Marijuana Business MJBizCon

Pre-Clinical/Clinical Approaches to Cannabis Product Development

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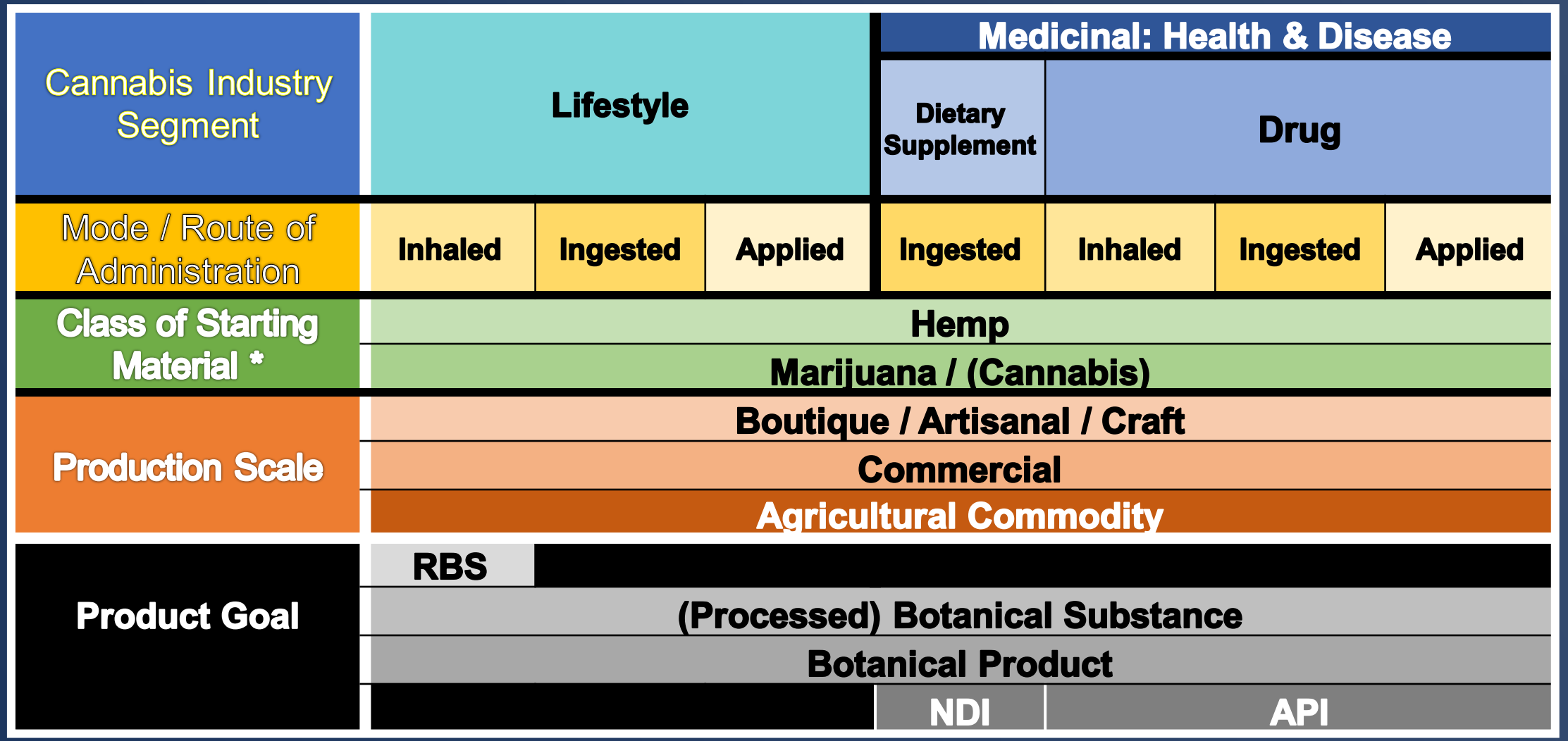
Cannabis Industry Product Matrix



* Cultivar(s) Selected ?

Preclinical Discovery

Previously, Medicinal Product Development

Product Differentiation

R&D → COMMERCIALIZATION

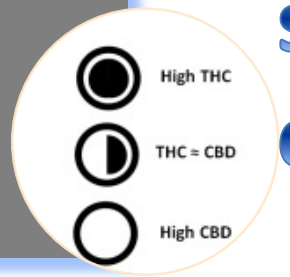
proceeded as a series of sequential steps . . .

Formulation Development:

Clinical Studies

Observational Study - The Dosing Project

Product Differentiation- ChemoMark

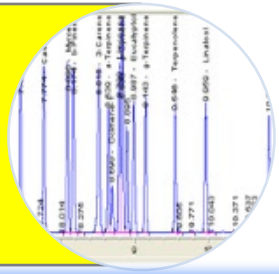


. . . But under this New Paradigm, the steps begin with clinical observation

R&D → COMMERCIALIZATION

and products are commercialized sooner

Formulation Development:



Clinical Studies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Emerald Conf
CRO
Phase IV
CESC
Collaboration
BioMarker Discovery
Quality
Form Dev
Fill / Finish

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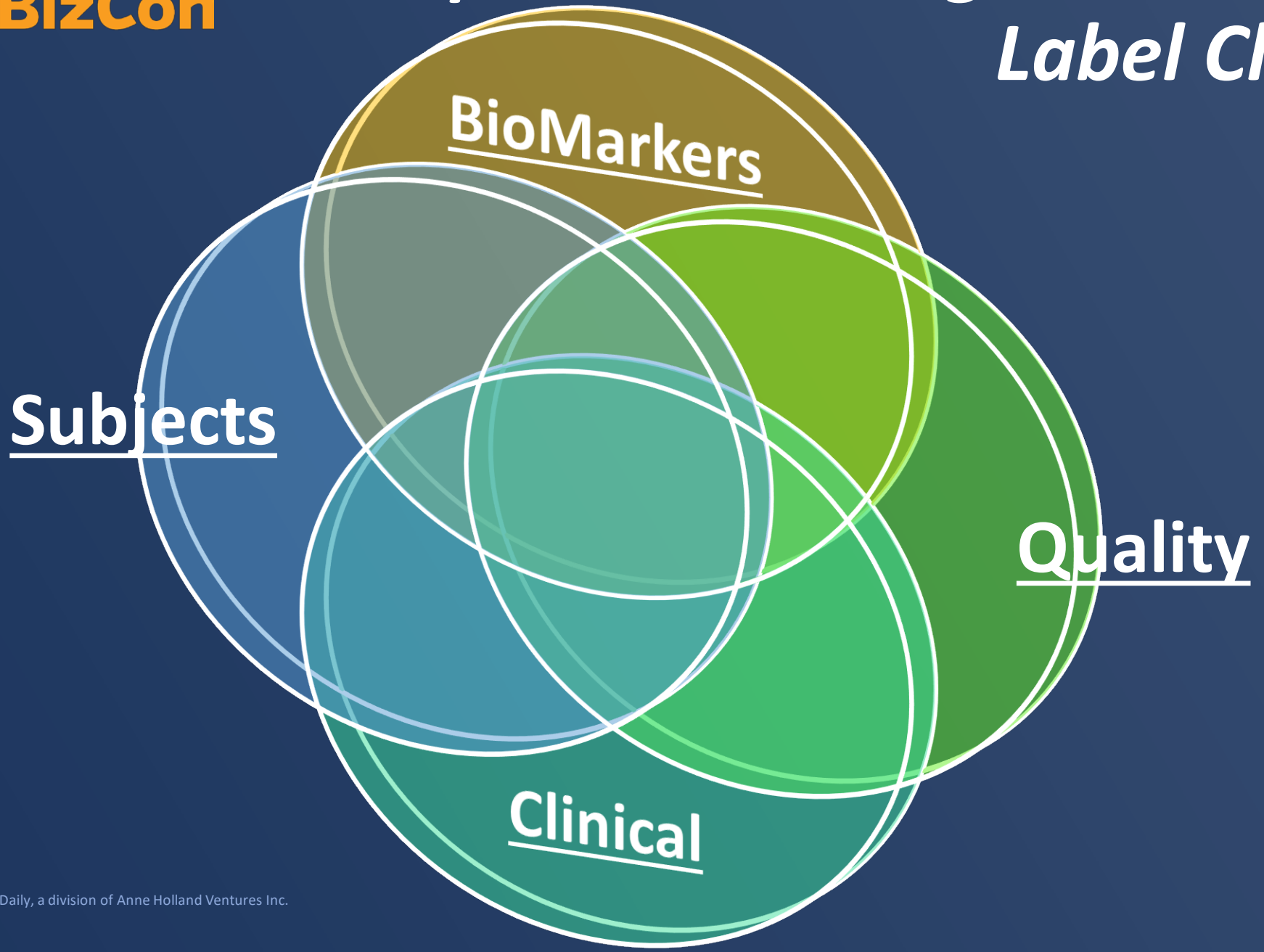
4 Compass Points Together Enable Label Claims



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Elements Enabling Successful Label Claims

✓ Quality

- Risk / Gap / SWOT Analysis
- QRM Driven Process Dev
- QMS

✓ Subjects

- Demographics
  - Personal
    - Genetics
  - Social

- BioMarkers
  - Responses
  - EndoCannabinoid System (ECS) Tone

✓ Clinical

- Outcomes (Dose & Interactions)
- Adverse Events (AEs)

