The implementation of innovative experimental design technologies on Trametinib

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Pharmaceuticals

- **Prescription medicines**
- Vaccines
- Consumer Health

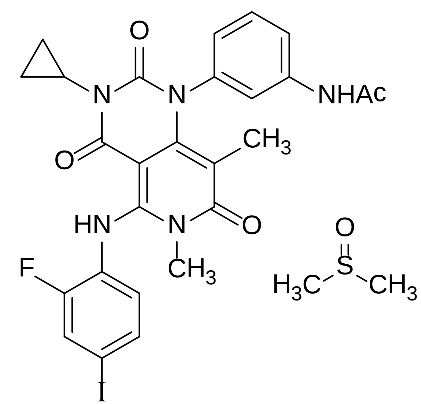
What we do

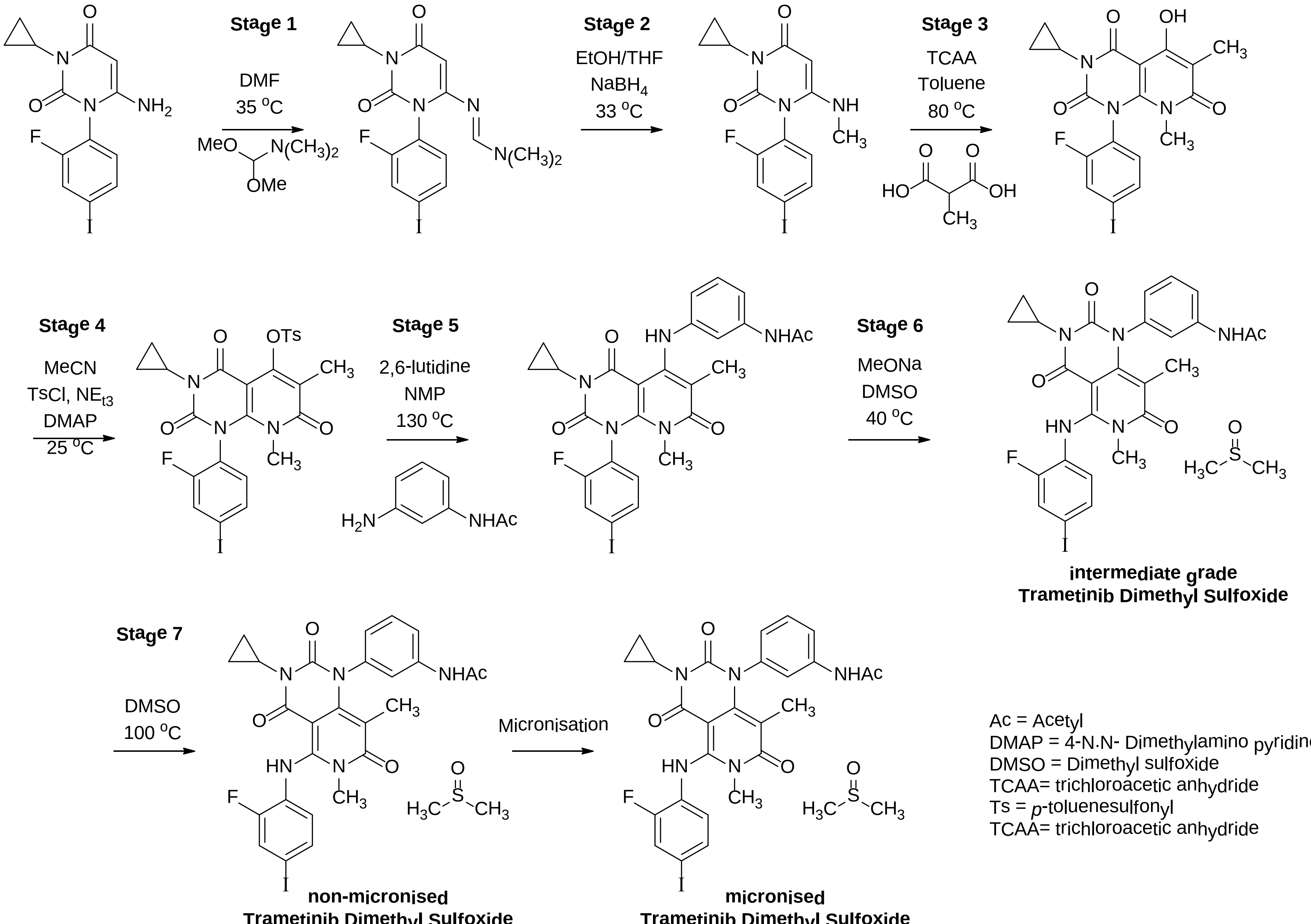
- Drug discovery research
- **Product development**
- Pilot plant
- Manufacture

“Quality by Design”

