TRANSFORM

pharmaceuticals, inc.

Strategies for High Throughput Biomolecular Formulation Screening

Wm. Randy Forsyth

Importance of Form & Formulation

Candidate Selection

Formulation Design

Small molecule drugs:

- Stability
- Solubility
- Bioavailability
- Patents

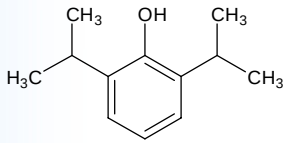
Biologics/Vaccines:

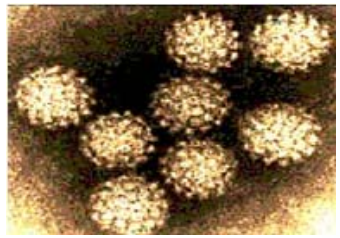
- Stability
- Solubility
- Delivery profile
- Patents

Optimize Value to Patient

Increasing Levels of Complexity Favor Empirical Approaches

Traditional Drugs → **Proteins (Therapeutics and Vaccines)** → **Live Virus Vaccines**





Need for empirical data in formulation design

Value of high throughput approach

Ideal fit for high throughput experimentation

Shortcomings of Traditional Approaches to Formulation Development

- **Enhanced conditions are often missed**
  - Limited exploration of experimental space (tens of formulations)
    - Too few conditions explored
    - Non-obvious synergies missed
  - Linear processes are slow and laborious
    - Only explore some conditions after others have failed
    - Stop searching when something minimally adequate is found
- **Failures require re-initiating the search**

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Vastness of Combinatorial Experimental Space

Number of variables	Unary	Binary	Ternary	Total
10	10	45	120	175
15	15	105	455	575
20	20	190	1140	1350
25	25	300	2300	2625
30	**30**	**435**	**4060**	**4525**
35	35	595	6545	7175
40	40	780	9880	10700
45	45	990	14190	15225
50	50	1225	19600	20875

Very large number of formulation options

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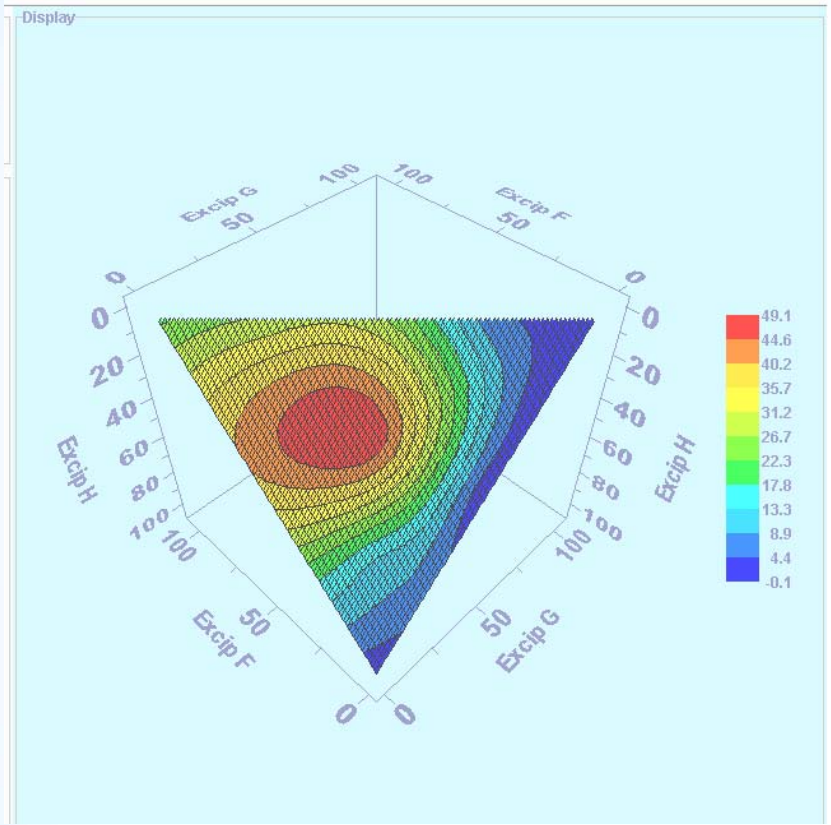
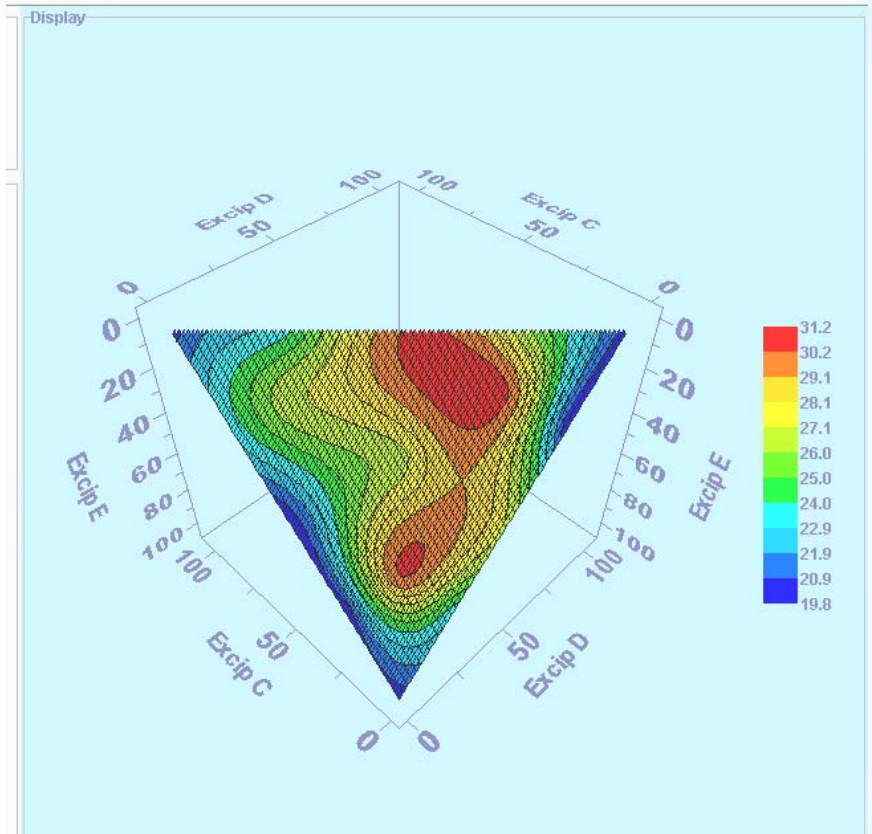
Formulation Response Space is Nonlinear





