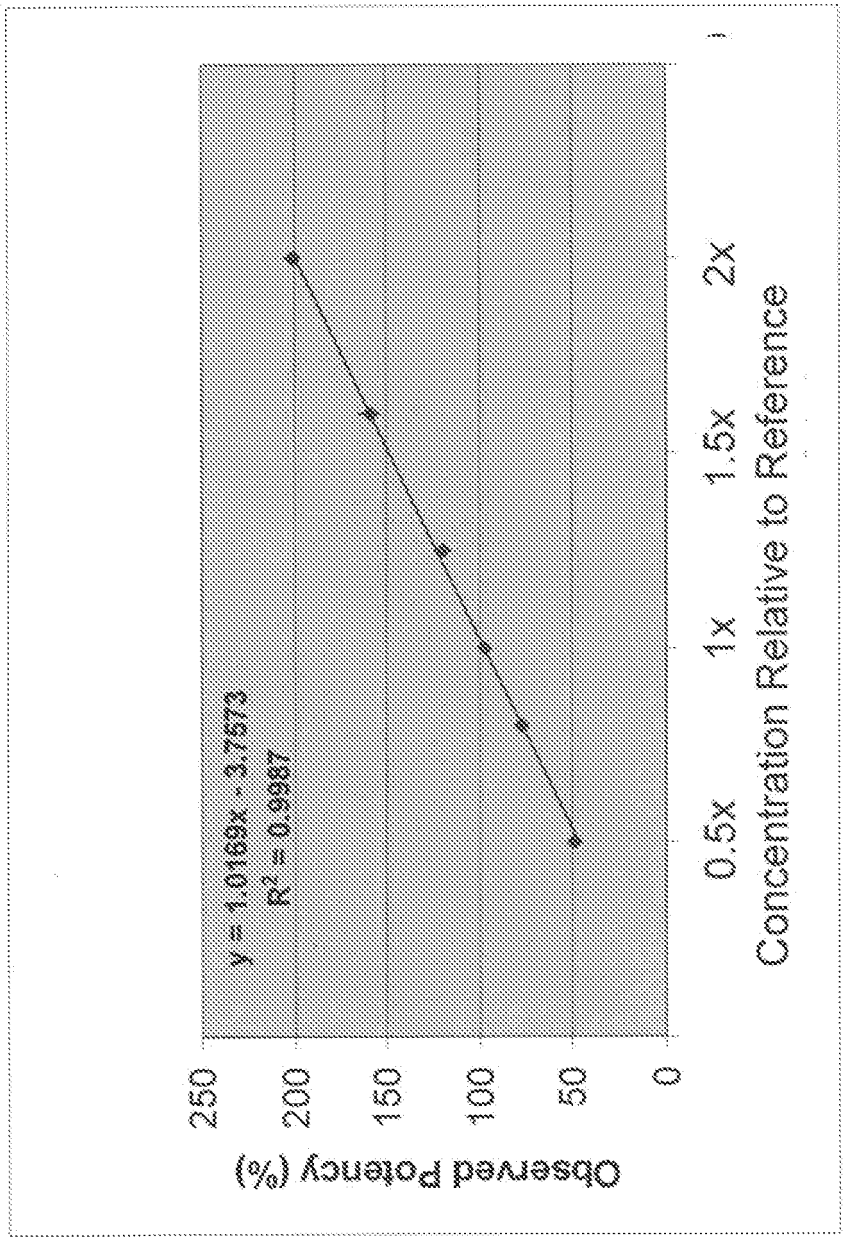
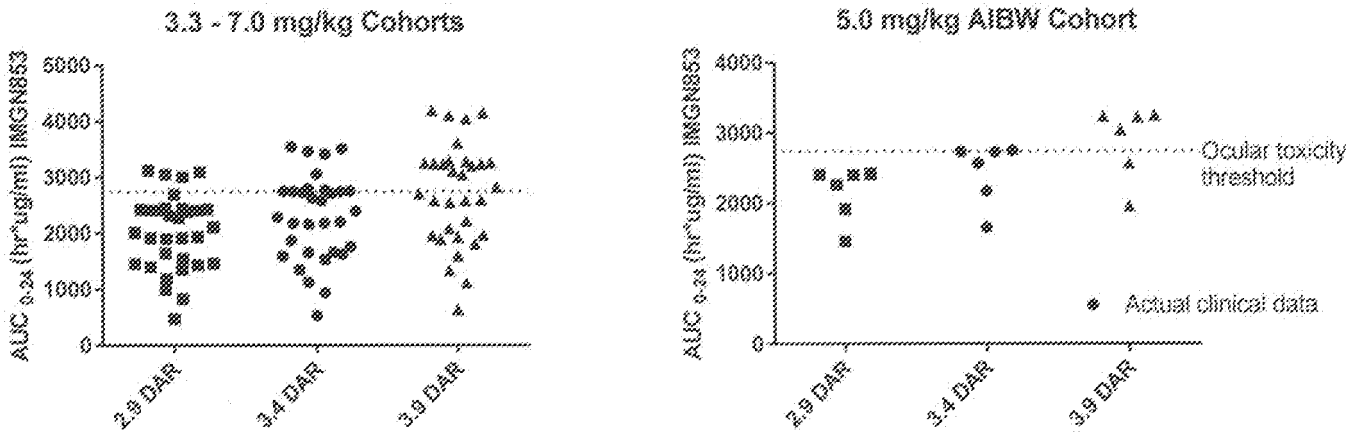

Dependence of Cytotoxic Potency on huMov19-sulfo-SPDB-DM4 concentration
Observed Potency (%)
250
200
150
100
50
0
y = 1.0169x - 3.7573
R² = 0.9987
0.5x
1x
1.5x
2x
Concentration Relative to Reference