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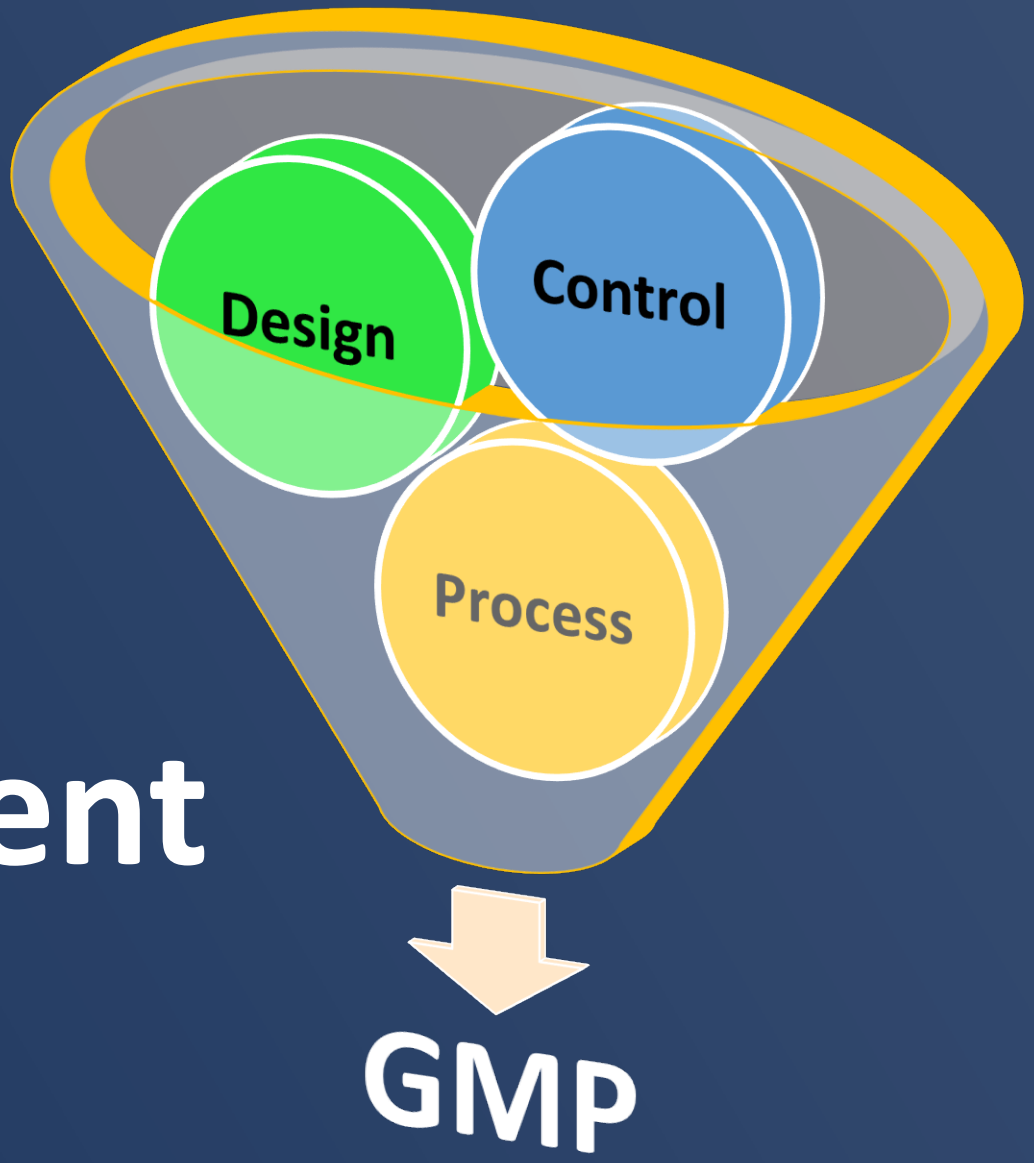
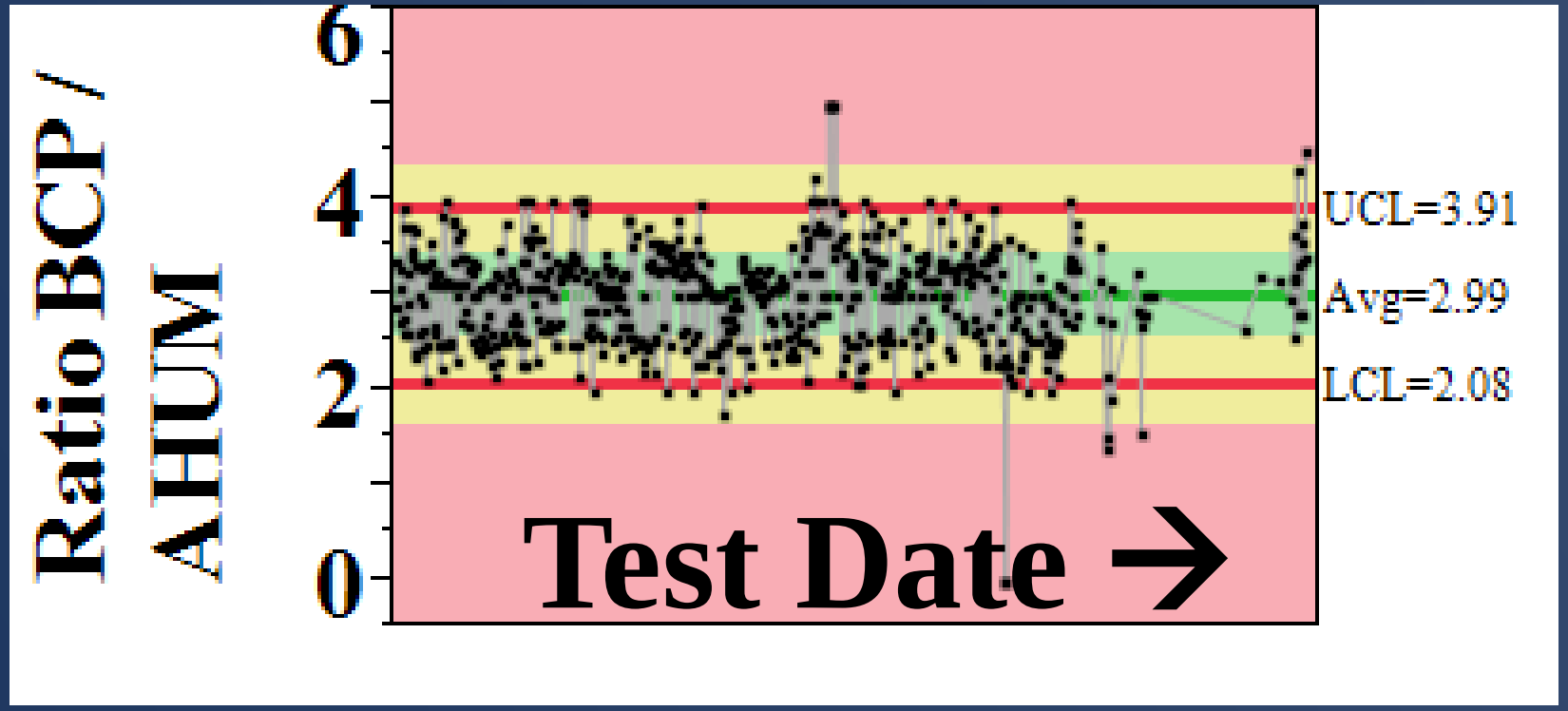
Quality Management System



Quality: Control (Charts)

- ✓ Identify Dependent Variables (Outcomes) that can be optimized and controlled



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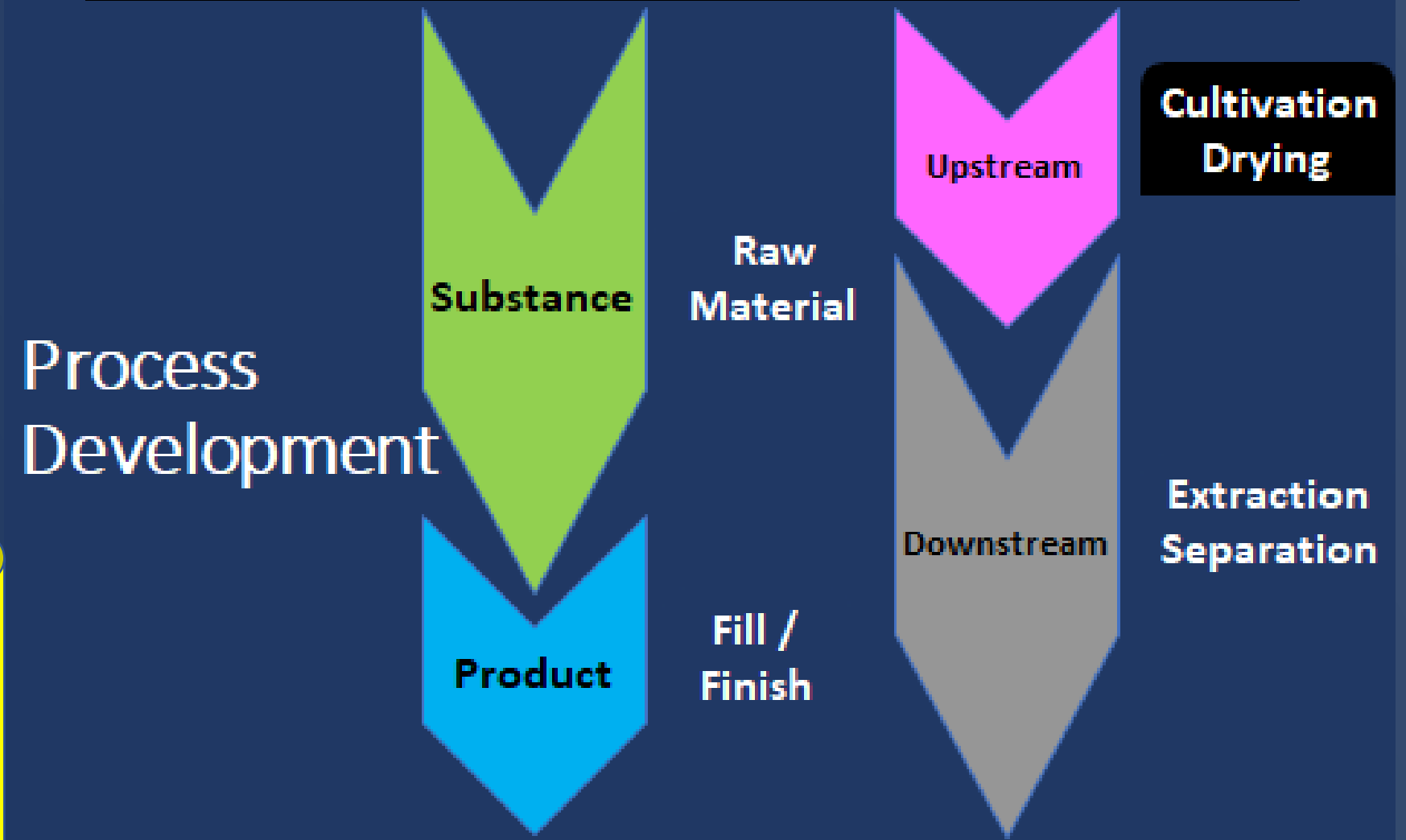
Quality: Management System



Process Development

Gantt Chart

Desired Outcome: 3 Consistent Batches

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Quality: By Design (of Experiments)

Quality by Design

Design of Experiments

The Context:

- **Cannabis industry needs robust sampling guidance**
- **Use an *ad-hoc* Design of Experiments (DOE) Approach**
- **Analyze potency variance to derive sampling size guidelines from Power Analysis**

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Factors To Test:

Strains: Tangie, OG, Ogre, & Candyland

- Sampling Variance: within plant vs between plants
- Bed Location: inner vs border
- Branch Position: L, M, C
- Source Depth: B, M, T