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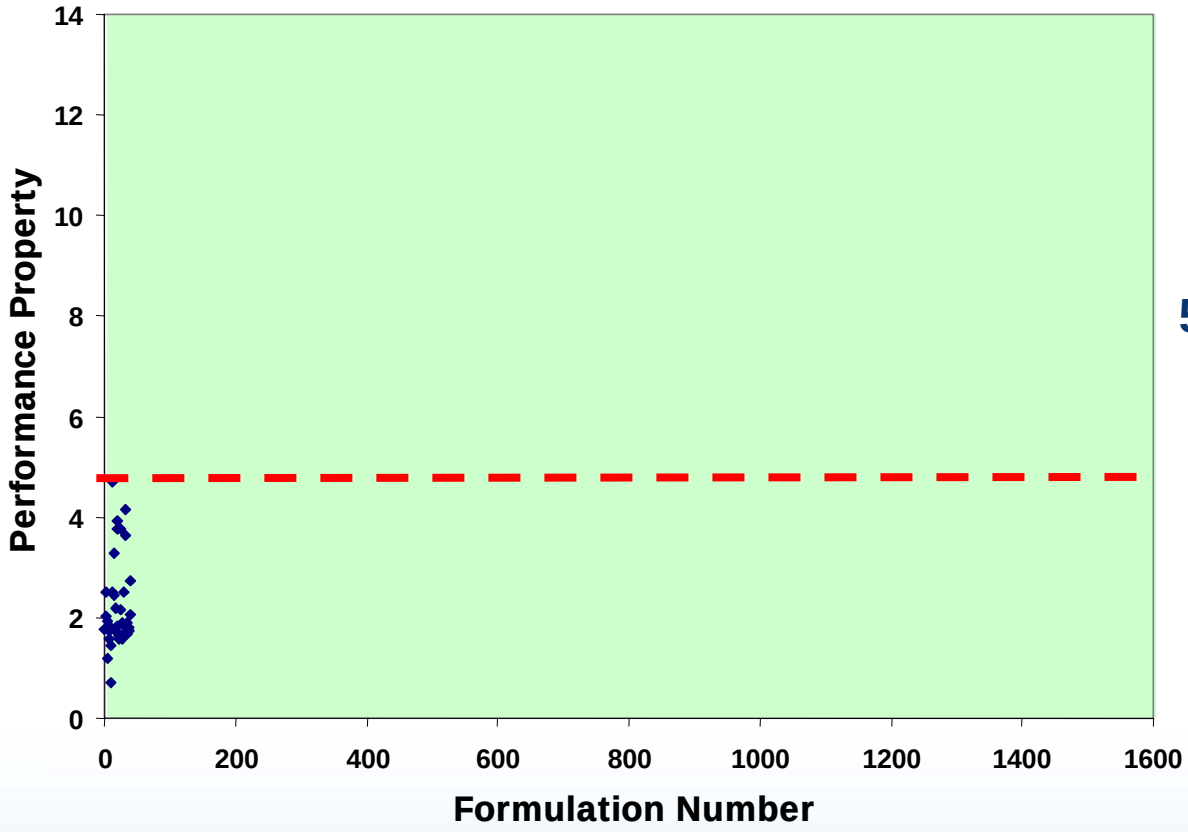
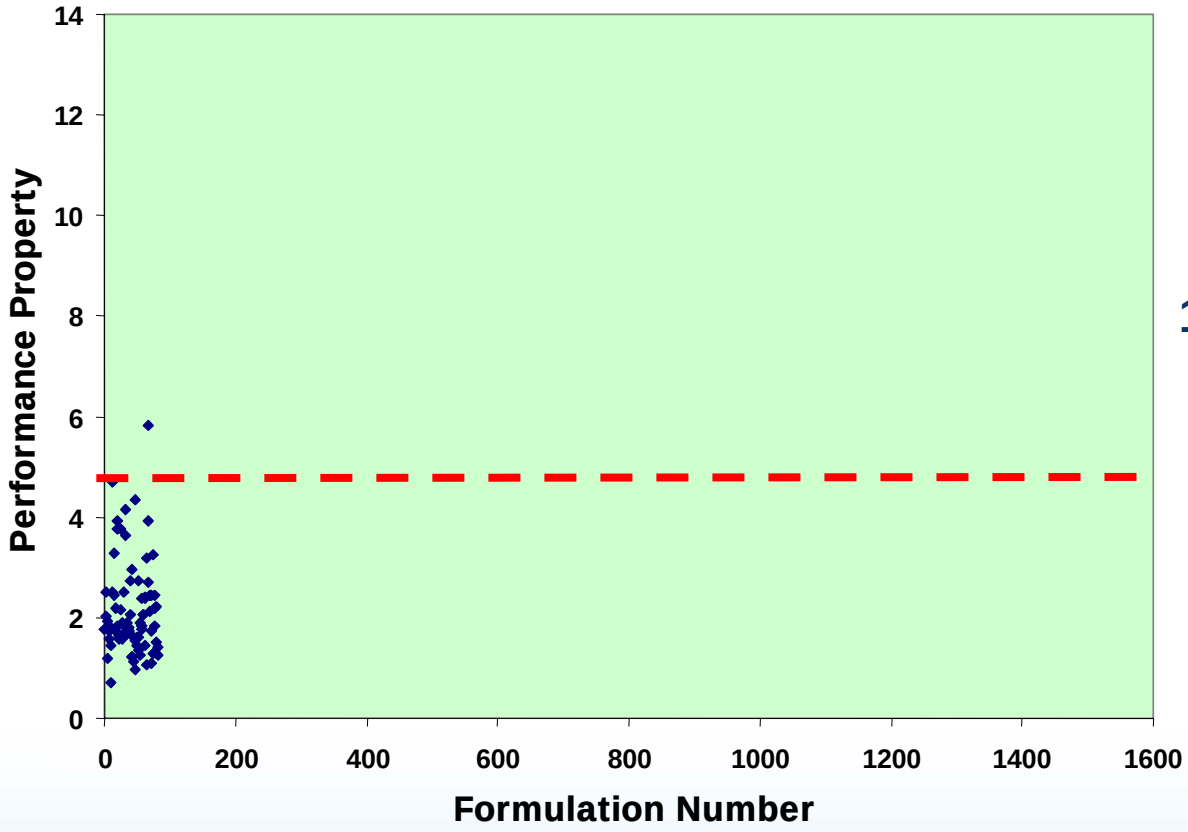
Few Results Represent Few Choices