Figure 3

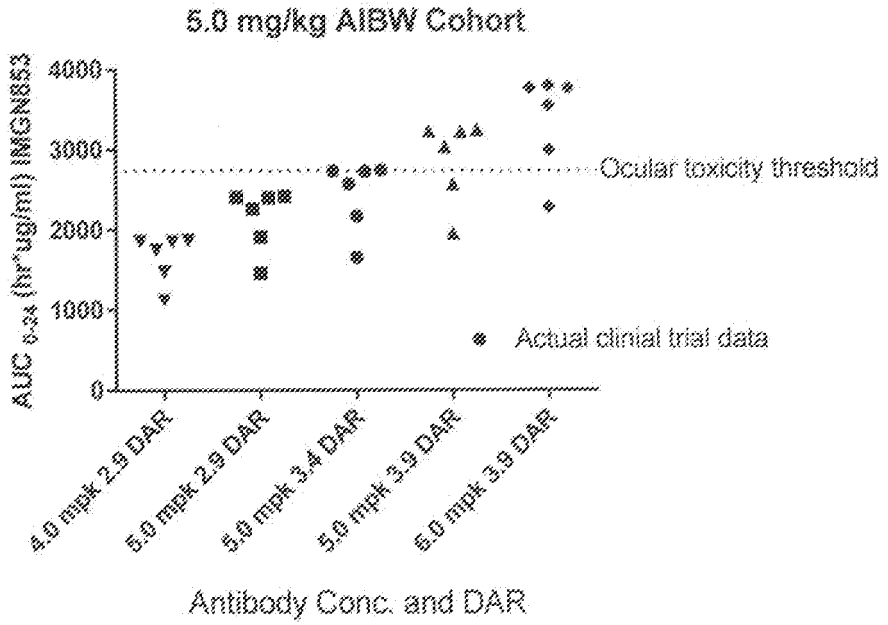
Impact of DAR on Eye Toxicity



	Percent of Patients Above Ocular Tox Threshold		
Patient Population	DAR 2.9	DAR 3.4	DAR 3.9
All 3.3 – 7 mg/kg	13%	32%	48%
5 mg/kg AIBW Only	0%	14%	57%

Figure 4

Impact of DAR and Concentration on Eye Toxicity



	Percent of Patients Above Ocular Tox Threshold				
Antibody Concentration	4 mpk	5 mpk	5 mpk	5 mpk	6 mpk
DAR	2.9	2.9	3.4	3.9	3.9
Percent Above Threshold	0%	0%	14%	57%	83%

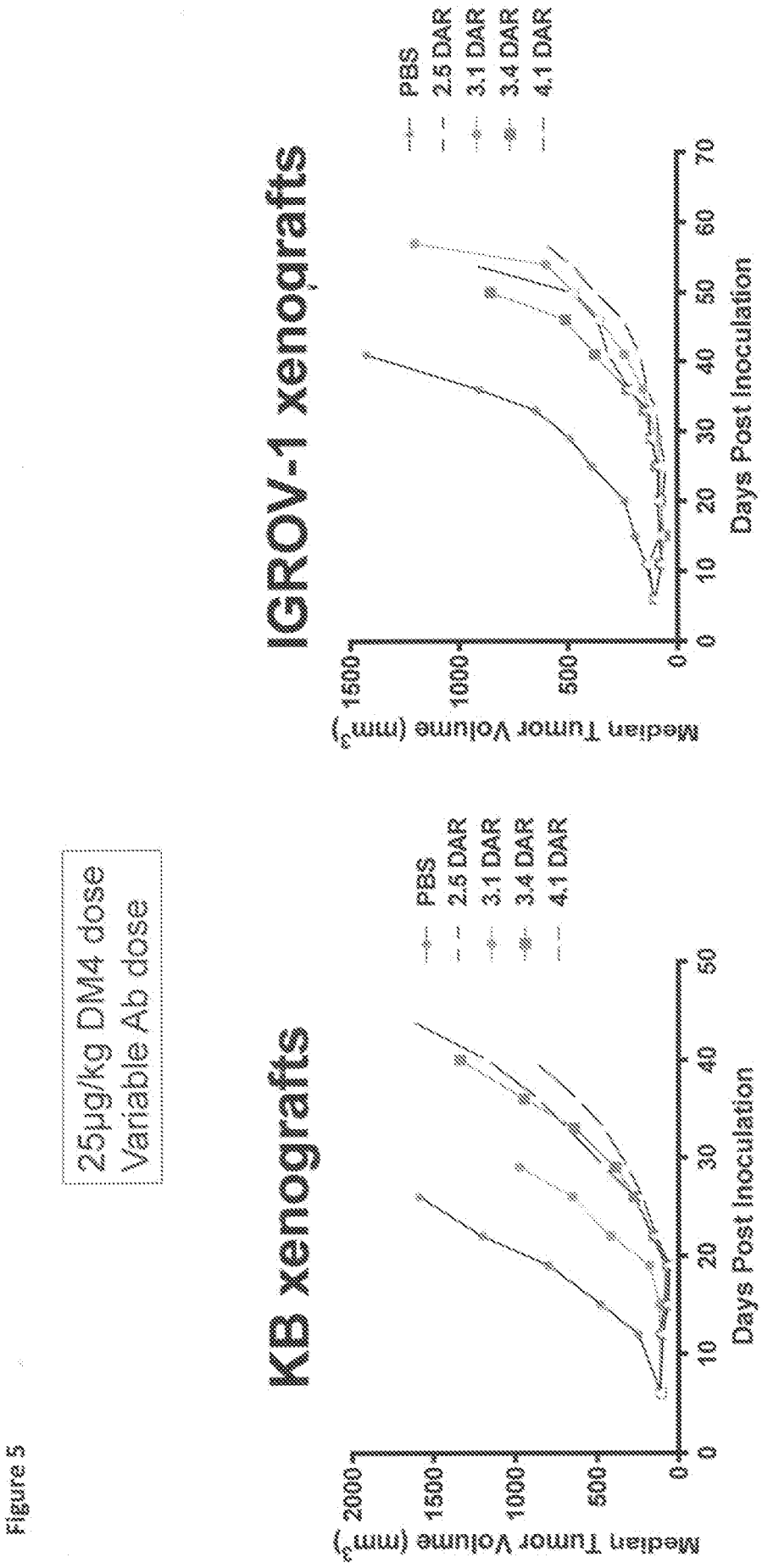

25μg/kg DM4 dose
Variable Ab dose
KB xenografts
IGROV-1 xenografts
PBS
2.5 DAR
3.1 DAR
3.4 DAR
4.1 DAR
Median Tumor Volume (mm³)
Days Post Inoculation
0
500
1000
1500
2000
10
20
30
40
50
60
70