Strain: OG

- Plot Location: GH vs Outdoor

Strain: OG & Plant

- Trim: Y / N

- 4 X 125 sq ft beds
- ~ 42 plants used in DOE & Analysis
  - half of each bed

Candyland	border	Outdoor	C	M	N
Candyland	border	Outdoor	L	B	N
Candyland	border	Outdoor	M	T	N
Candyland	inside	Outdoor	C	B	N
Candyland	inside	Outdoor	L	T	N
Candyland	inside	Outdoor	M	M	N
Candyland	Plant	Outdoor	C	B	N
Candyland	Plant	Outdoor	C	M	N
Candyland	Plant	Outdoor	L	B	N
Candyland	Plant	Outdoor	L	T	N
Candyland	Plant	Outdoor	M	M	N
Candyland	Plant	Outdoor	M	T	N
OG	border	GH	C	B	N
OG	border	GH	L	T	N
OG	border	GH	M	M	N
OG	border	Outdoor	C	B	N
OG	border	Outdoor	L	T	N
OG	border	Outdoor	M	M	N
OG	inside	GH	C	T	N
OG	inside	GH	L	M	N
OG	inside	GH	M	B	N
OG	inside	Outdoor	C	T	N
OG	inside	Outdoor	L	M	N
OG	inside	Outdoor	M	B	N
OG	Plant	GH	C	B	Y
OG	Plant	GH	C	T	Y
OG	Plant	GH	L	M	Y
OG	Plant	GH	L	T	Y
OG	Plant	GH	M	B	Y
OG	Plant	GH	M	M	Y
OG	Plant	GH	C	B	N
OG	Plant	GH	C	T	N
OG	Plant	GH	L	M	N
OG	Plant	GH	L	T	N
OG	Plant	GH	M	B	N
OG	Plant	GH	M	M	N

37	225	OG	Plant	Outdoor	C	B	Y
38	226	OG	Plant	Outdoor	C	T	Y
39	227	OG	Plant	Outdoor	L	M	Y
40	228	OG	Plant	Outdoor	L	T	Y
41	229	OG	Plant	Outdoor	M	B	Y
42	230	OG	Plant	Outdoor	M	M	Y
43	231	OG	Plant	Outdoor	C	B	N
44	232	OG	Plant	Outdoor	C	T	N
45	233	OG	Plant	Outdoor	L	M	N
46	234	OG	Plant	Outdoor	L	T	N
47	235	OG	Plant	Outdoor	M	B	N
48	236	OG	Plant	Outdoor	M	M	N
49	401	Tangie	border	Outdoor	C	T	N
50	402	Tangie	border	Outdoor	L	M	N
51	403	Tangie	border	Outdoor	M	B	N
52	404	Tangie	inside	Outdoor	C	M	N
53	405	Tangie	inside	Outdoor	L	B	N
54	406	Tangie	inside	Outdoor	M	T	N
55	407	Tangie	Plant	Outdoor	C	M	N
56	408	Tangie	Plant	Outdoor	C	T	N
57	409	Tangie	Plant	Outdoor	L	B	N
58	410	Tangie	Plant	Outdoor	L	M	N
59	411	Tangie	Plant	Outdoor	M	B	N
60	412	Tangie	Plant	Outdoor	M	T	N
61	401	Ogre	border	Outdoor	C	M	N
62	402	Ogre	border	Outdoor	L	B	N
63	403	Ogre	border	Outdoor	M	T	N
64	404	Ogre	inside	Outdoor	C	B	N
65	405	Ogre	inside	Outdoor	L	T	N
66	406	Ogre	inside	Outdoor	M	M	N
67	407	Ogre	Plant	Outdoor	C	B	N
68	408	Ogre	Plant	Outdoor	C	M	N
69	409	Ogre	Plant	Outdoor	L	B	N
70	410	Ogre	Plant	Outdoor	L	T	N
71	411	Ogre	Plant	Outdoor	M	M	N
72	412	Ogre	Plant	Outdoor	M	T	N

Quality By Design of Experiments Provides:

I. HARVEST GUIDANCE:
- Based on CBGA as Biomarker

II. VARIANCE ANALYSIS:
- Compare with Historical Variance Trends for THCA %

III. SAMPLING PLAN:
- Flower position can be a significant factor affecting THCA % (in some strains / conditions)
- Sampling across a Sentinel Plant should be representative of sampling across the entire grow plot

Ad-hoc DOE; targeting main effects only

Quality By Design of Experiments Provides:

I. HARVEST GUIDANCE:

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II. VARIANCE ANALYSIS:

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III. SAMPLING PLAN:

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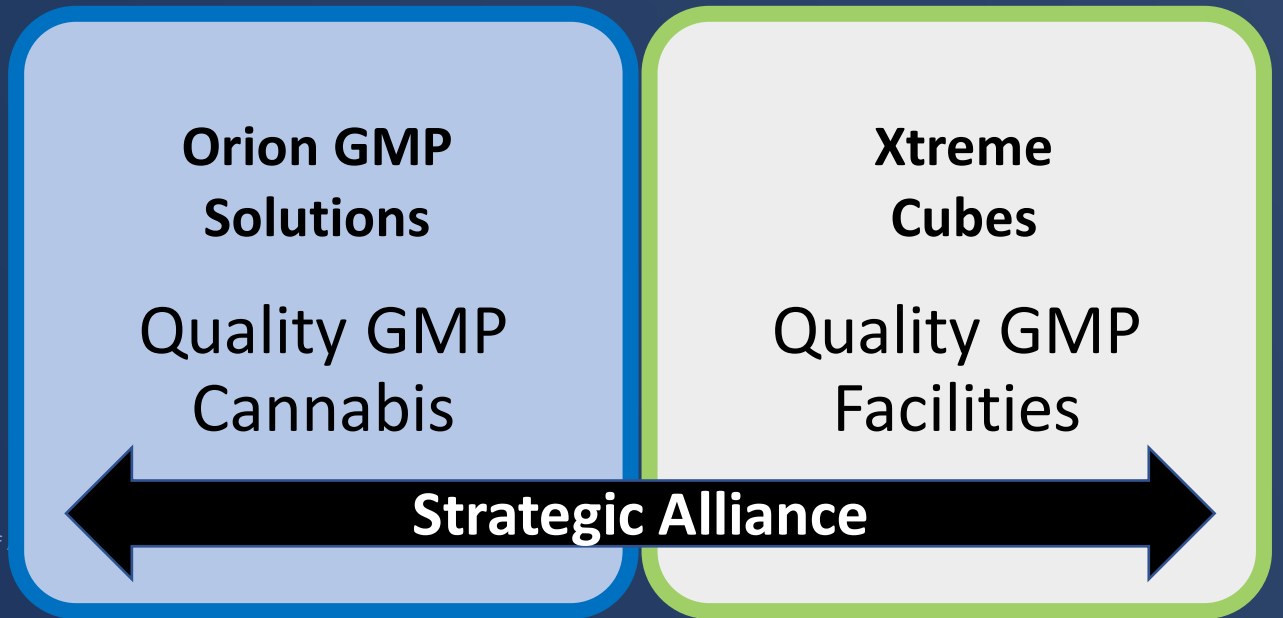
Orion / Xtreme Cubes Facilities

:

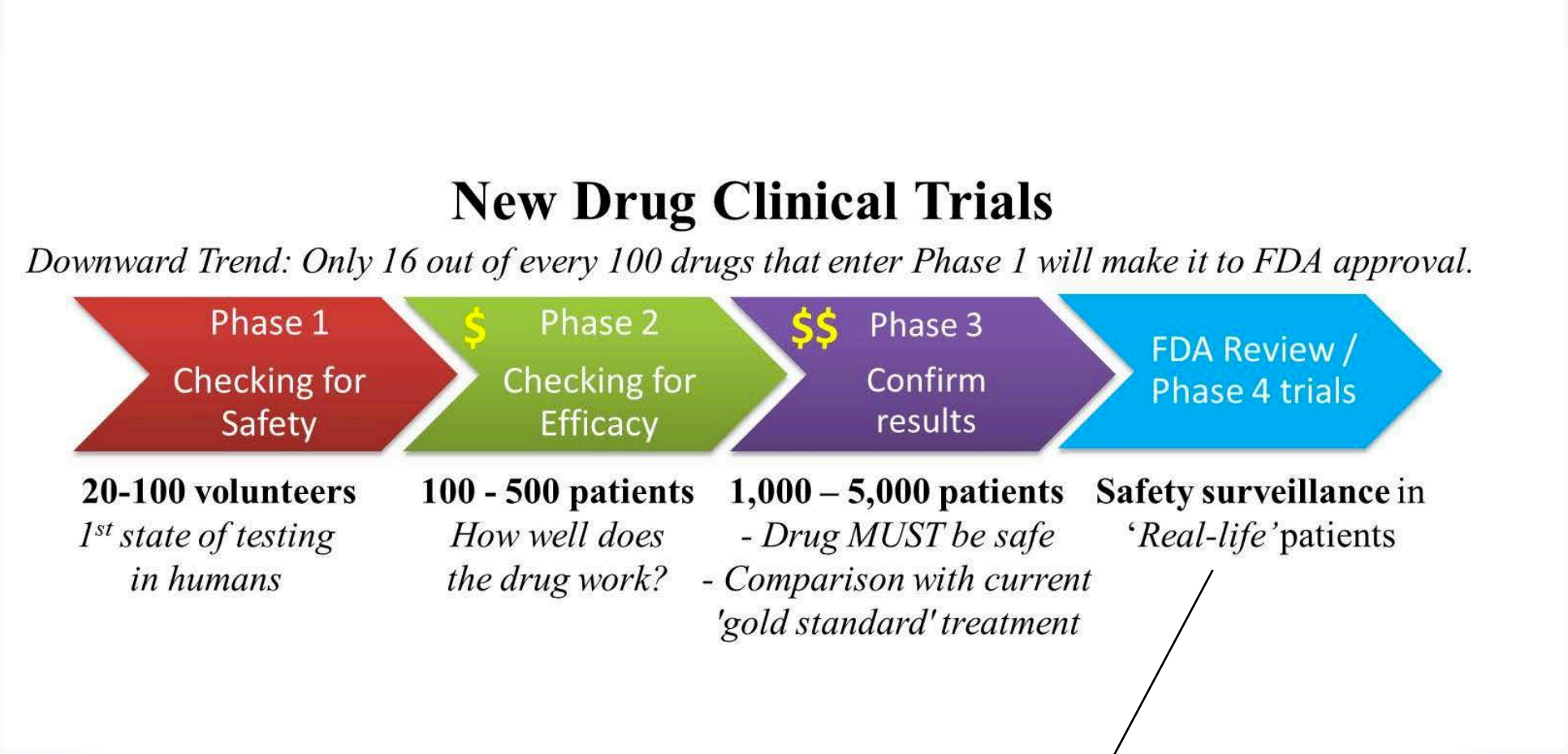
working together for turn key solutions

“Quality by Design” Narrative to describe “Turn-Key Solutions”

- ✓Risk based engineering approach to design decisions
- ✓Design of Experiments for demonstrating repeatability
- ✓Pilot GMP Enabled turn-key modular facilities



Starting at the End



THE DOSING PROJECT™

Why is The Dosing Project Needed?