50 formulations

Few Results Represent Few Choices



100 formulations

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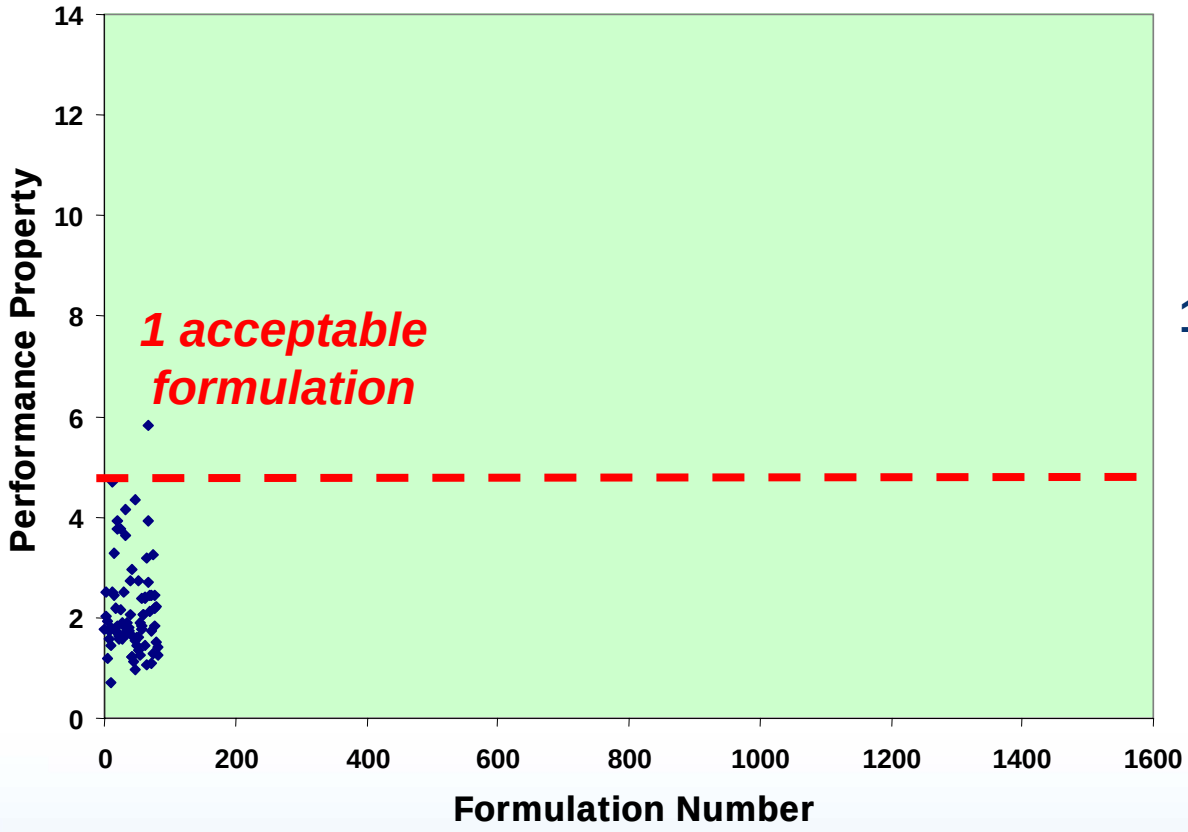
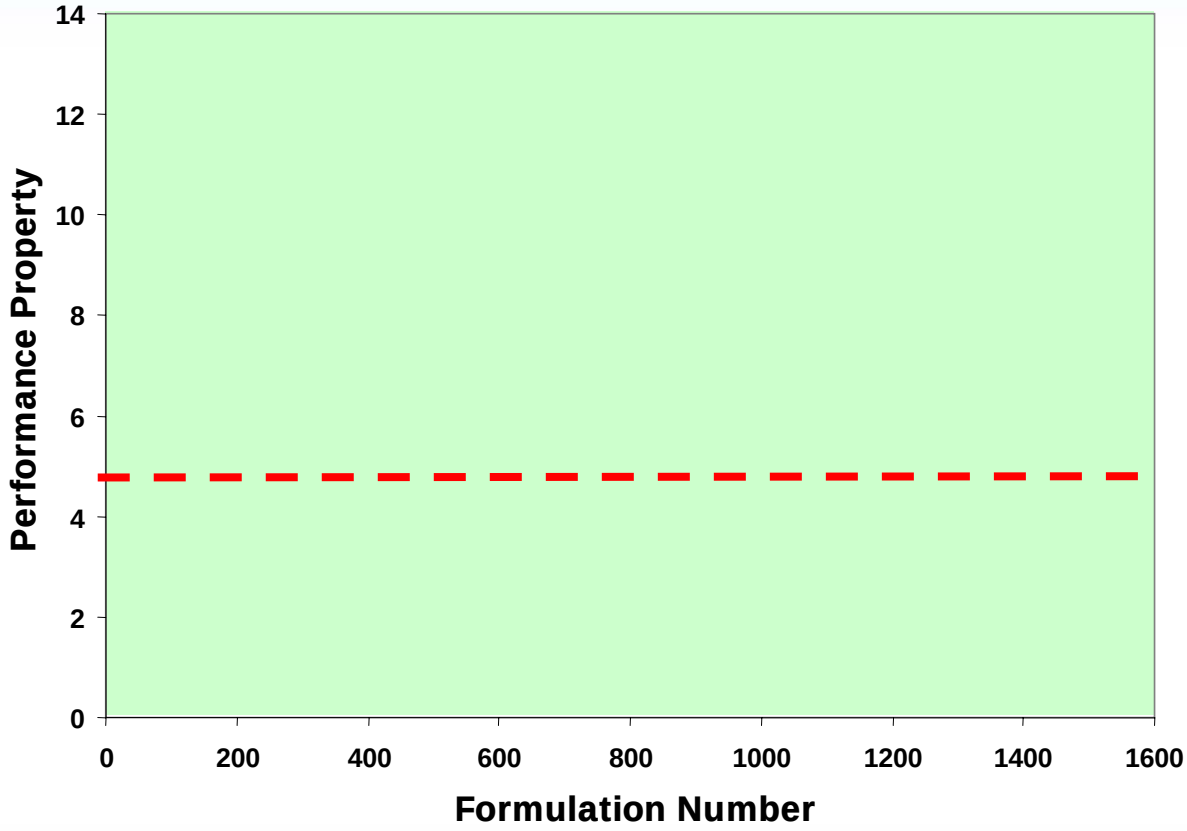
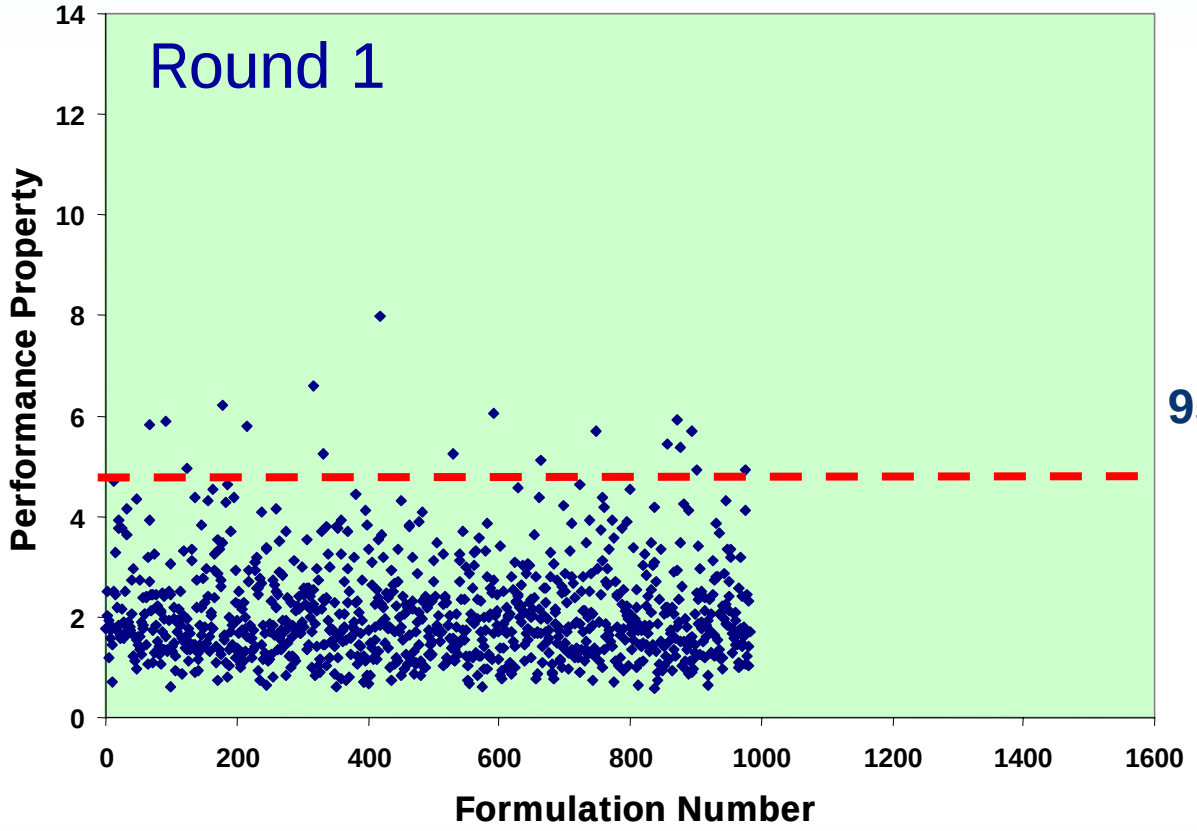


100 formulations

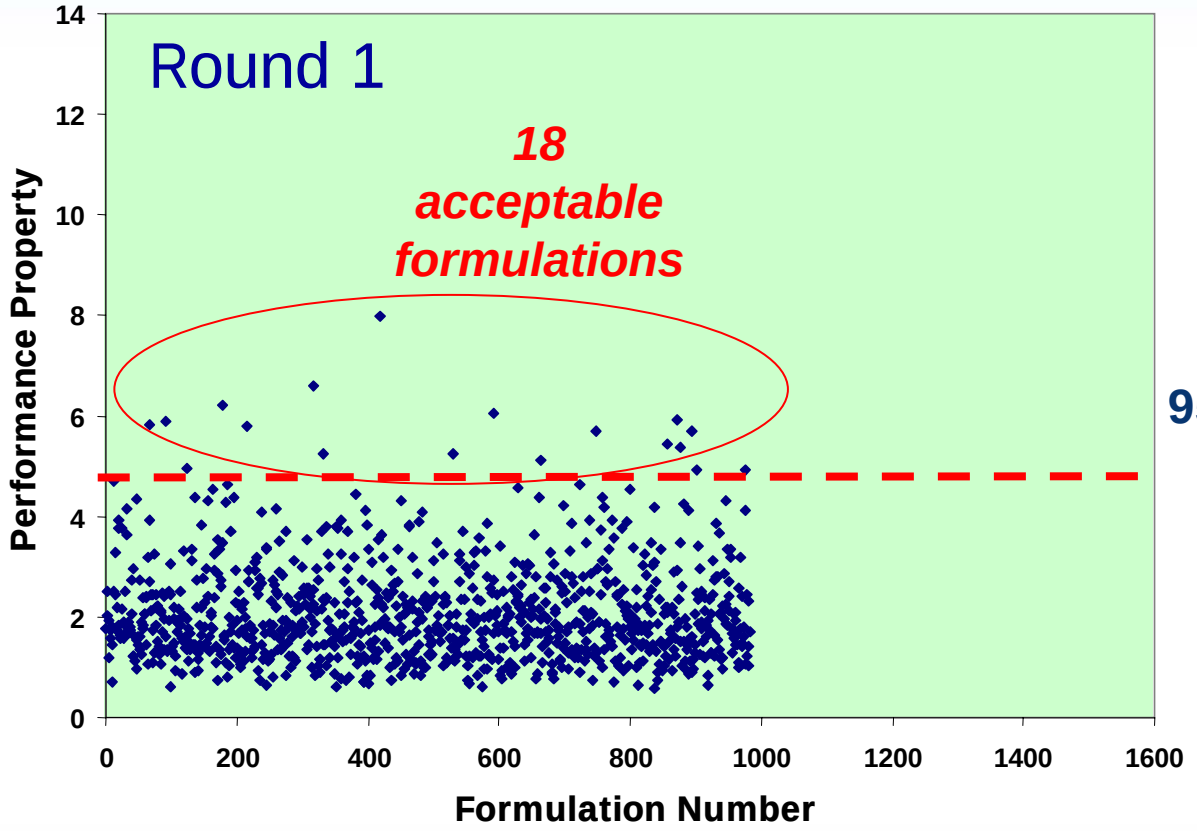

Performance Property
14
12
10
8
6
4
2
0
0
200
400
600
800
1000
1200
1400
1600
Formulation Number