Figure 5

Figure 6

Impact of DAR on MTD of huMov19-sulfo-SPDB-DM4

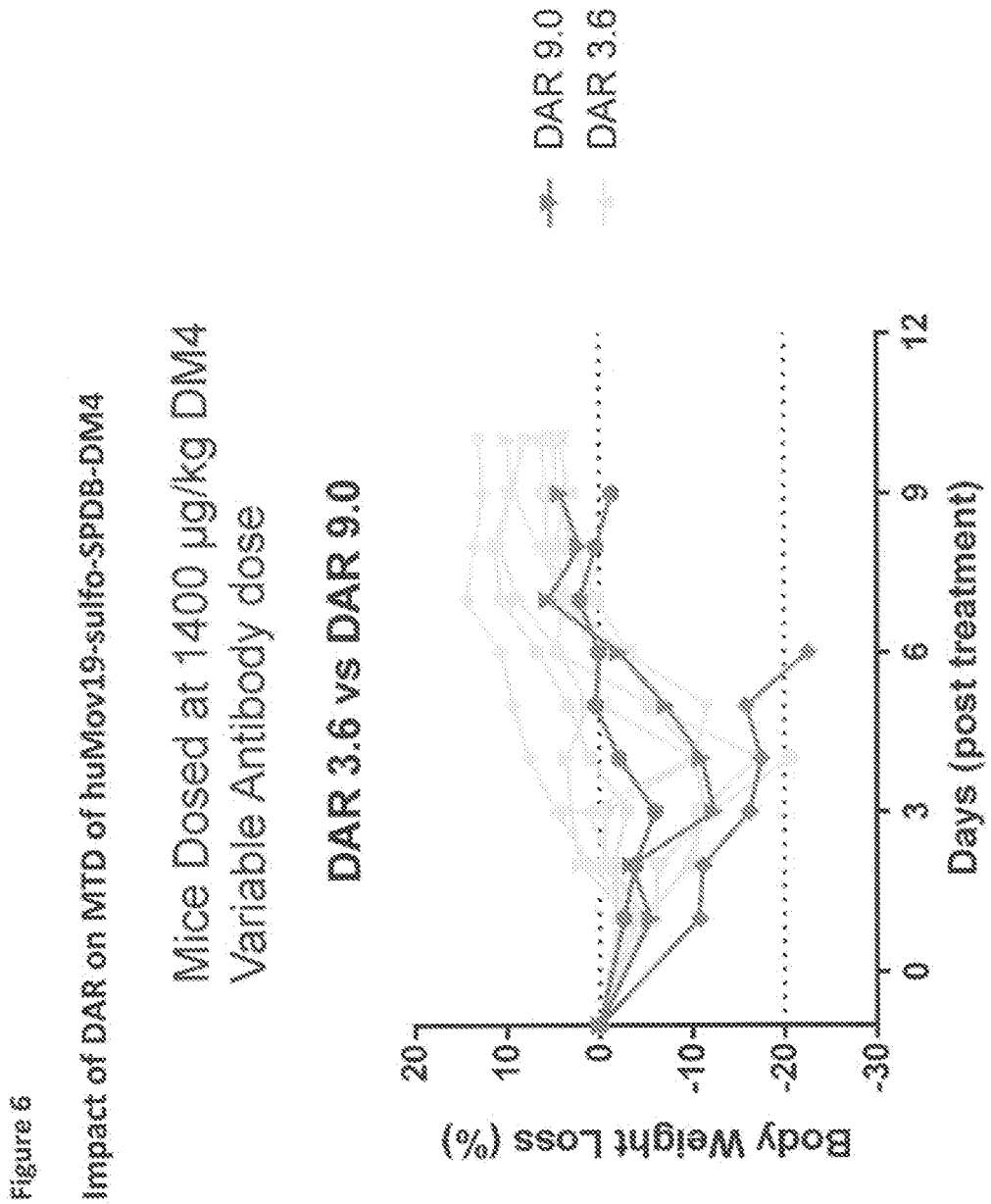
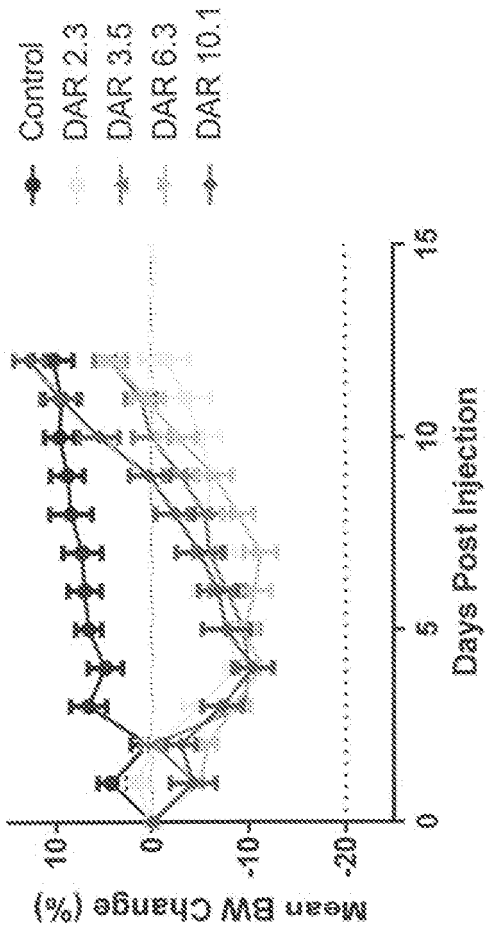