To Provide Accurate Dosing Guidelines for Cannabis Use

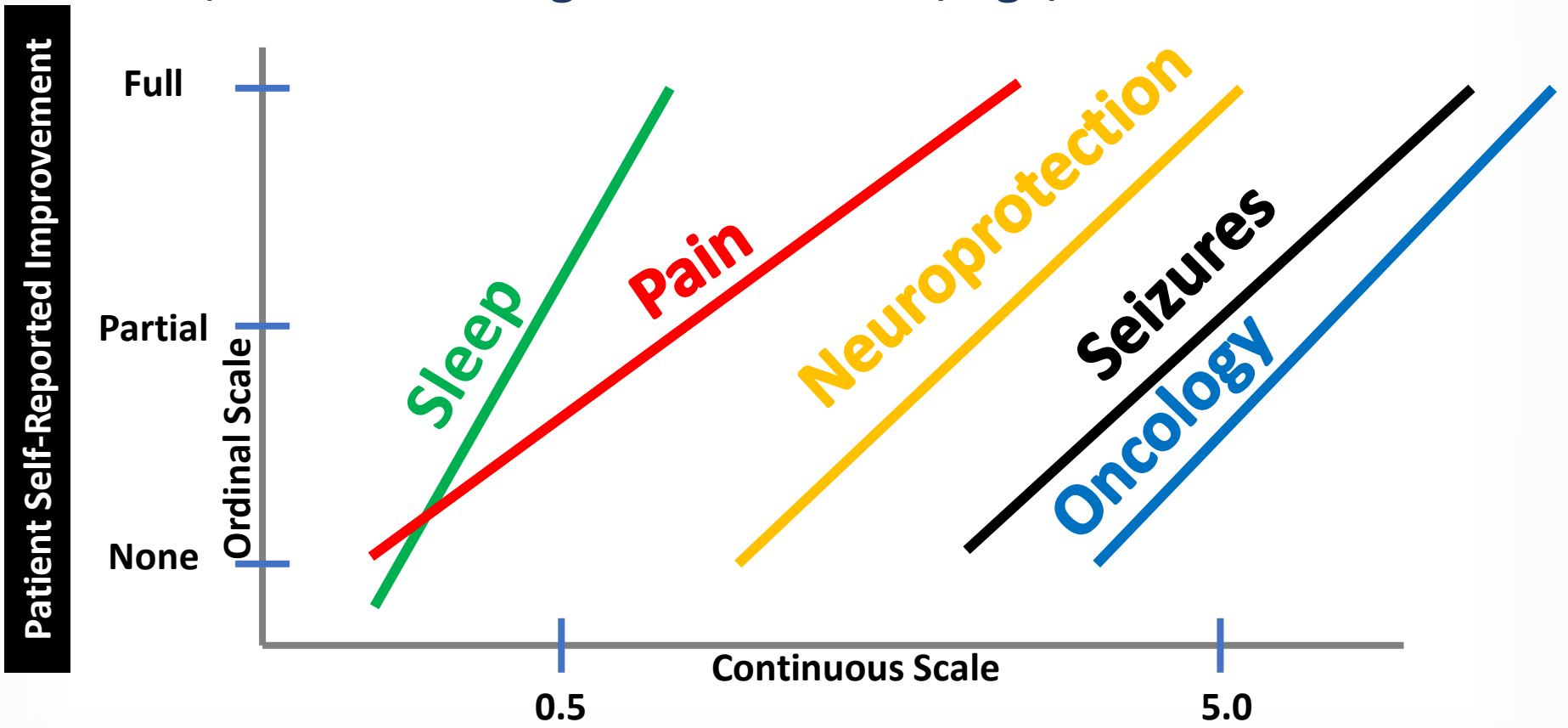
We propose a web-based, crowd-sourced observational study designed to establish dosing standards with a Phase 4 approach

Goals:

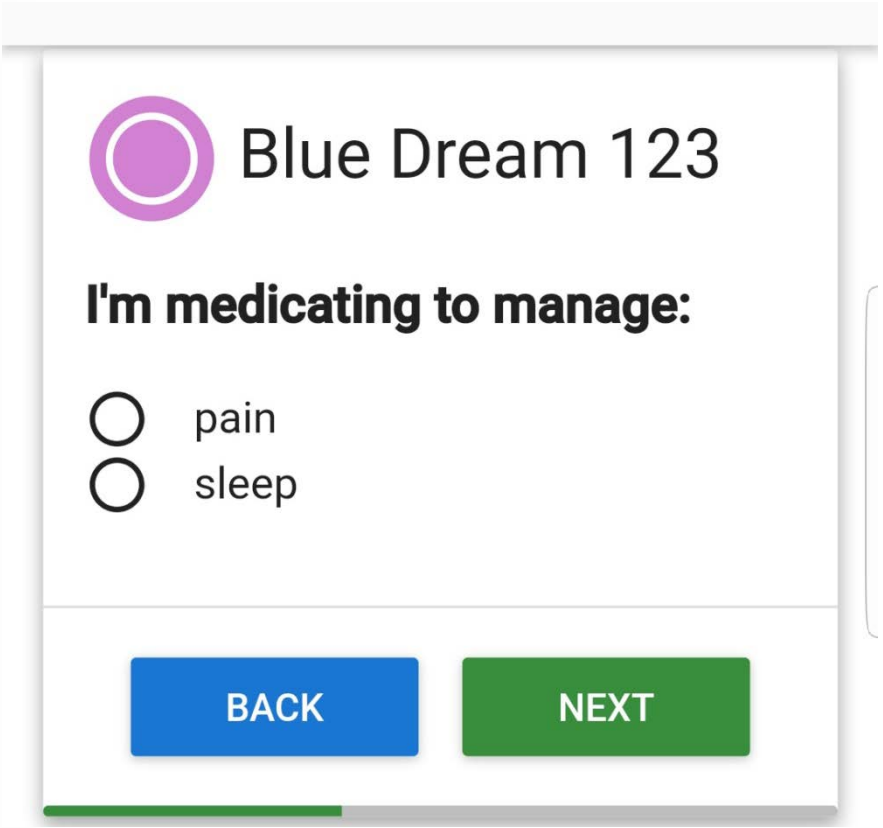
- **Determine** Effective Dose & Mode of Administration (MOA)
- **Identify** viable indications for Cannabis products
- **Survey** for Adverse Events

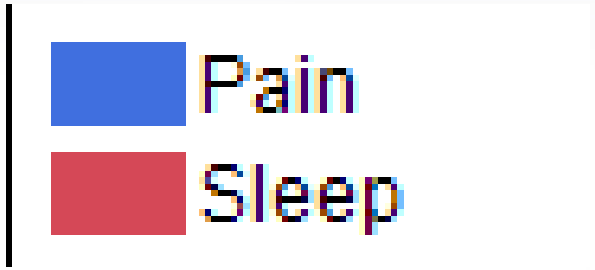
Ordinal Logistic Regression: Significant χ^2

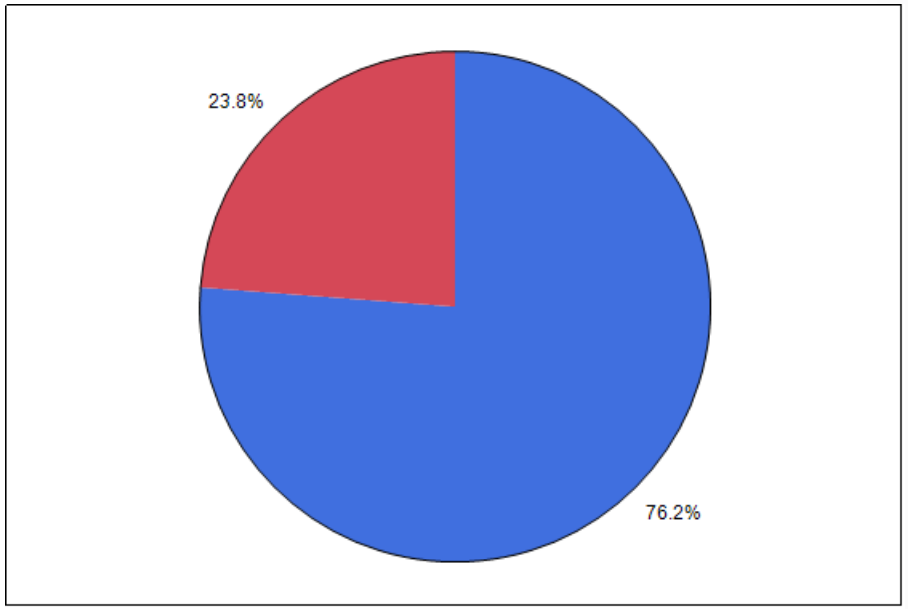
Stratified by Indication; Grouped by Cannabis product type & MOA; Additional Regressors: Gender, Age, & Genetic Profiles