High Throughput Screening



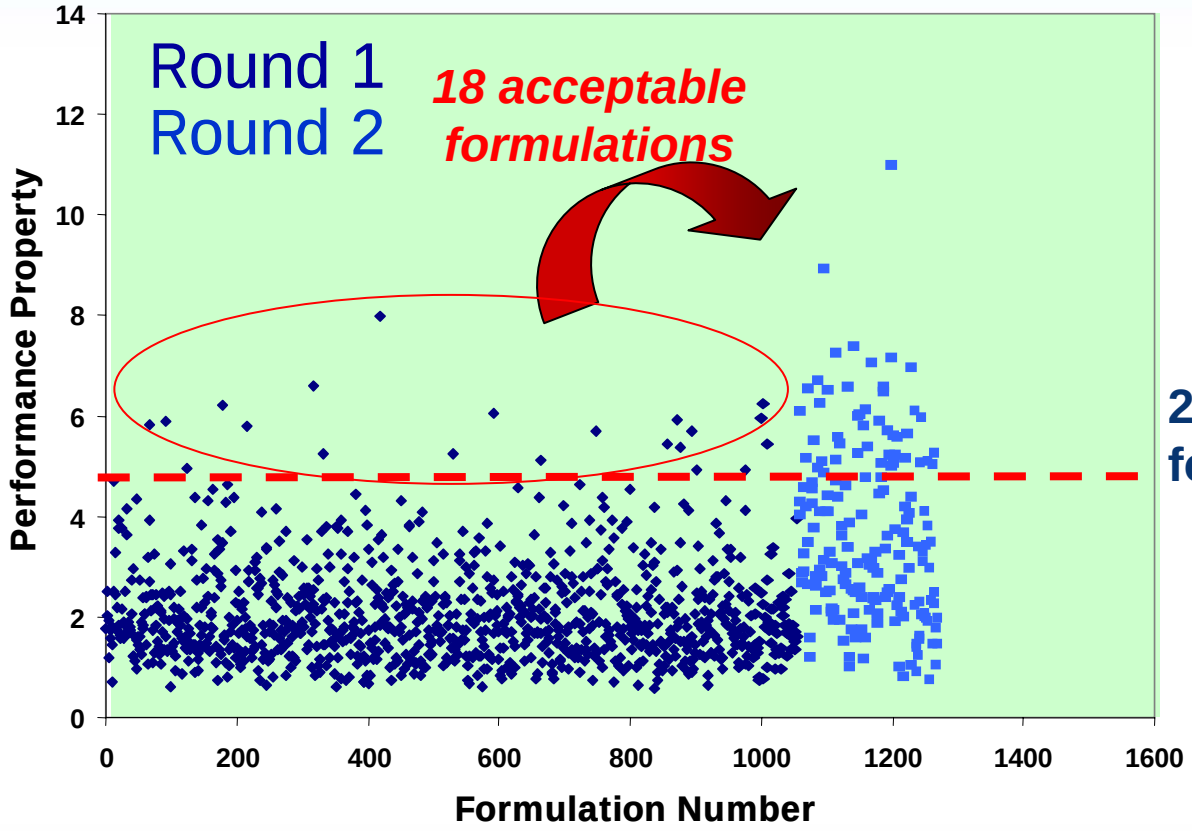
950 formulations

High Throughput Screening



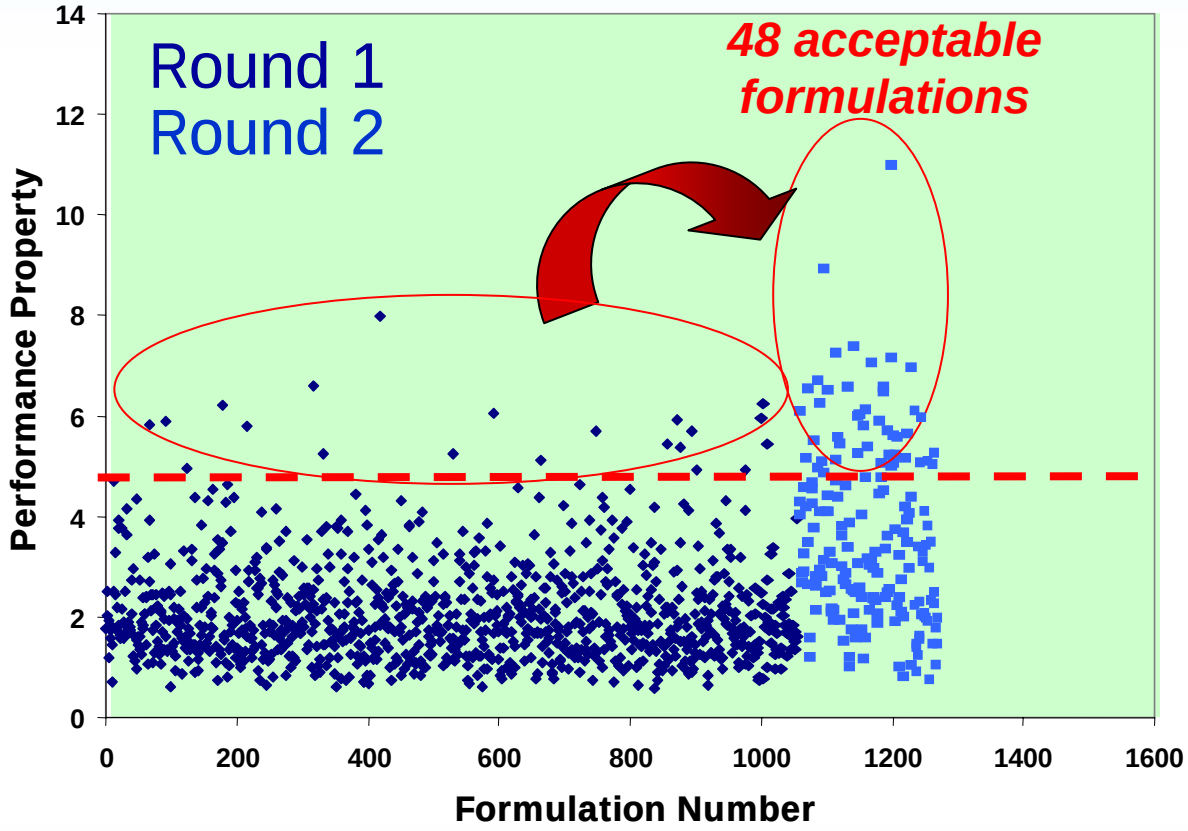
950 formulations

Informatics Aided Iterative Design



250 more formulations

Informatics Aided Iterative Design



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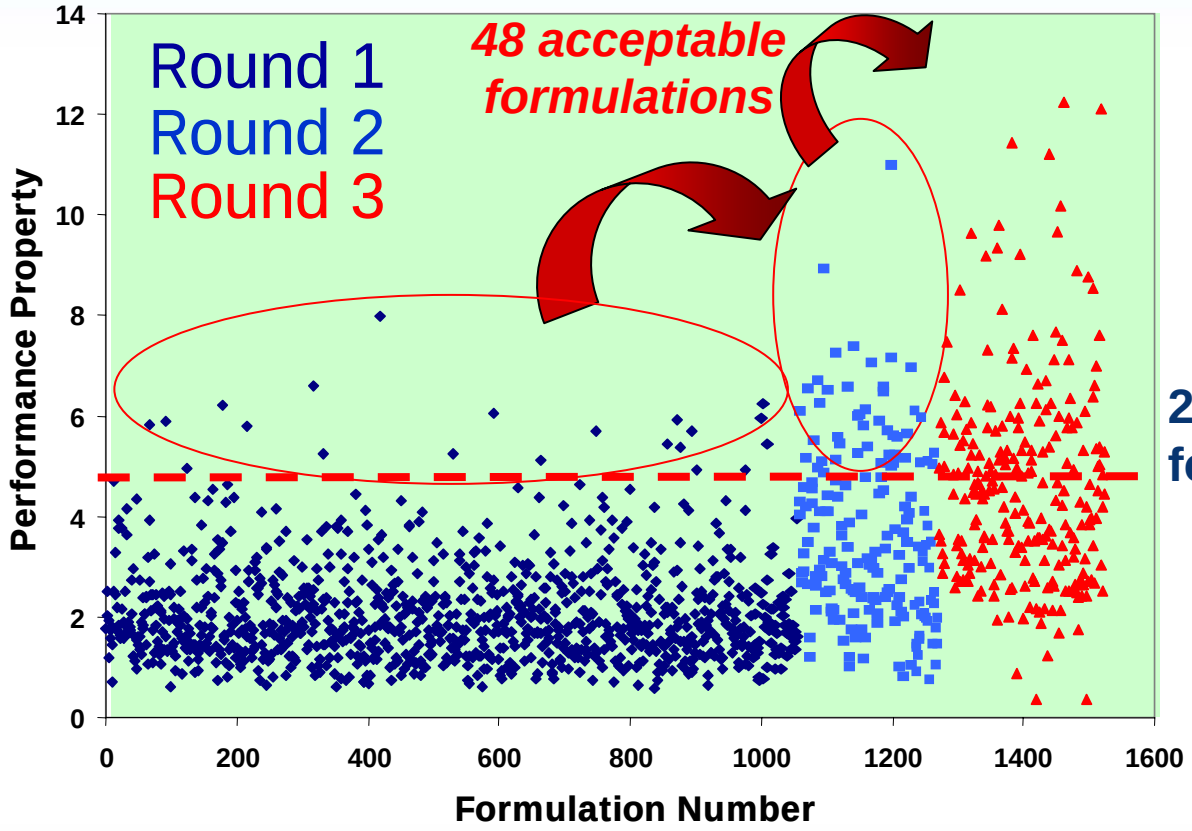