Figure 7

Impact of DAR on toxicity of huEGFR-7R-MCC-DM1



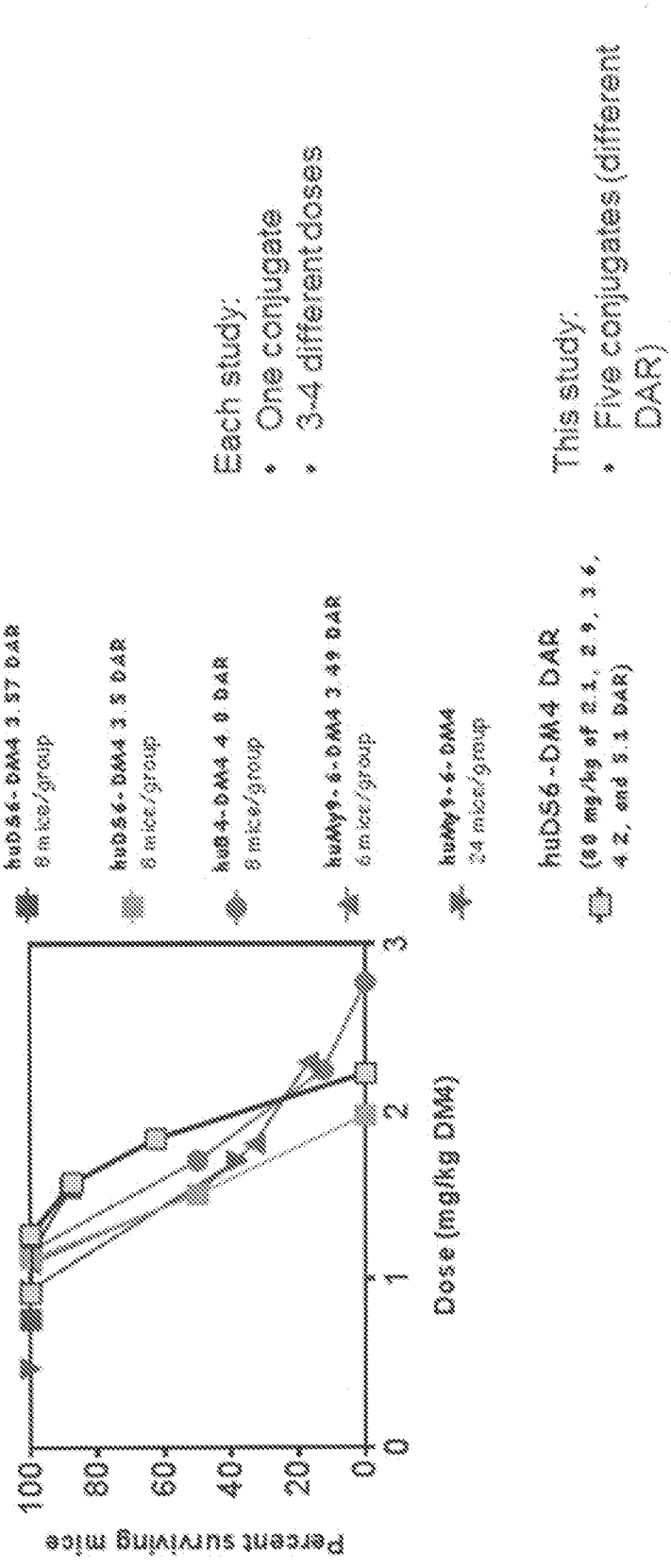

Each study:
• One conjugate
• 3-4 different doses
This study:
• Five conjugates (different DAR)
• 80 mg/kg Ab dose
huD56-DM4 3.57 DAR
8 mice/group
huD56-DM4 3.3 DAR
8 mice/group
huB4-DM4 4.0 DAR
8 mice/group
huMy9-6-DM4 3.49 DAR
6 mice/group
huMy9-6-DM4
24 mice/group
huDS6-DM4 DAR
(80 mg/kg of 2.1, 2.9, 3.6, 4.2, and 5.1 DAR)
Percent surviving mice
100
80
60
40
20
0
0
1
2
3
Dose (mg/kg DM4)