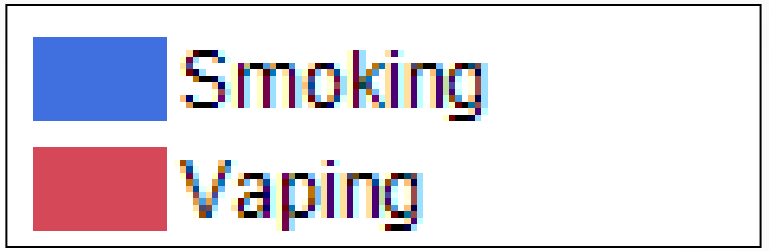
Indication

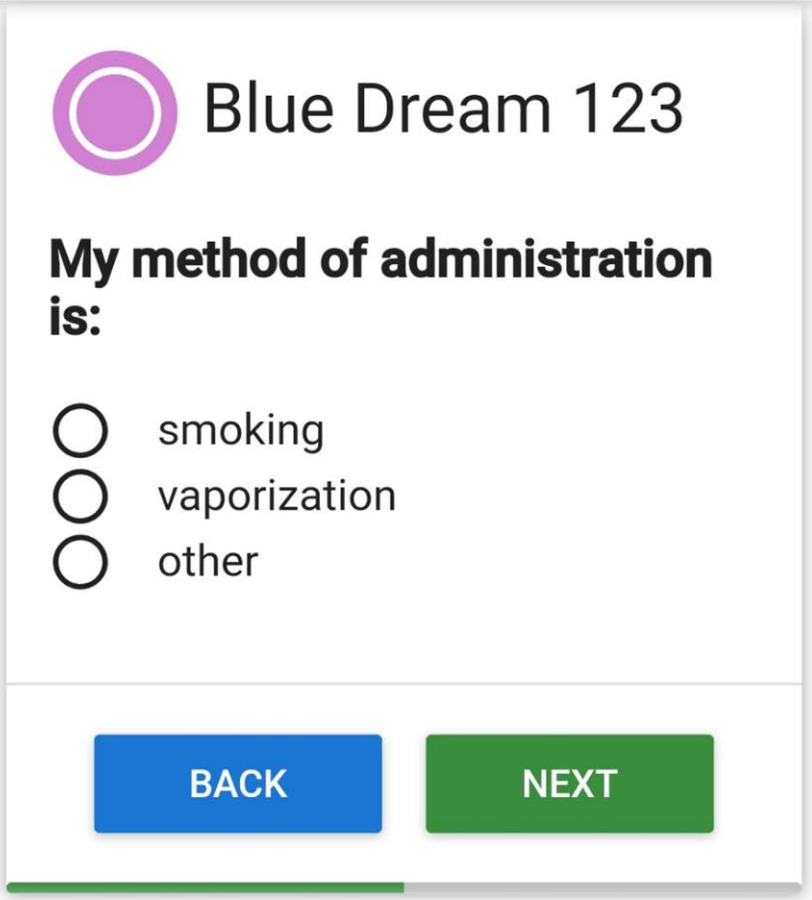


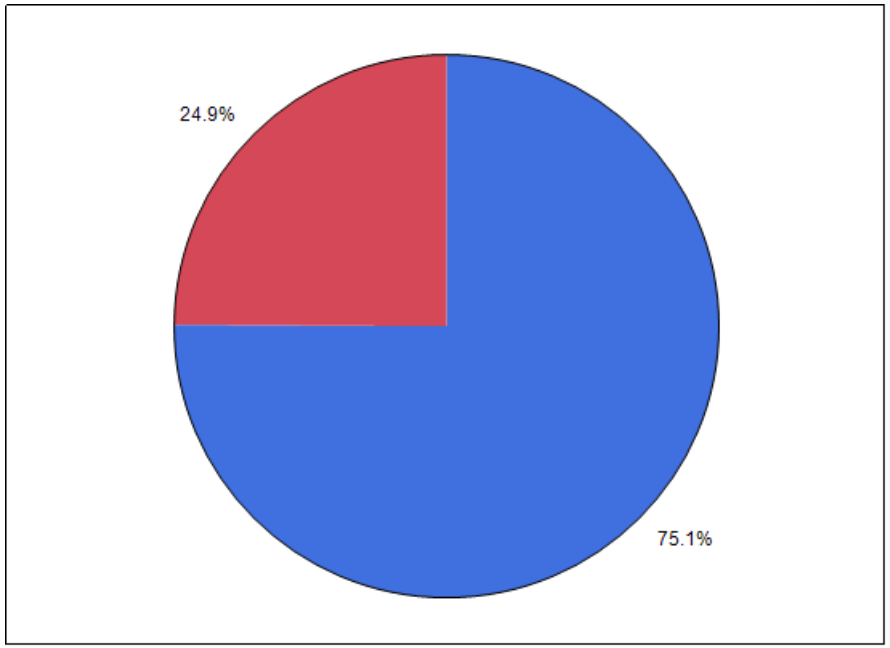




Mode of Administration







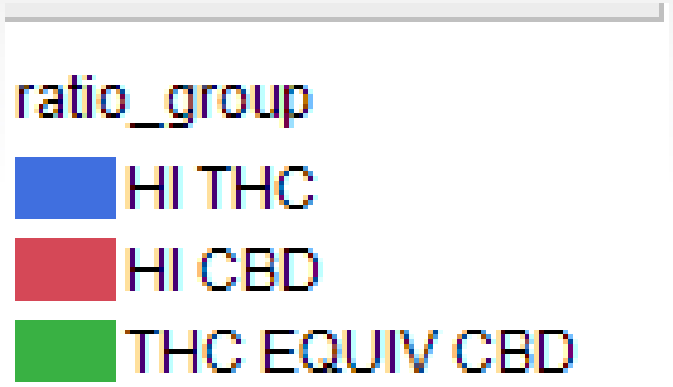
CANNABINOID RATIO GROUP

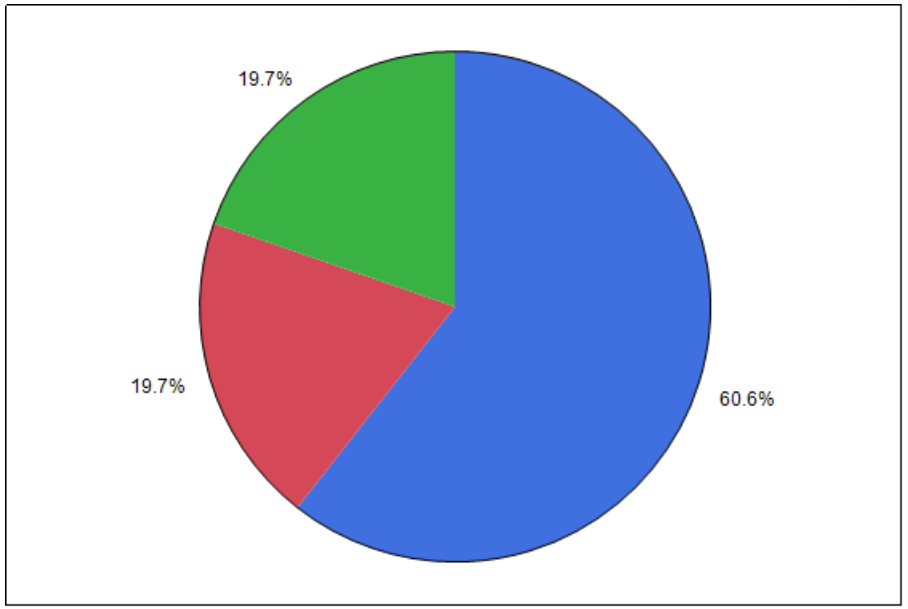
THC and CBD

Let's identify the percentage (%) of THC and CBD for the medicine you most recently used:

Ratio Help

- High THC
- High CBD
- One to One



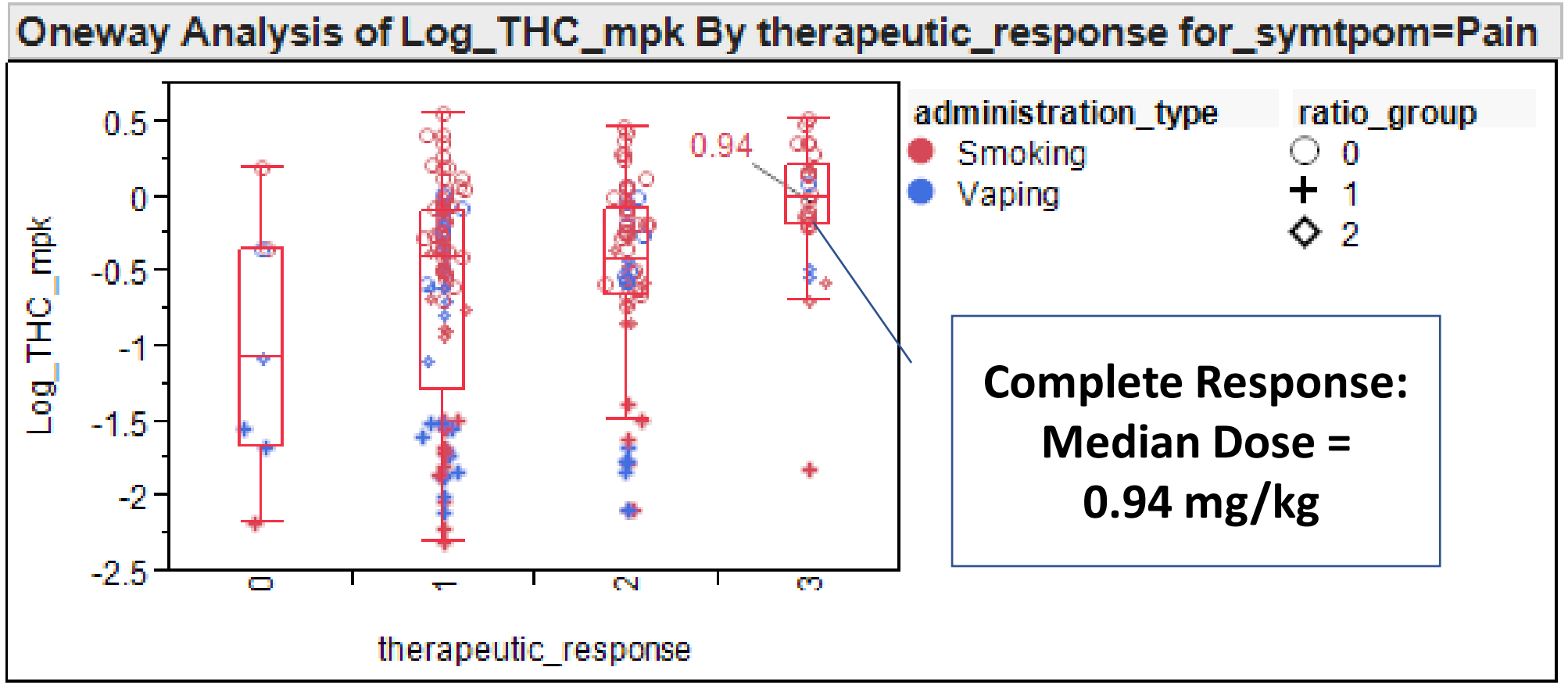


Ordinal Logistic Regression for Therapeutic Response

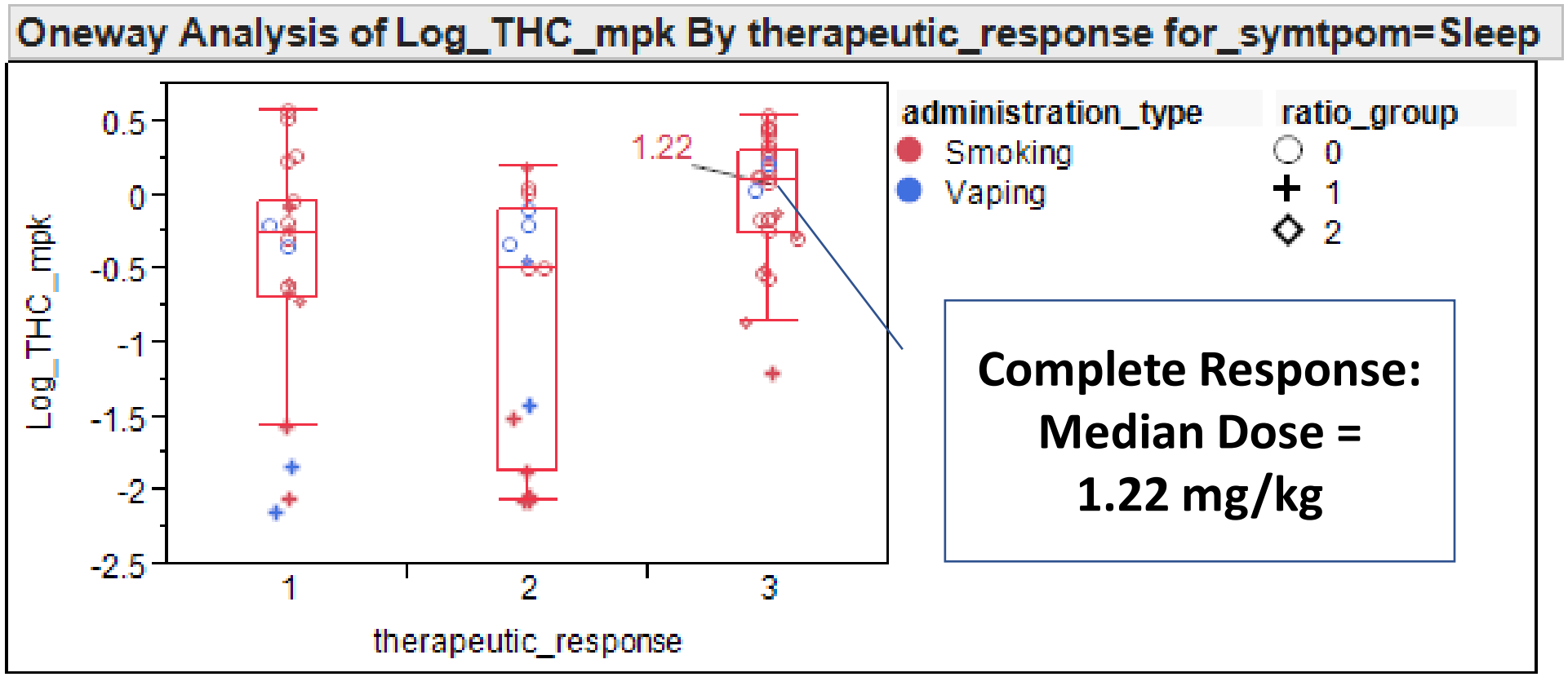
Indication	Whole Model Test		Effect Likelihood Ratio Tests	
	N	Prob>ChiSq	Source	Prob>ChiSq
Pain	205	0.0042	Log THC mg/kg	0.037
			Log CBD mg/kg	0.8693
			MOA	0.2427
Sleep	63	0.0272	Log THC mg/kg	0.0102
			Log CBD mg/kg	0.4145
			MOA	0.1475