250 more formulations

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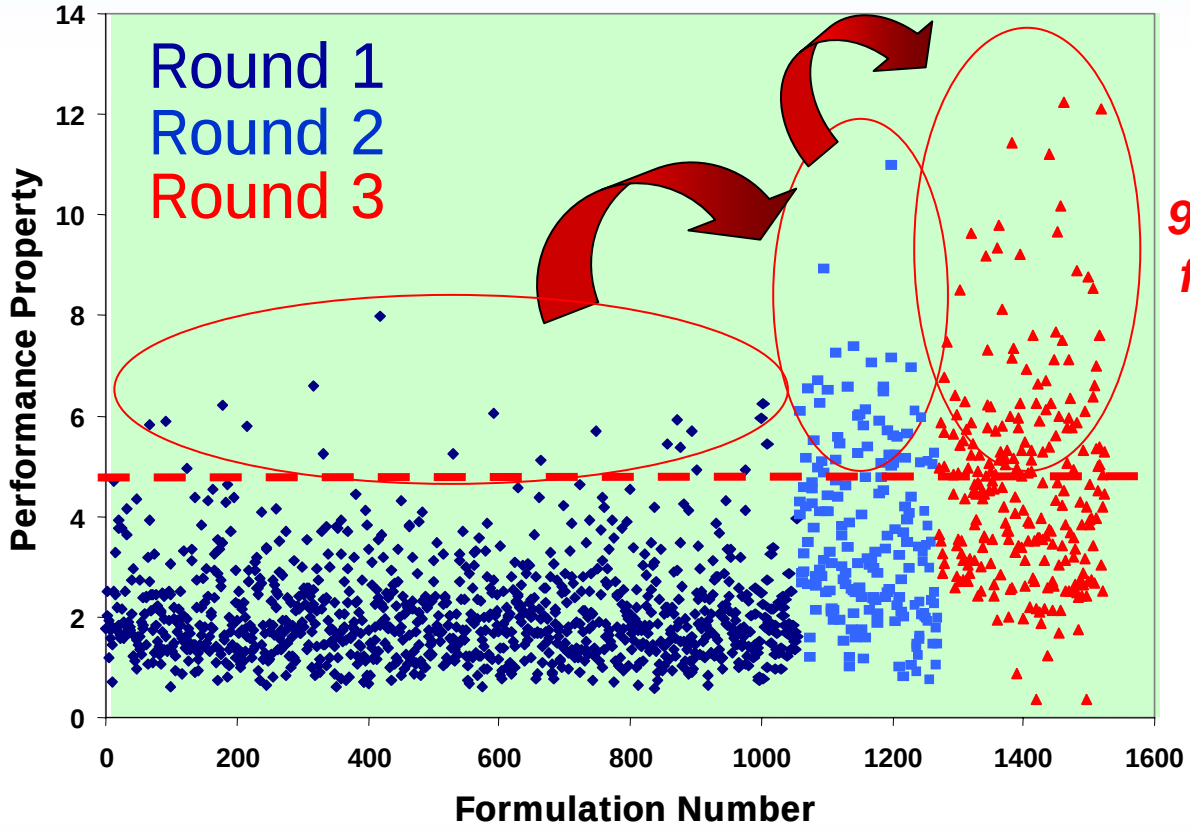
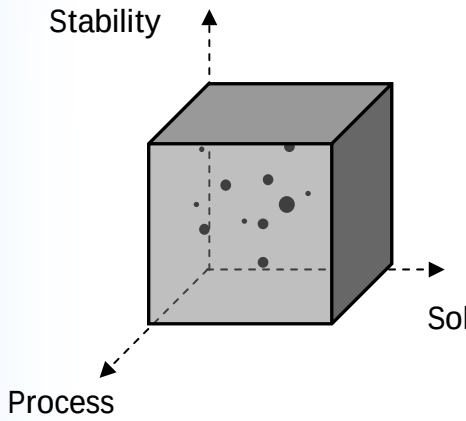


90 acceptable formulations

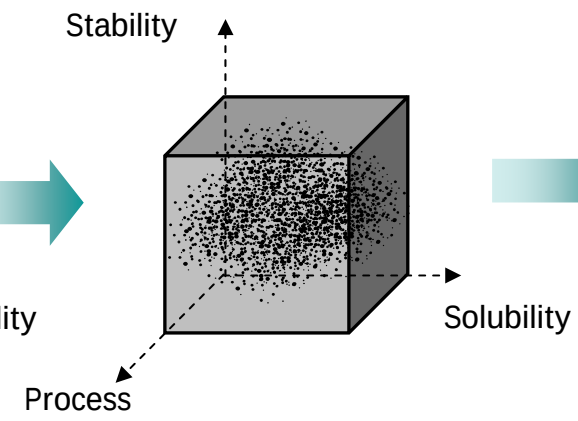
TransForm's Approach to Formulation Discovery

Traditional



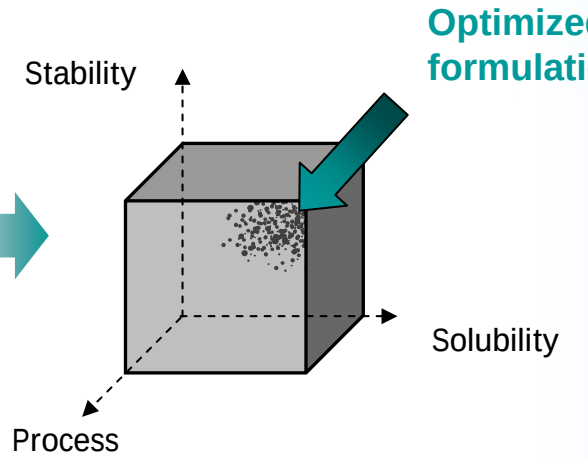
- Limited experiments
- Satisfactory formulation