Figure 8

Figure 9A: Advantage of preparing an ADC composition based on DM4 concentration

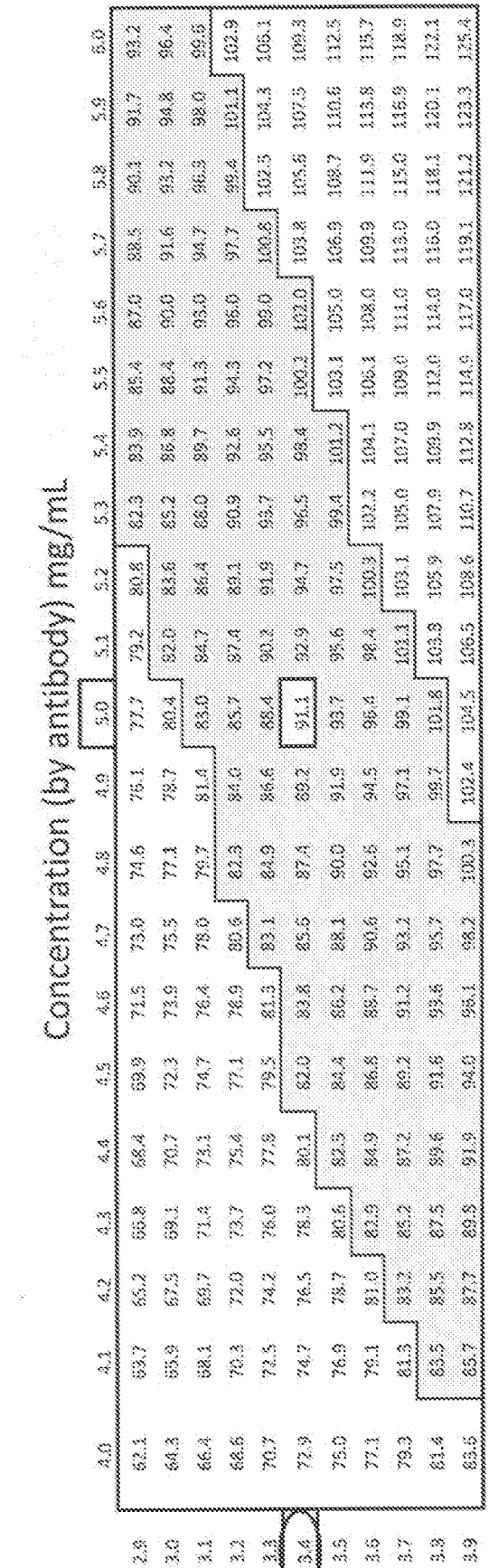


Figure 9B: Antibody concentration specification fails at the high-low extremes

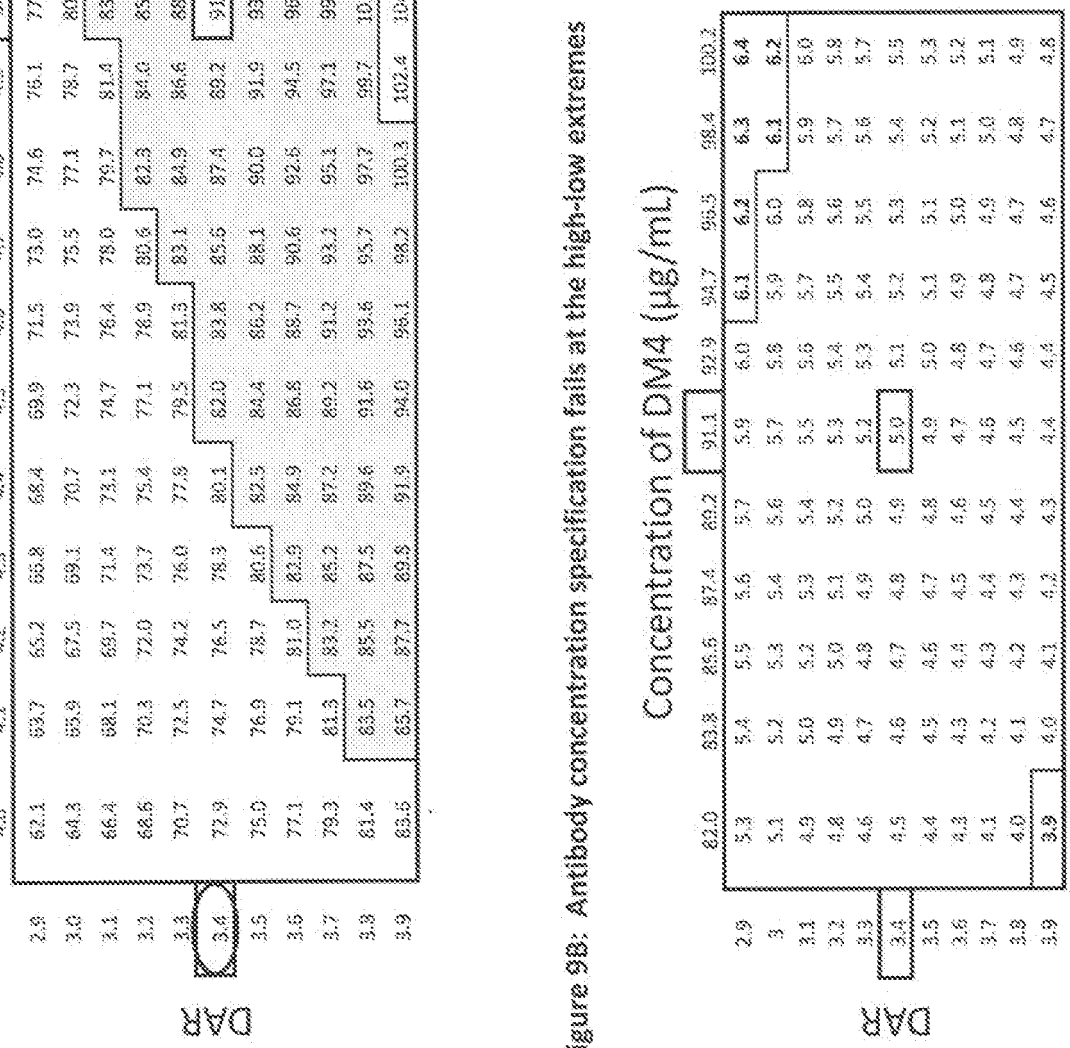
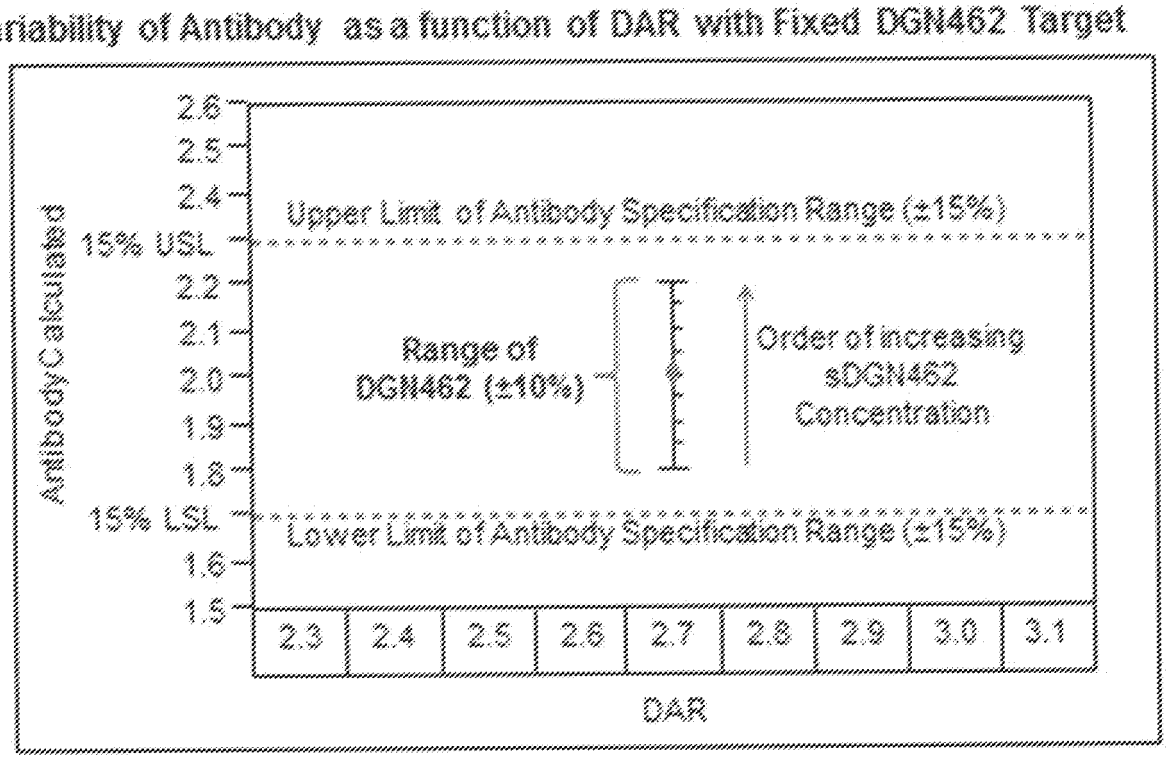


Figure 10A Effect of Preparing an ADC composition by Fixed DGN462 on Antibody Concentration