*** P < 0.05**

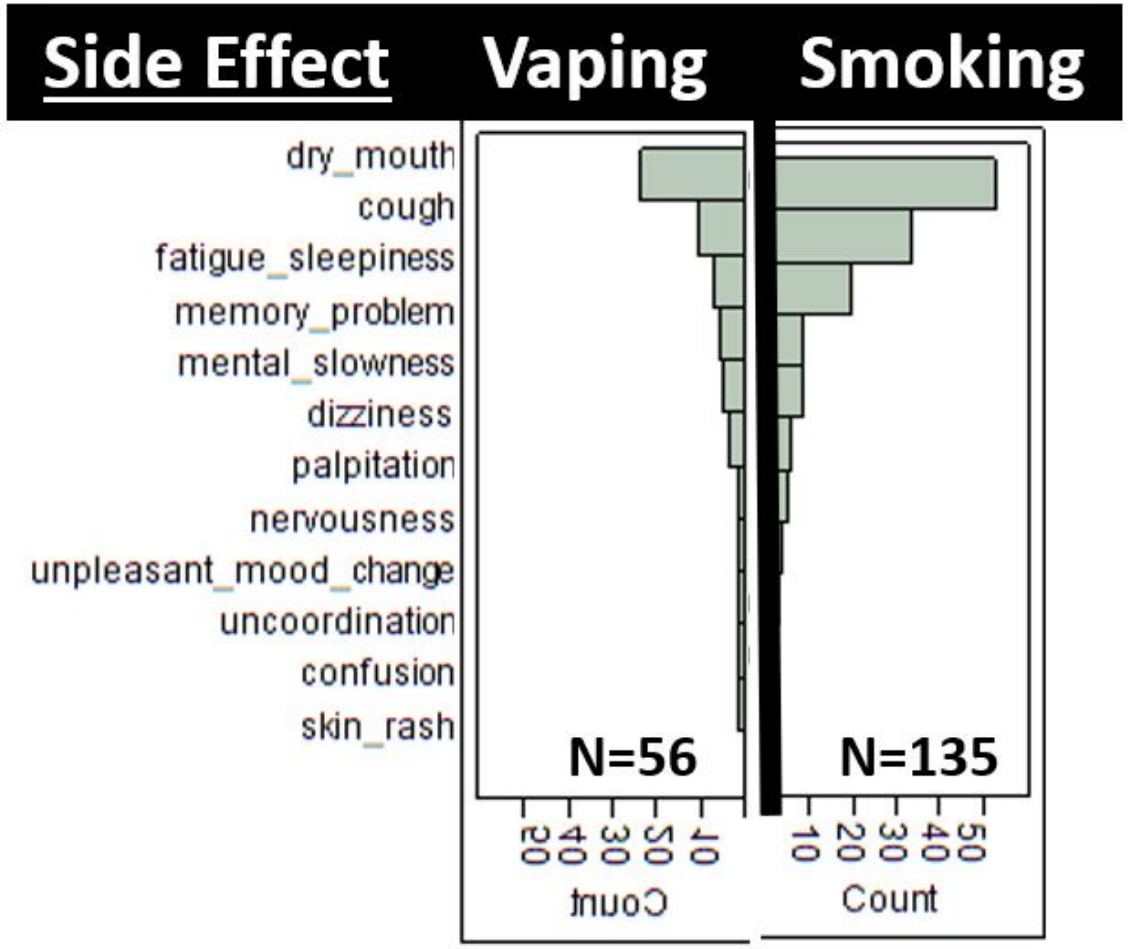
Response – Dose for Pain



Response – Dose for Sleep



Reported Side Effect Frequencies for Smoking or Vaping Cannabis Flower



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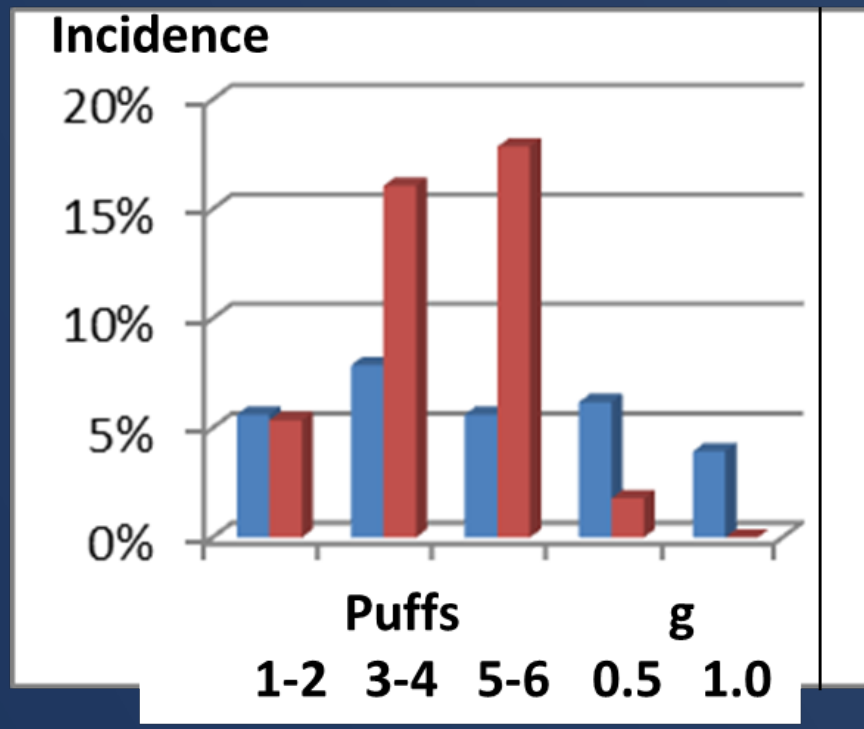
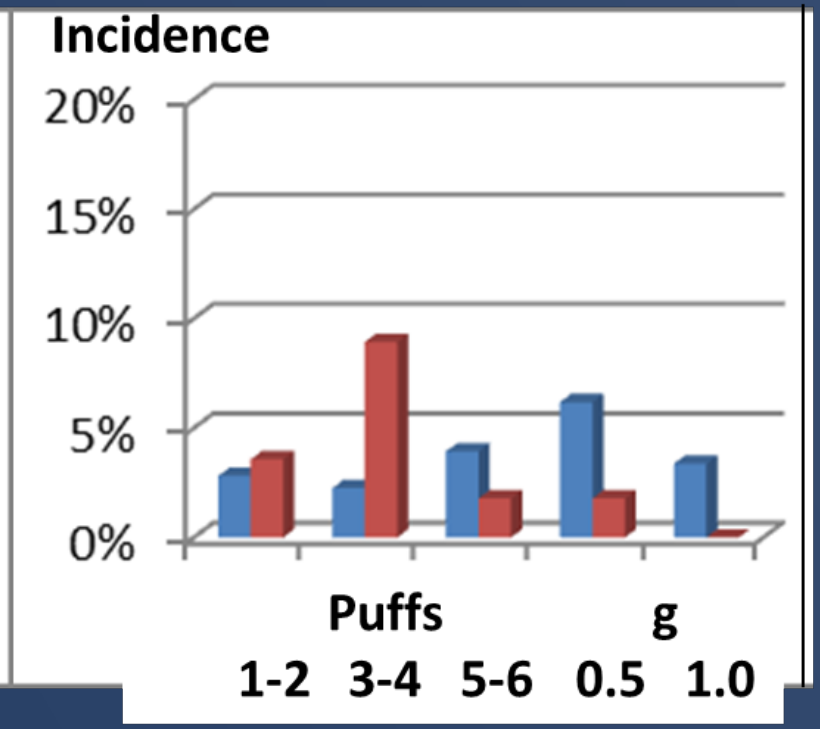
Most Frequent Adverse Events by Dose