High Throughput Platform



- Many experiments
- New knowledge

Informatics-Enhanced Experimental Design



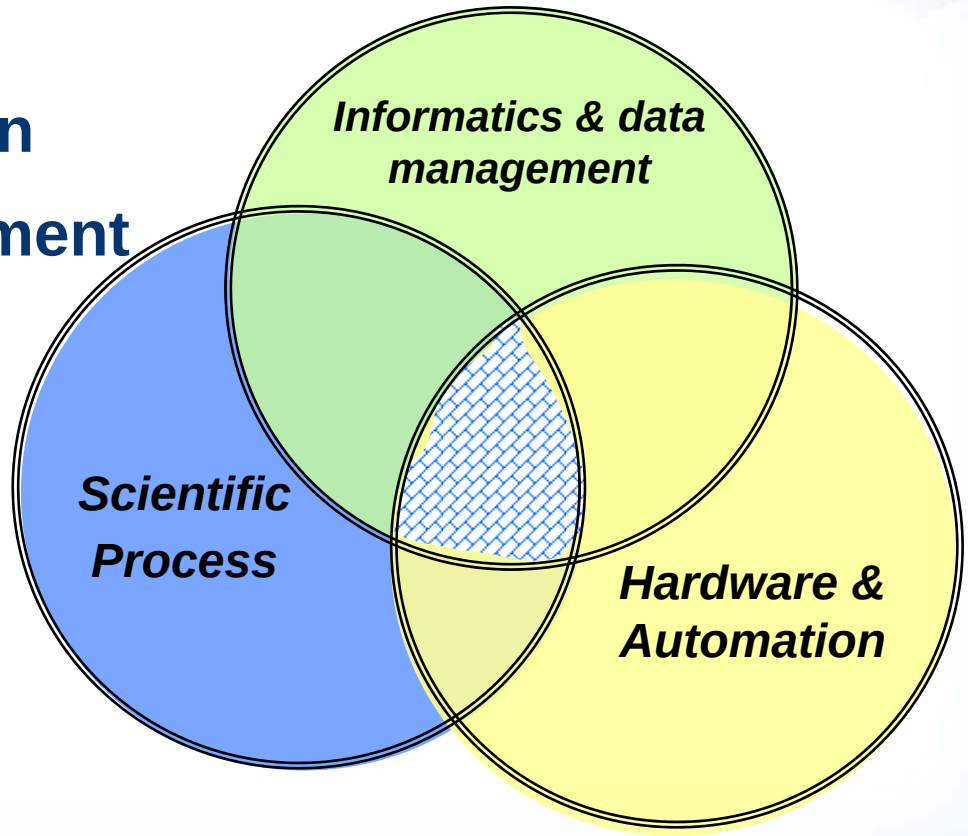
- Data capture & mining
- Optimized formulations

Strategic Opportunities for HTE in Formulation Development

- **Identification of improved formulations**
  - **Greater number of experiments has a greater chance of identifying those with more desirable properties**
    - Solubility, Stability, Process Compatibility (Manufacturing)…etc
  - **Non-obvious synergies may be identified**
- **Shorter timelines**
  - **Linear processes can be parallelized**
  - **Multiple inputs and outputs can be evaluated simultaneously**
  - **Greater potential for readily identifiable backup formulations**
- **Generation of knowledge**
  - **Information gained from one round can be leveraged into subsequent experimental designs**
  - **Increased coverage in intellectual property**

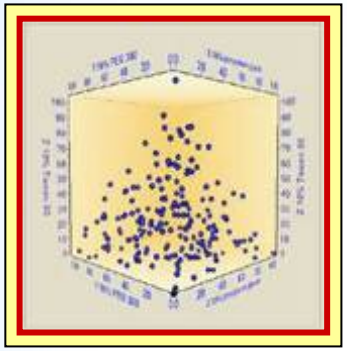
Cornerstones of Automation Platforms

- **Integration of:**
  - Science
  - Hardware/Automation
  - Information Management



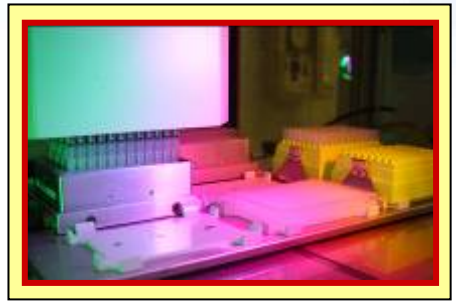
Elements of a High Throughput Process

Design of Experiment



Create Excipient Combinations

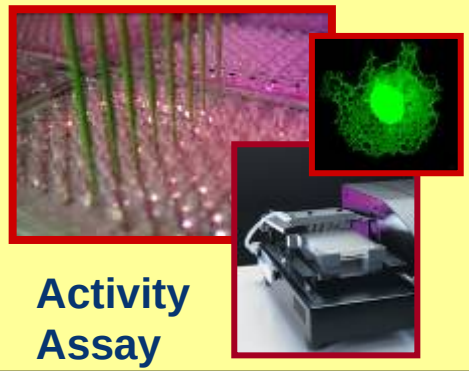
Create Formulations & Challenge Samples



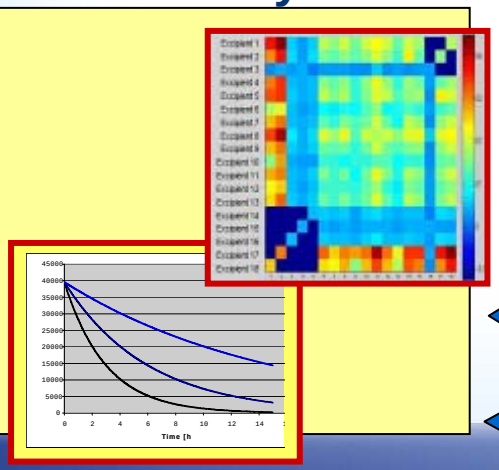
Evaluate Formulations

Physical Properties

Activity Assay



Analyze Data



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General Concerns with High Throughput Experimentation

- **Strategic**
  - Navigating formulation space
  - Assay choice
  - Informatics
- **Practical**
  - Formulation creation
  - Sample tracking
  - Sterility
- **Technical**
  - Robotics
  - Station controllers
  - Integration

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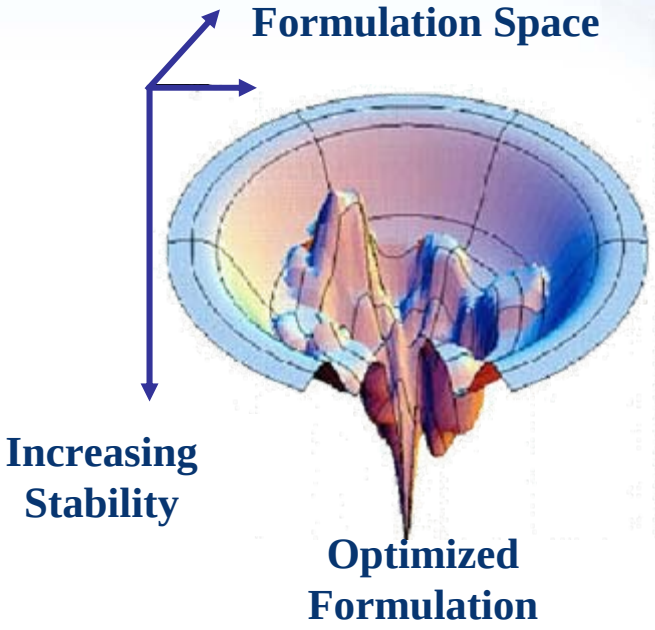
The Challenge of Exploring a Universe of Formulation Space…

Efficiently Exploring a Vast Formulation Space

- How Large is the space?
  - Solvents
  - Stabilizers
  - Solubilizers
  - Tonicifiers
  - Preservatives



- A full factorial design of a 3 excipient mixture in which 20 excipients may be used in one of three possible concentrations yields a total of 30,780 possible formulations