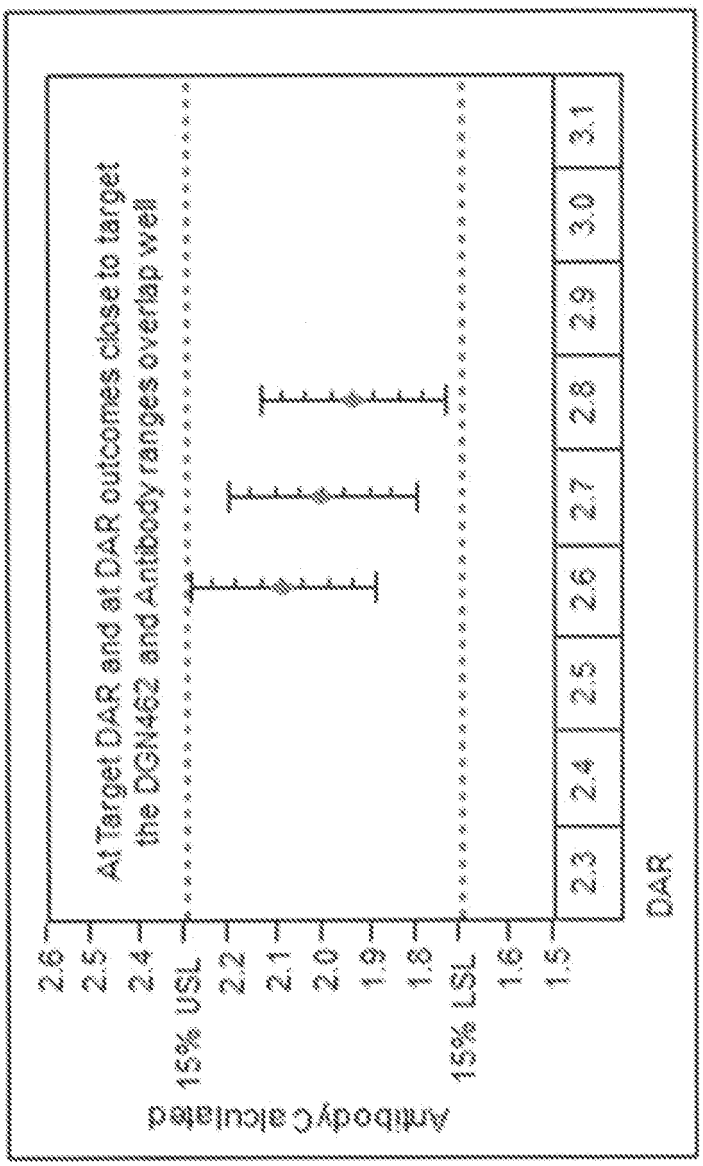

Variability of Antibody as a function of DAR with Fixed DGN462 Target
At Target DAR and at DAR outcomes close to target the DGN462 and Antibody ranges overlap well
Antibody Calculated
2.6
2.5
2.4
15% USL
2.2
2.1
2.0
1.9
1.8
15% LSL
1.6
1.5
2.3
2.4
2.5
2.6
2.7
2.8
2.9
3.0
3.1
DAR

Figure 10B

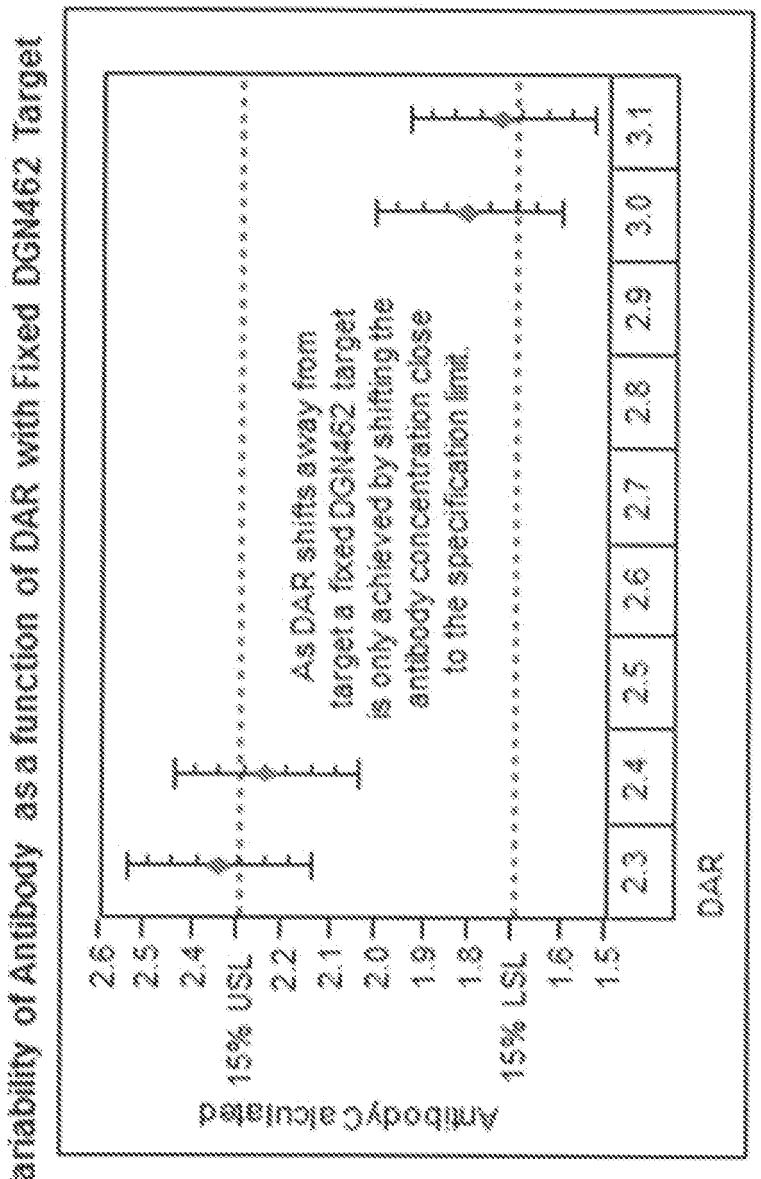

Variability of Antibody as a function of DAR with Fixed DGN462 Target
Antibody calculated
2.6
2.5
2.4
15% USL
2.2
2.1
2.0
1.9
1.8
15% LSL
1.6
1.5
As DAR shifts away from target a fixed DGN462 target is only achieved by shifting the antibody concentration close to the specification limit.
2.3
2.4
2.5
2.6
2.7
2.8
2.9
3.0
3.1
DAR