Dry Mouth



Cough



N = 234

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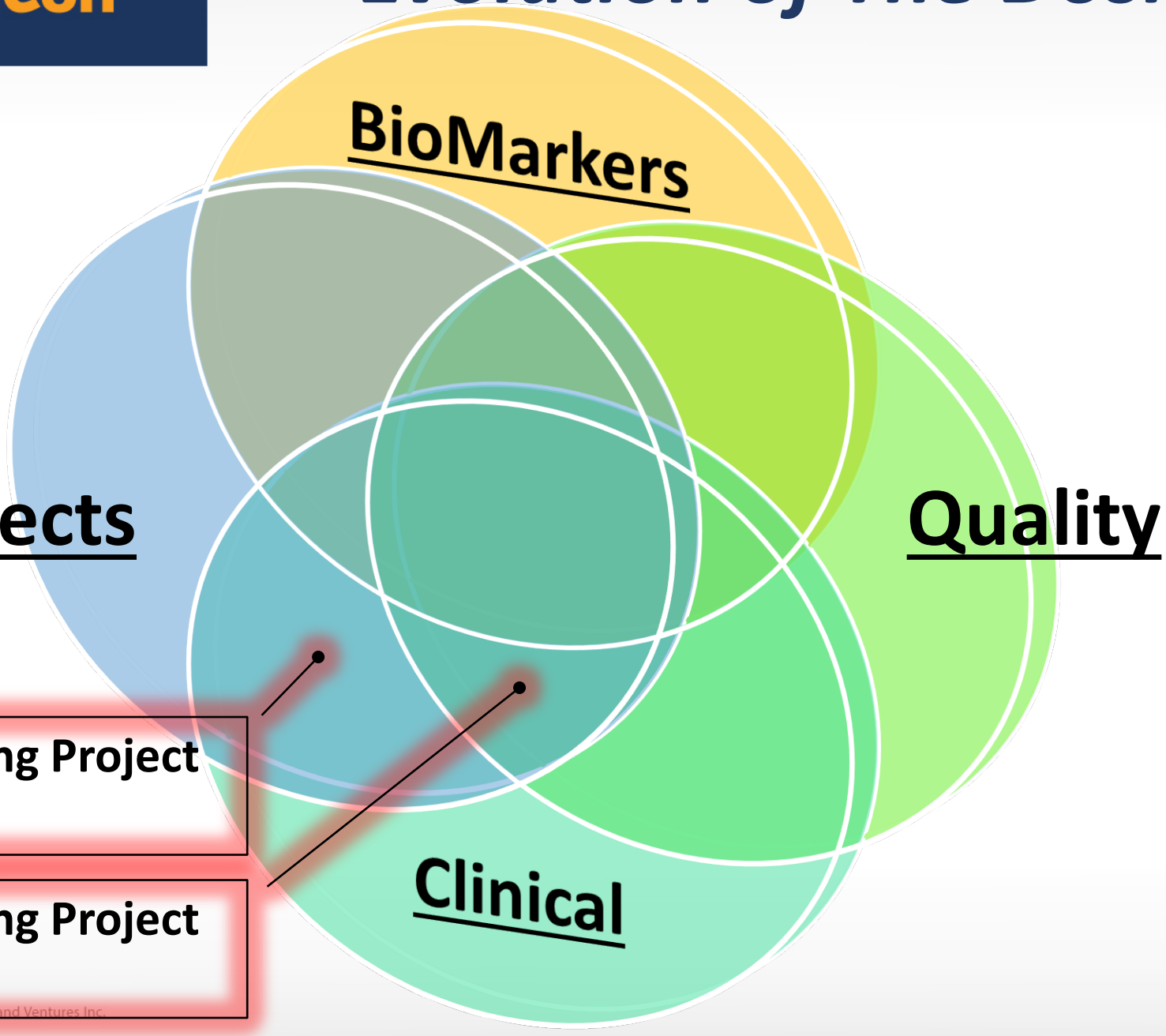
Evolution of The Dosing Project



The Dosing Project v POC

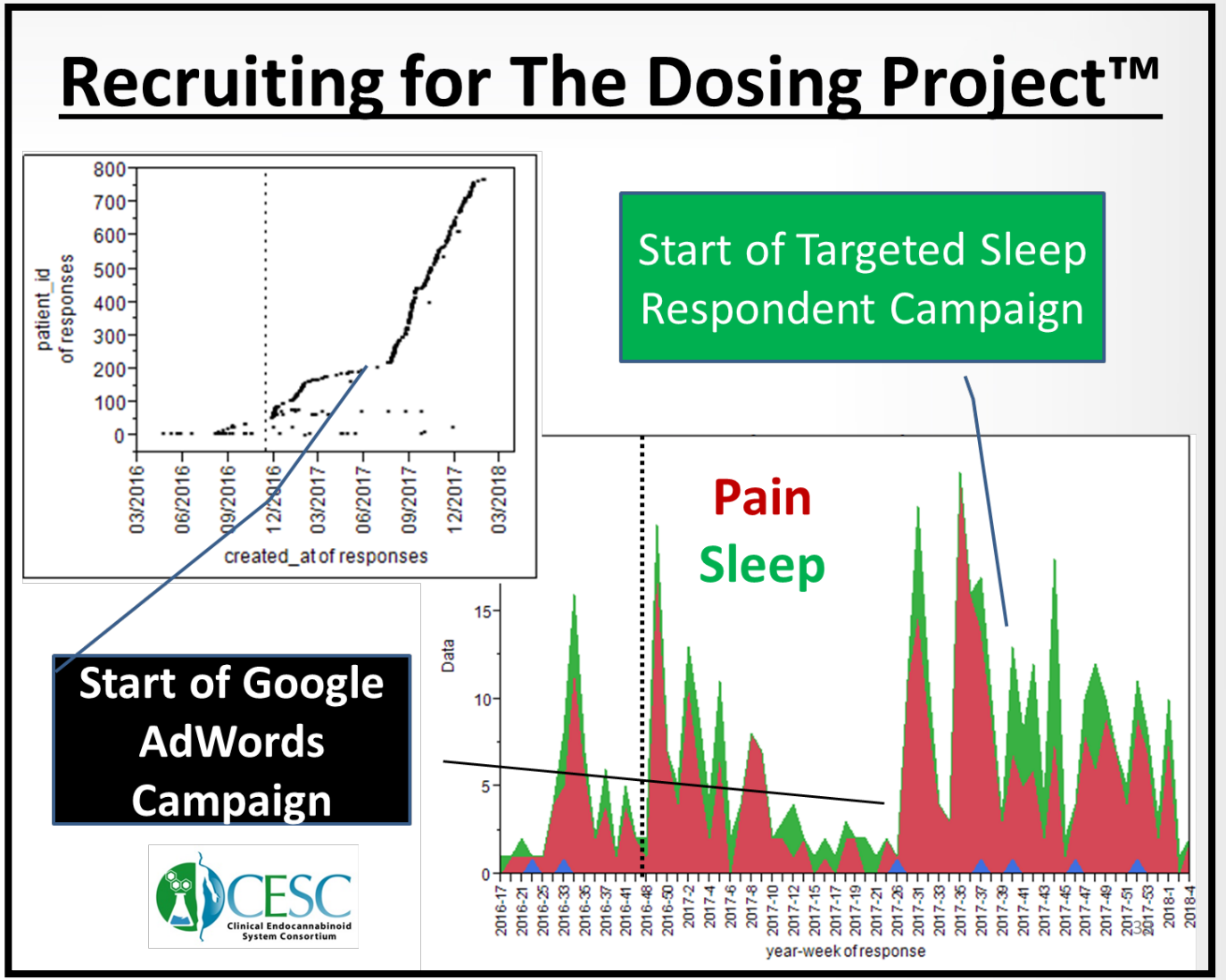
The Dosing Project v 2.0

BioMarkers Under Development

- qEEG
- CBD(A) *In Vitro* cell-based Potency Bioassay
- EndoCannabinoid System Tone Assays
  - based on Receptor activation states
- CB2 antibodies

Subjects

- IRB
- Recruiting
- Genetics
- Ethics (includes Data Security)



Subject	Cluster	Strain	N Rows	N[Delta]	N[Delta1]	N[Theta]	N[Alpha]	N[Alpha1]	N[Alpha2]	N[Beta]	N[Beta2]	N[Gamma]
SUBJ1	1	EDEL	140	0	0	0	20	0	20	20	20	20
SUBJ1	1	GP	60	0	0	0	0	0	20	20	20	20
SUBJ1	1	SD	220	20	20	20	20	20	20	20	20	20
SUBJ1	3	EDEL	80	20	20	20	0	20	0	0	0	0
SUBJ1	3	GP	160	20	20	20	20	20	20	0	0	0
SUBJ7	1	SD	180	20	20	20	0	0	20	20	20	20
SUBJ7	2	EDEL	220	20	20	20	20	20	20	20	20	20
SUBJ7	2	GP	220	20	20	20	20	20	20	20	20	20
SUBJ7	2	SD	40	0	0	0	20	20	0	0	0	0

Simple Pattern

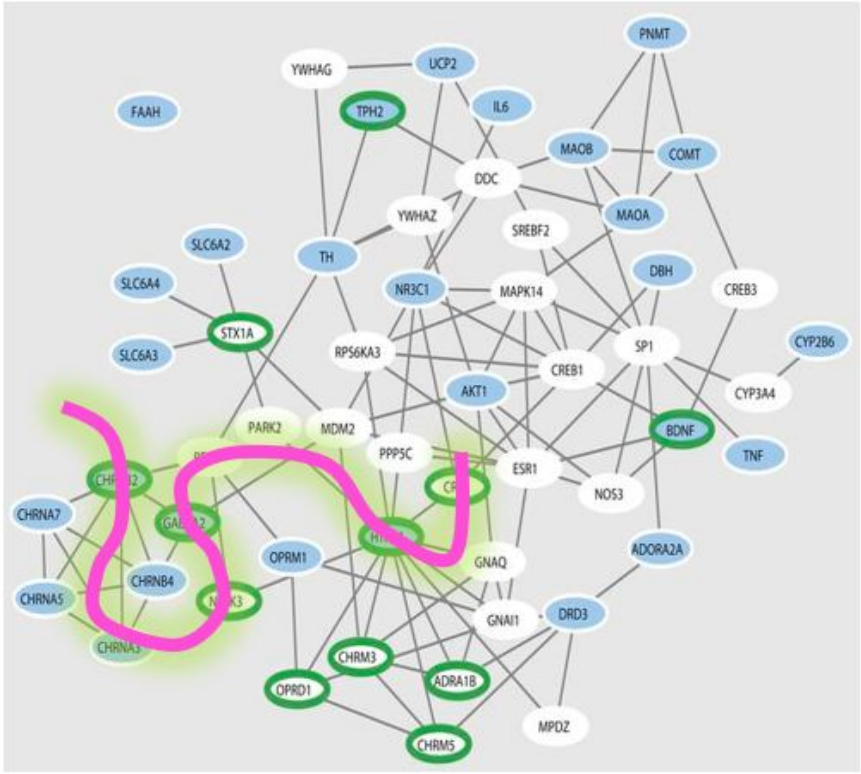
Subject	Cluster	Strain	N Rows	N[Delta]	N[Delta1]	N[Theta]	N[Alpha]	N[Alpha1]	N[Alpha2]	N[Beta]	N[Beta2]	N[Gamma]
SUBJ2	1	EDEL	100	20	20	20	0	0	0	0	0	0
SUBJ2	1	GP	40	0	0	0	0	0	0	0	0	0
SUBJ2	1	SD	80	0	20	0	20	20	20	0	0	0
SUBJ2	2	EDEL	60	0	0	0	0	20	0	0	20	20
SUBJ2	2	GP	100	0	0	0	20	20	0	20	20	20
SUBJ2	3	GP	60	20	20	20	0	0	0	0	0	0
SUBJ2	3	SD	140	20	0	20	0	0	0	20	20	20
SUBJ2	4	EDEL	60	0	0	0	20	0	20	20	0	0
SUBJ2	4	GP	20	0	0	0	0	0	20	0	0	0
SUBJ6	1	SD	60	20	20	0	0	0	0	0	0	20
SUBJ6	2	EDEL	80	20	20	20	0	20	0	0	0	0
SUBJ6	2	GP	140	0	20	0	0	20	0	20	20	20
SUBJ6	2	SD	100	0	0	20	0	0	0	20	20	0
SUBJ6	3	GP	40	20	0	20	0	0	0	0	0	0
SUBJ6	4	EDEL	140	0	0	0	20	0	20	20	20	20
SUBJ6	4	GP	40	0	0	0	20	0	20	0	0	0
SUBJ6	4	SD	60	0	0	0	20	20	20	0	0	0
SUBJ8	1	EDEL	100	0	20	20	0	0	0	20	0	0
SUBJ8	1	GP	220	20	20	20	20	20	20	20	20	20
SUBJ8	1	SD	60	20	20	20	0	0	0	0	0	0
SUBJ8	2	EDEL	60	20	0	0	0	0	0	0	20	20
SUBJ8	2	SD	120	0	0	0	0	0	20	20	20	20
SUBJ8	3	EDEL	60	0	0	0	20	20	20	0	0	0
SUBJ8	4	SD	40	0	0	0	20	20	0	0	0	0
SUBJ9	1	EDEL	100	20	20	0	0	0	20	0	20	20
SUBJ9	1	GP	40	0	0	0	0	0	0	0	20	20
SUBJ9	1	SD	40	0	0	0	0	0	0	0	20	20
SUBJ9	2	EDEL	100	0	0	20	20	0	0	20	0	0
SUBJ9	2	GP	180	20	20	20	20	20	20	20	0	0
SUBJ9	2	SD	60	20	20	20	0	0	0	0	0	0
SUBJ9	4	EDEL	20	0	0	0	0	20	0	0	0	0
SUBJ9	4	SD	120	0	0	0	20	20	20	20	0	0