- Constant emphasis on space reduction

Energy landscape image from the Dill Research Group's website

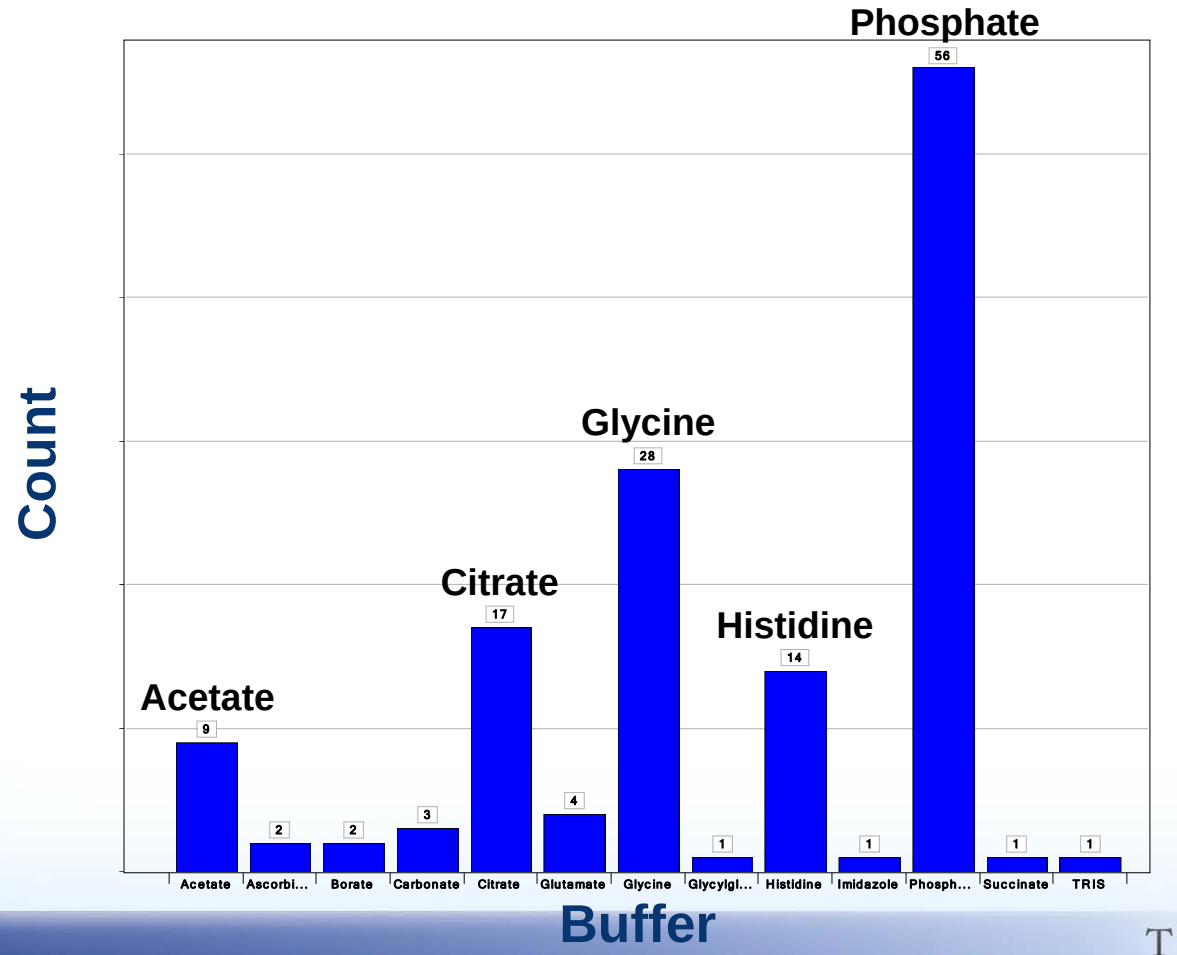
Formulation Space Critical Questions

- **How to reduce the space?**
  - Identify promising excipient classes by testing class representatives
  - Limit number of formulation components

- **How to minimize risk of missing formulations?**
  - Screen multiple representatives of each excipient class
  - Broader screen within promising classes
  - Diversity in lead candidates
    - Carry through a number of candidates to next formulation round
  - Fine tune at multiple stages

Excipient Selection & Prioritization

- Learn from commercial formulations
- Reduce space by focusing on common excipients



- Antibodies
- Proteins
- Vaccines

Other Common Excipients

- **Amino Acids**
  - Arginine
  - Lysine
  - Glycine
  - Proline
- **Salts**
  - Ammonium sulfate
  - Magnesium sulfate
  - Calcium chloride
  - Sodium chloride
- **Sugars and Polyols**
  - Cyclodextrins
  - Mannitol
  - Sucrose
  - Maltose
  - Sorbitol
  - Trehalose
- **Surfactants**
  - Poloxamer 188/407
  - Polysorbate 20/80
- **Antioxidants and Preservatives**
  - Ascorbic acid
  - Citric acid
  - Methionine
  - Benzyl alcohol
  - *m*-cresol
  - Methylparaben
- **Polymers**
  - Dextran
  - Polyethylene glycol
- **Other**
  - Albumin
  - Thioglycolic acid

Be Aware of Excipient Incompatibilities

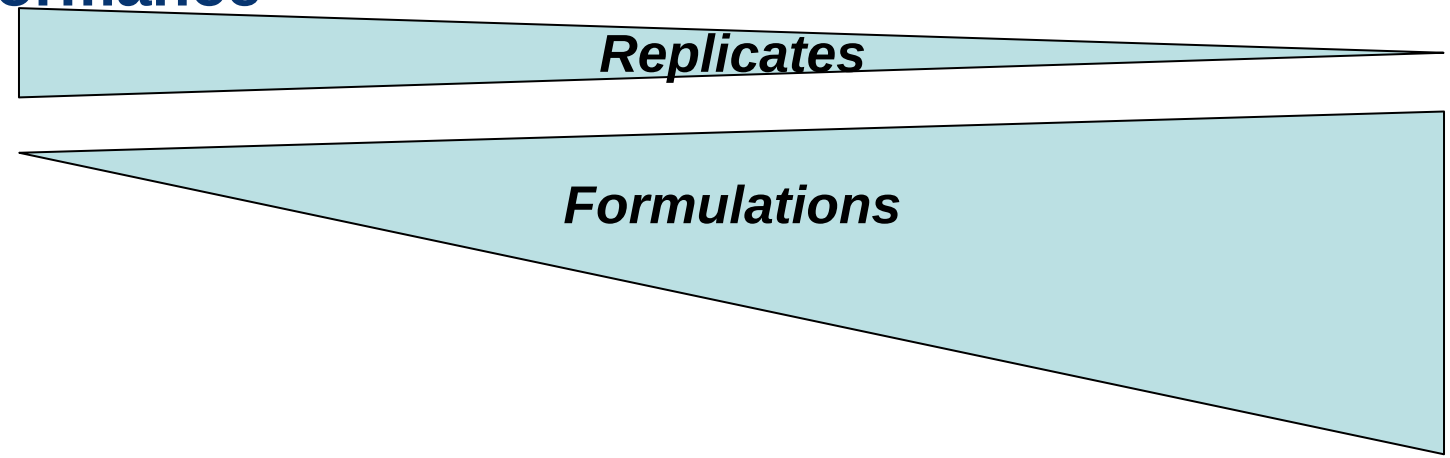
- **Are there known excipient interactions to be avoided?**
- **Material/process incompatibility**
  - **Will excipients degrade containers, etc**
- **Assay incompatibility**
  - **Will the excipients interfere with the readout**

Define Concentration Screening Limits

- **Maximum**
  - Amount allowed in FDA-approved drugs
  - Tonicity (total number of dissolved particles)
  - Toxicity (per component basis)
- **“Nominal”**
  - Existing formulations
- **Minimal**
  - How to determine?
    - CMC for surfactants
    - Some set factor below “nominal”

Transitioning from Validation to High Throughput Screening

- Evaluate process performance
- Screening



- Growing emphasis on exploring formulation space

Set Throughput Levels & Goals

- **Medium Throughput**
  - Manual at first with increasing levels of automation
  - Goals
    - Optimize process
    - Establish assay robustness
    - Identify starting points from which to explore broader formulation space
  - Example throughput: 6-12 plates per week average

- **High Throughput**
  - Final automated process
  - Goals
    - Large scale combinatorial formulation experimentation
    - Achieve target stability goals
  - Example throughput: ~ 100 plates per week average

General Concerns with High Throughput Experimentation

- **Strategic**
  - **Navigating formulation space**
  - **Assay choice**
  - **Informatics**
- **Practical**
  - **Formulation creation**
  - **Sample tracking**
  - **Sterility**
- **Technical**
  - **Robotics**
  - **Station controllers**
  - **Integration**

Choose a Balance of Analytic Techniques

Visual Inspection

Absorbance Optical Density

Nephelometry

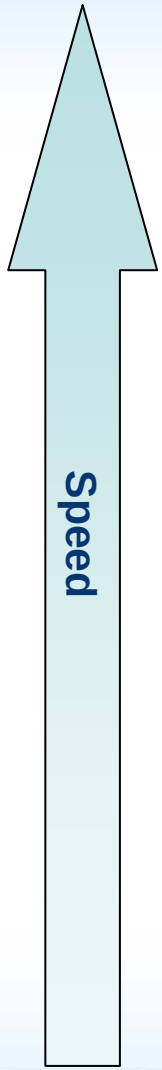
Light Scattering

CD, DSC, FL

CZE, cIEF, FFF

Size Exclusion Chromatography

AUC



- No need to perform detailed data analysis
  - Rank order
- Compare "fingerprints"
  - Look for differences
- Can advance later stage tests