Figure 10C

Figure 11A

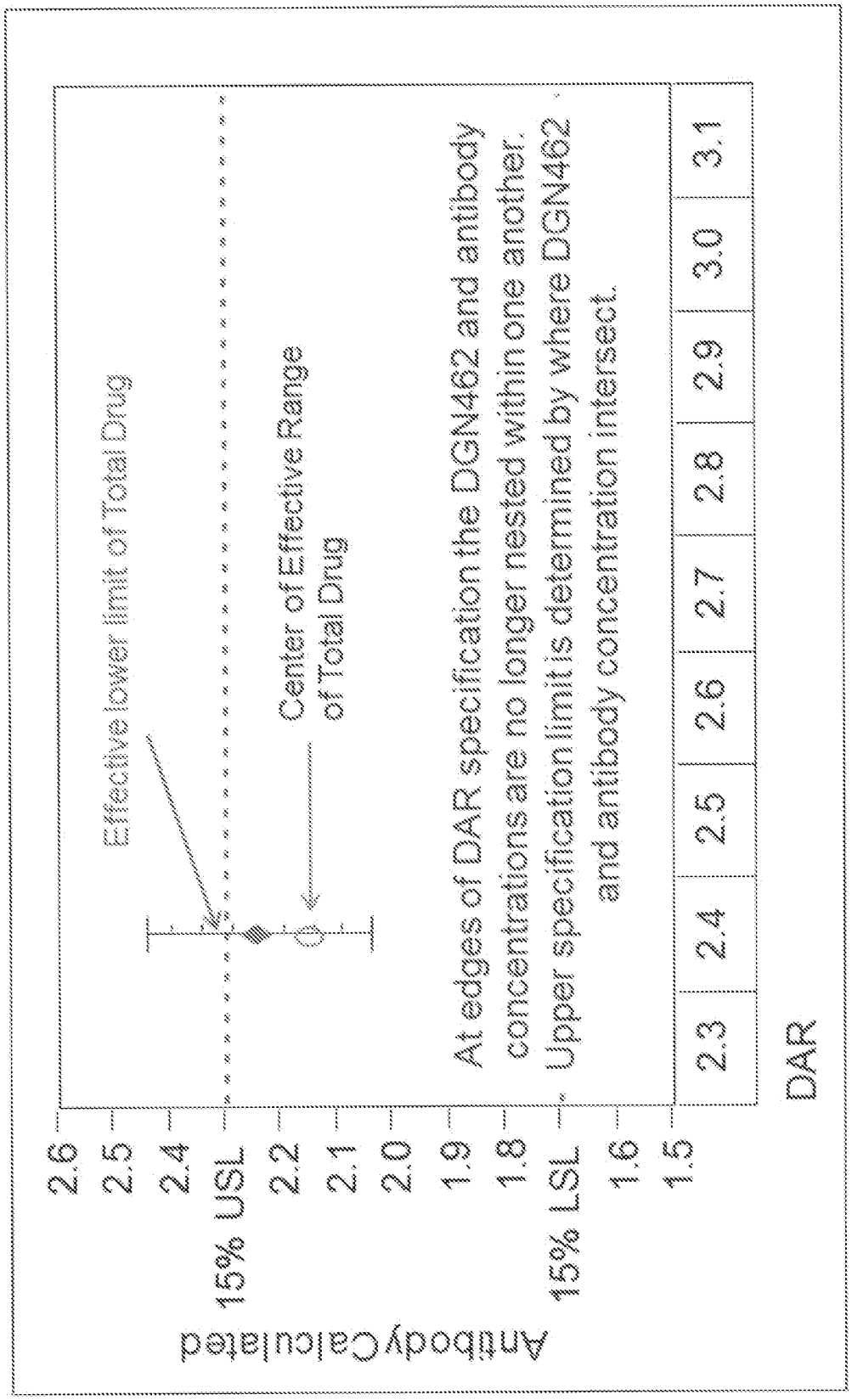
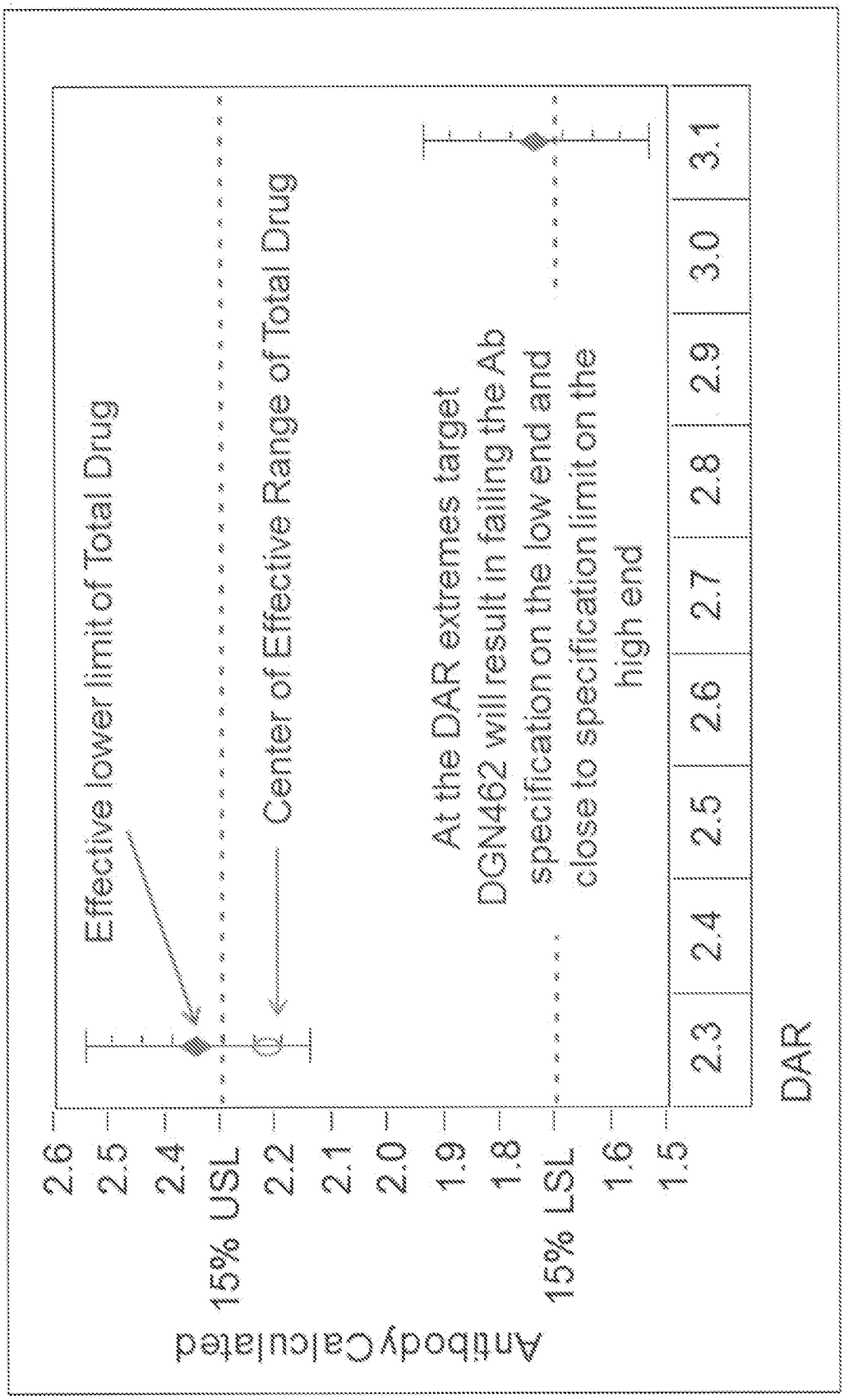