Subject	Cluster	Strain	N Rows	N[Delta]	N[Delta1]	N[Theta]	N[Alpha]	N[Alpha1]	N[Alpha2]	N[Beta]	N[Beta2]	N[Gamma]
SUBJ3	1	EDEL	40	0	0	0	0	0	0	0	0	0
SUBJ3	1	GP	80	0	0	20	0	0	0	20	0	0
SUBJ3	1	SD	60	20	0	0	0	0	0	0	20	20
SUBJ3	2	EDEL	60	0	0	0	0	0	0	20	20	20
SUBJ3	2	GP	40	0	0	0	20	20	0	0	0	0
SUBJ3	2	SD	60	0	0	20	0	0	0	0	0	0
SUBJ3	3	EDEL	60	20	20	20	0	0	0	0	0	0
SUBJ3	3	GP	80	20	20	0	0	0	0	0	20	20
SUBJ3	3	SD	20	0	20	0	0	0	0	0	0	0
SUBJ3	4	EDEL	60	0	0	0	20	20	20	0	0	0
SUBJ3	4	GP	20	0	0	0	0	0	20	0	0	0
SUBJ3	4	SD	80	0	0	0	20	20	20	20	0	0
SUBJ5	1	EDEL	80	0	0	0	20	0	20	0	20	20
SUBJ5	1	GP	120	20	20	20	0	0	0	20	0	0
SUBJ5	1	SD	100	0	0	0	20	0	20	20	0	0
SUBJ5	2	EDEL	120	20	20	20	0	0	0	20	0	0
SUBJ5	2	GP	40	0	0	0	0	0	0	0	20	20
SUBJ5	2	SD	40	0	0	20	0	20	0	0	0	0
SUBJ5	3	EDEL	20	0	0	0	0	20	0	0	0	0
SUBJ5	3	GP	60	0	0	0	20	20	20	0	0	0
SUBJ5	3	SD	40	0	0	0	0	0	0	0	20	20
SUBJ5	4	SD	40	20	20	0	0	0	0	0	0	0

Complex Pattern

Because Individual Responses ARE Different

Can a Placebo Neural Circuit be Identified?



Adapted from Figure 2: Network analysis of the genomic basis of the placebo effect
JCI Insight DOI: 10.1172/jci.insight.93911

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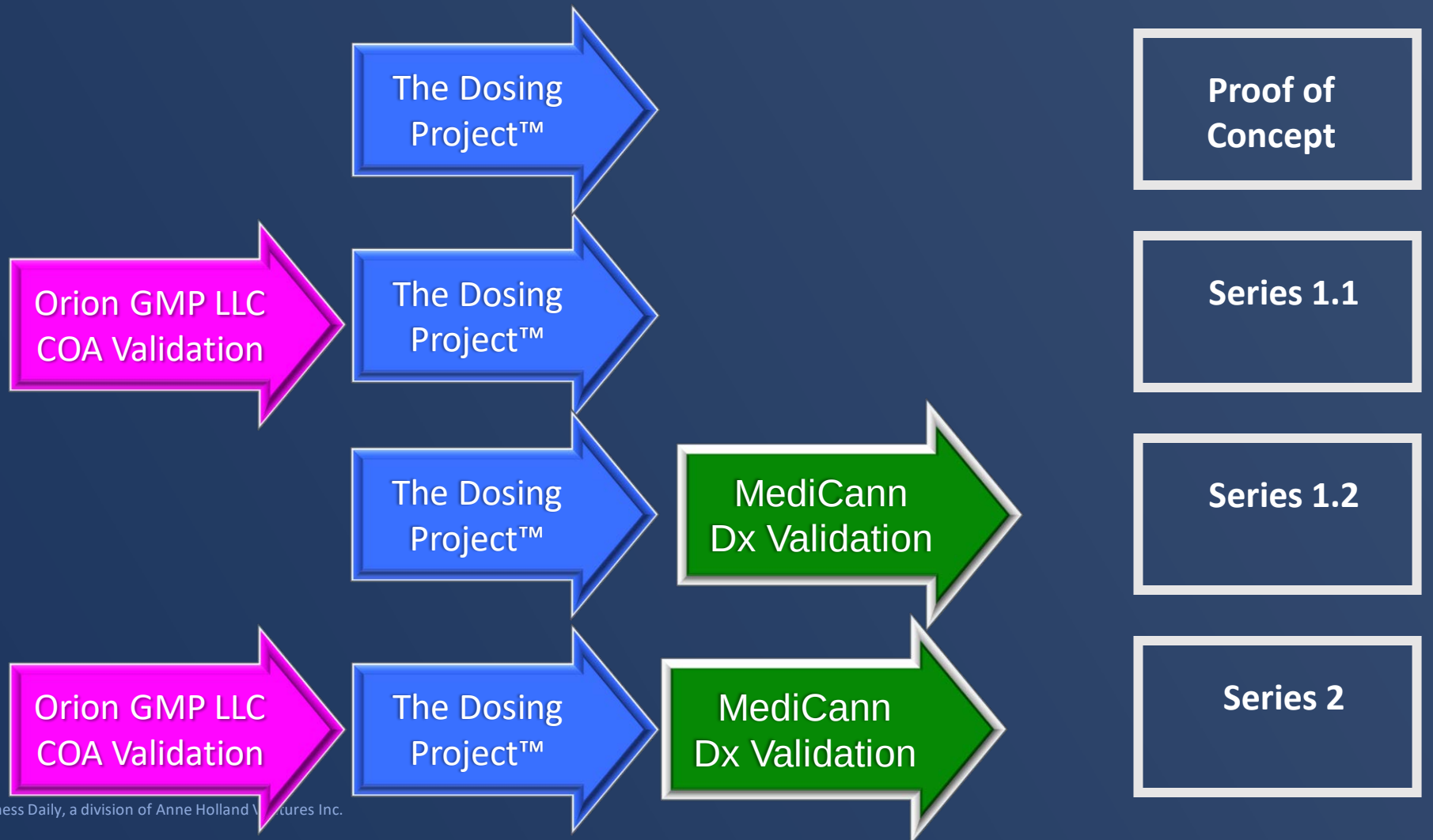
Big Data:
Creating a Product Line of Data Vectors



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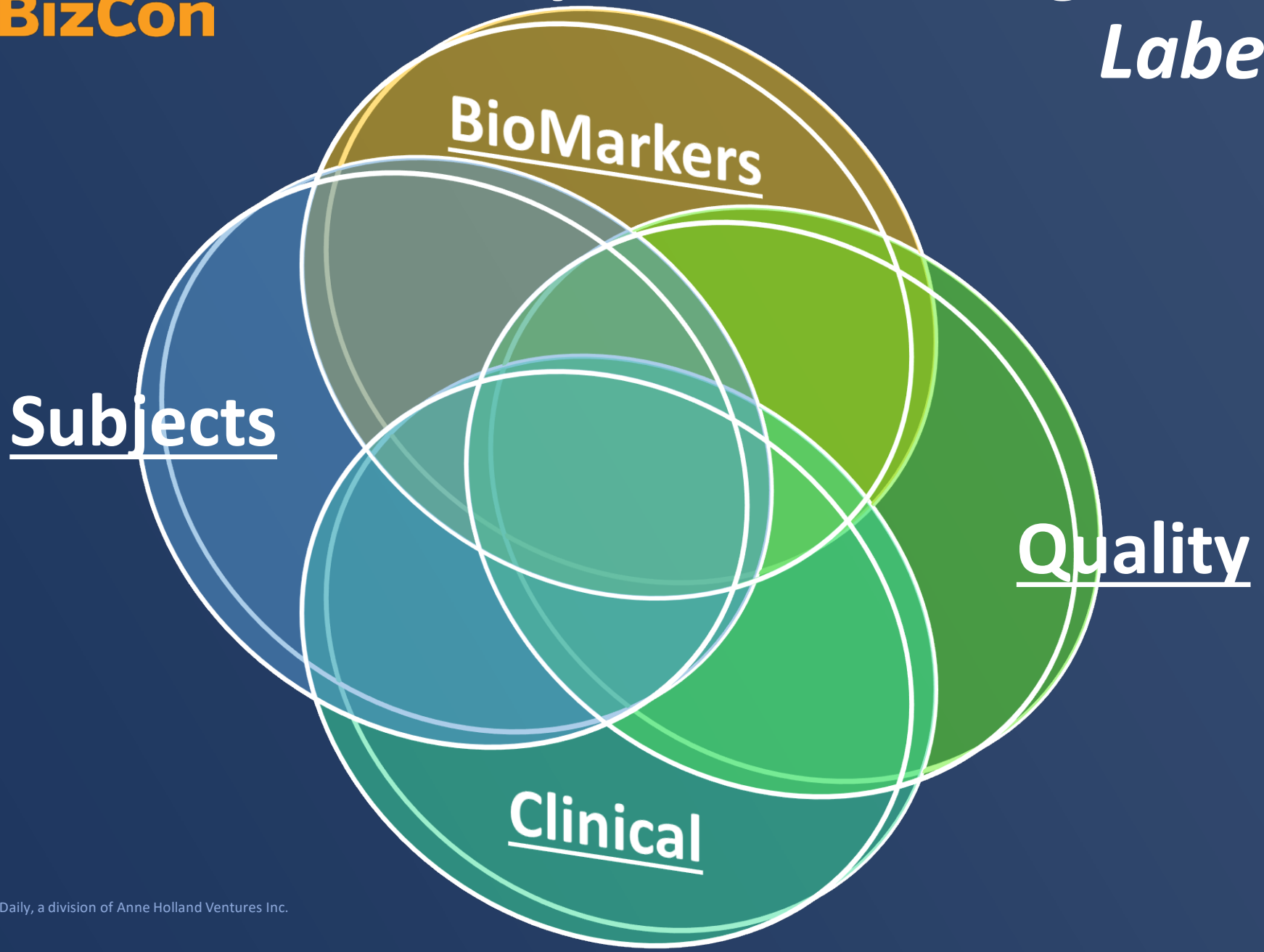
4 Compass Points Together Enable Label Claims



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