Criteria for Successful Assay Porting

- Obtain similar results with manual & automated process
- Low well-to-well variability (acceptable RSDs)
  - Trade off vs. platform capacity
- Consistent results plate-to-plate
- Achieve target throughput

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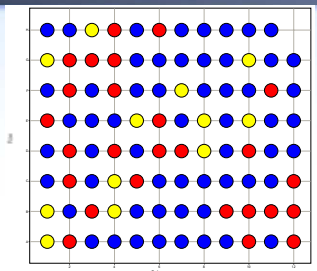
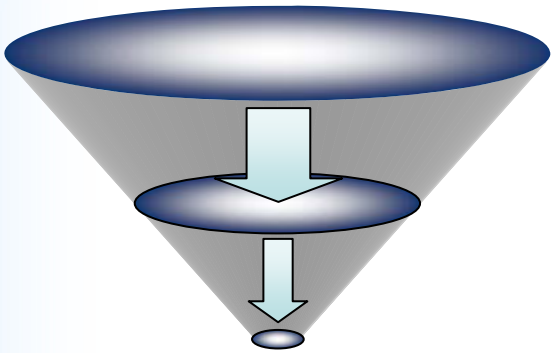
Sequential Decision Making



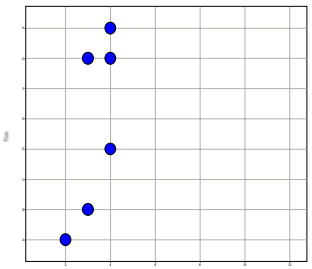
All Formulations



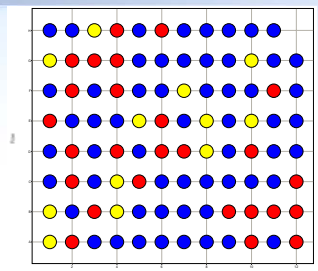
Assay 1

Assay 2

Assay 3



Lead Formulations



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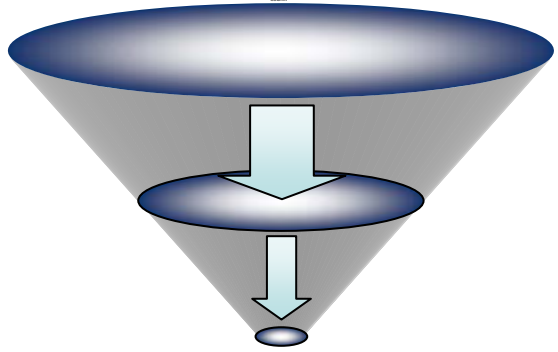
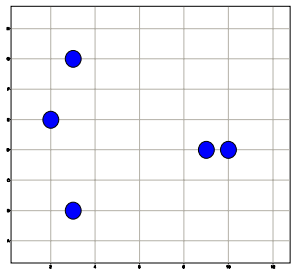


Assay 2

Assay 1

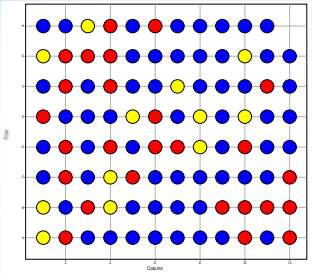
Assay 3



Lead Formulations

- Continuous reduction of data
- Outcome may depend on path
- Risk of missing formulations

Multidimensional Decision Making



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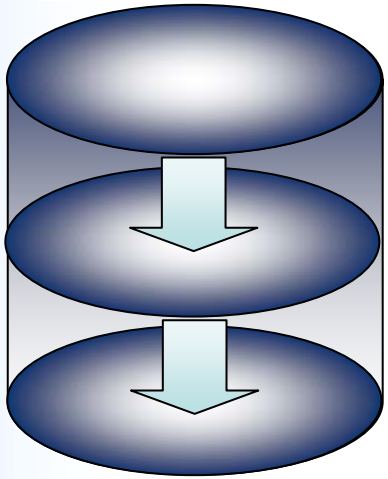

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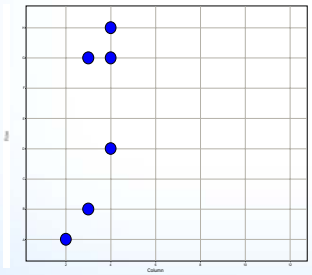

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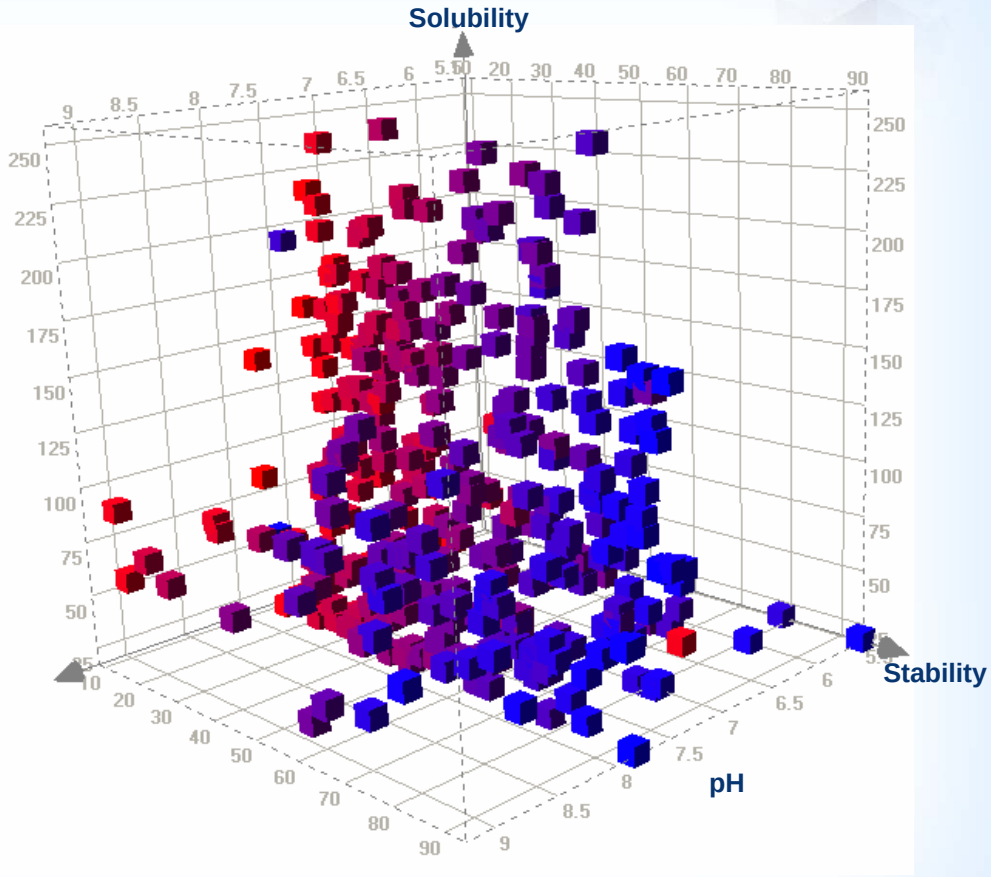

Role of Validation

- Validation is *critical*
  - Consequences of trading speed and sensitivity
  - Not a full characterization of every sample
  - Scaling issues
  - Materials
- Best performed manually
- Prevents going down the wrong path

Summary of High Throughput Experimentation

- **Advantages**
  - Efficiently explores a larger space
  - Increases throughput while increasing consistency
  - May allow for later stage assays to be brought up sooner
  - Reduces material requirements per experiment

- **Limitations**
  - Assay surrogacy
  - Devising appropriate screening strategies
  - Data analysis and interpretation
  - Scale-up
  - Risk of missing good formulations

- **High throughput technologies enable good science and create opportunities for products with enhanced properties**

Acknowledgements

Thanks to the people of TransForm

Who are TransForm Pharmaceuticals?

- ***Founded in 1999***
- ***Cutting edge technologies in high throughput formulation***
- ***Based in Lexington, MA***
- ***106 employees***
- ***Two compounds in the clinic (lead in Phase II)***
- ***Acquired in April '05 by Johnson and Johnson***

Johnson & Johnson

- Center of excellence for advanced form & formulation
- Leverage form & formulation innovation into new applications
- Foundation for Johnson & Johnson's emerging Boston pharmaceutical R&D presence

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