Variability of Antibody as a function of DAR with Fixed DGN462 Target
Antibody Calculated
2.6
2.5
2.4
15% USL
2.2
2.1
2.0
1.9
1.8
15% LSL
1.6
1.5
Effective lower limit of Total Drug
Center of Effective Range of Total Drug
At edges of DAR specification the DGN462 and antibody concentrations are no longer nested within one another. Upper specification limit is determined by where DGN462 and antibody concentration intersect.
2.3
2.4
2.5
2.6
2.7
2.8
2.9
3.0
3.1
DAR

Figure 11B


Variability of Antibody as a function of DAR with Fixed DGN462 Target
Antibody Calculated
2.6
2.5
2.4
15% USL
2.2
2.1
2.0
1.9
1.8
15% LSL
1.6
1.5
Effective lower limit of Total Drug
Center of Effective Range of Total Drug
At the DAR extremes target
DGN462 will result in failing the Ab
specification on the low end and
close to specification limit on the
high end
2.3
2.4
2.5
2.6
2.7
2.8
2.9
3.0
3.1
DAR

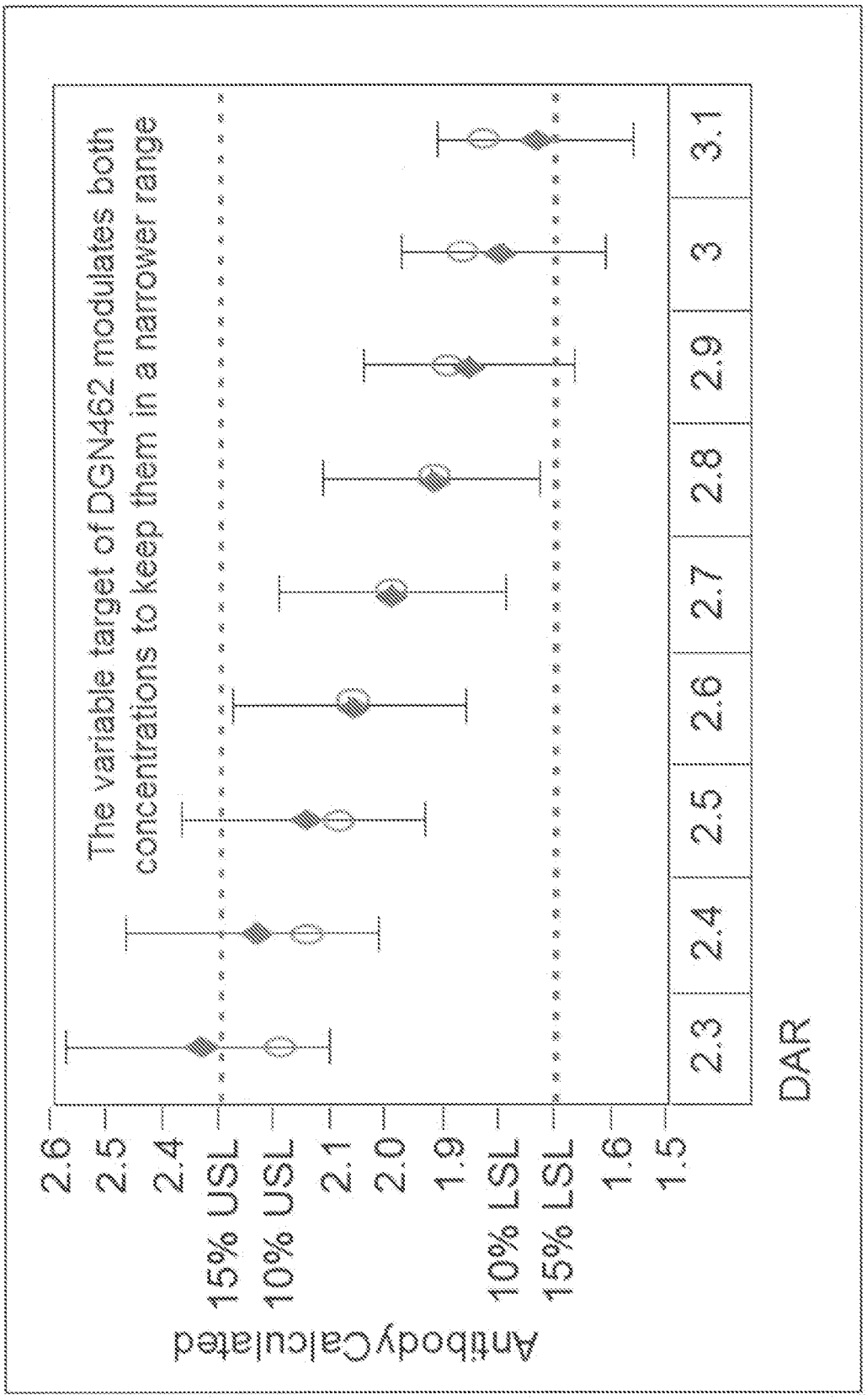

Variability Chart for Antibody Calculated
The variable target of DGN462 modulates both concentrations to keep them in a narrower range
AntibodyCalculated
2.6
2.5
2.4
15% USL
10% USL
2.1
2.0
1.9
10% LSL
15% LSL
1.6
1.5
2.3
2.4
2.5
2.6
2.7
2.8
2.9
3
3.1
DAR

Figure 11C