Trametinib Dimethyl Sulfoxide

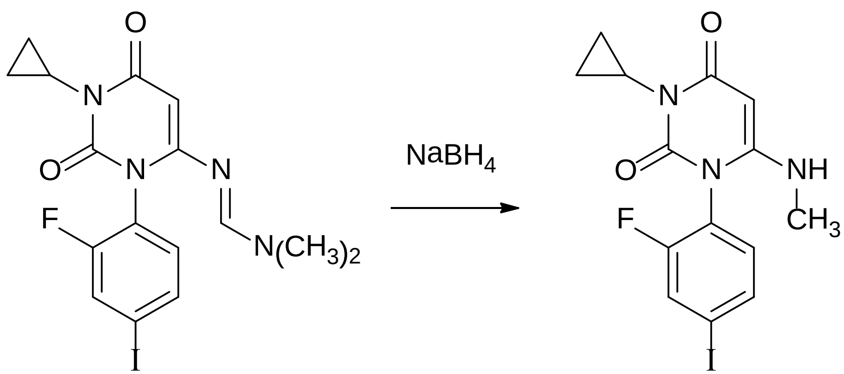
- Molecule discovered by Japan Tobacco
- Unusual DMSO solvate
- In-licenced to GSK in May 2006
- Potential applicability in a wide range of tumours
  - Driven by common Ras/Raf mutations
- Phase 3 study in metastatic melanoma
- Europe and US filing underway





Ac = Acetyl
DMAP = 4-N.N- Dimethylamino pyridine
DMSO = Dimethyl sulfoxide
TCAA= trichloroacetic anhydride
Ts = *p*-toluenesulfonyl
TCAA= trichloroacetic anhydride

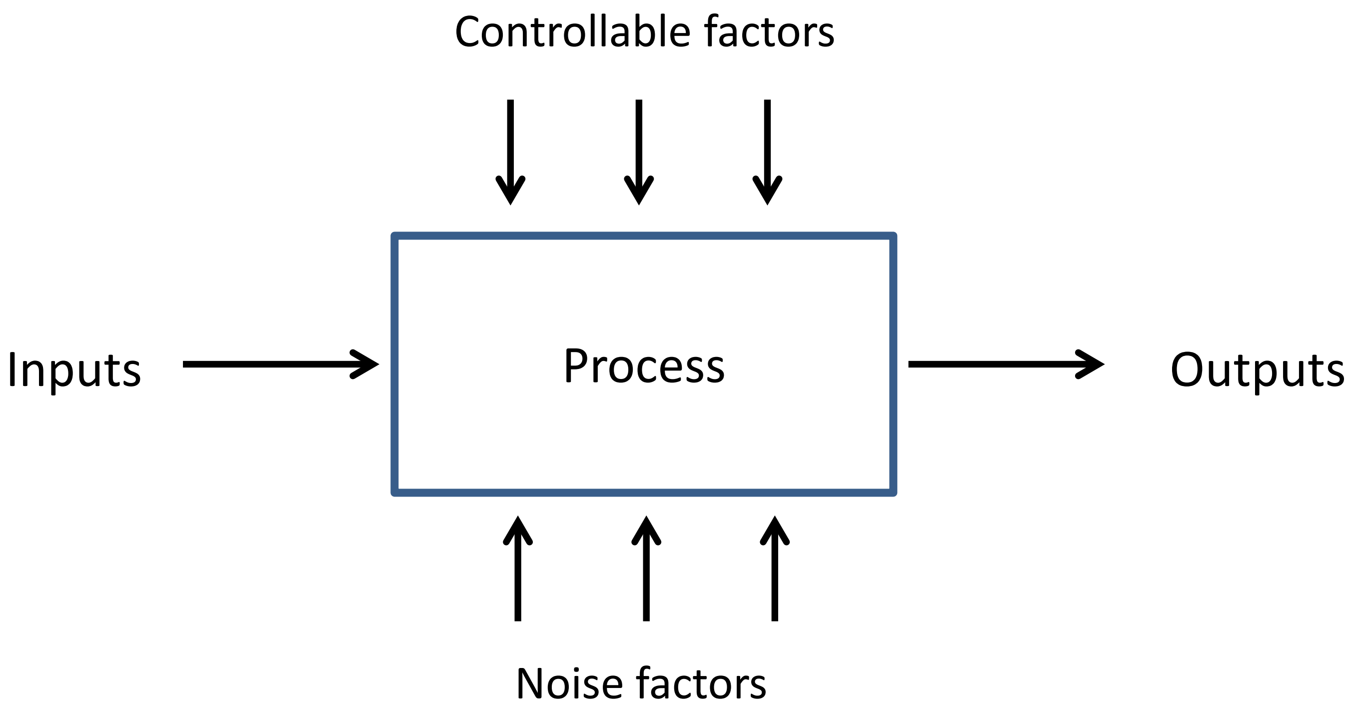
Stage 2



- Key de-iodinated impurity formed under reaction conditions
- Chemistry hard to control in early campaigns
  - Variability in purity
  - Operability issues
  - Reworks after this and subsequent stage
- Determine optimal process conditions for scale-up and file
  - Experimental design

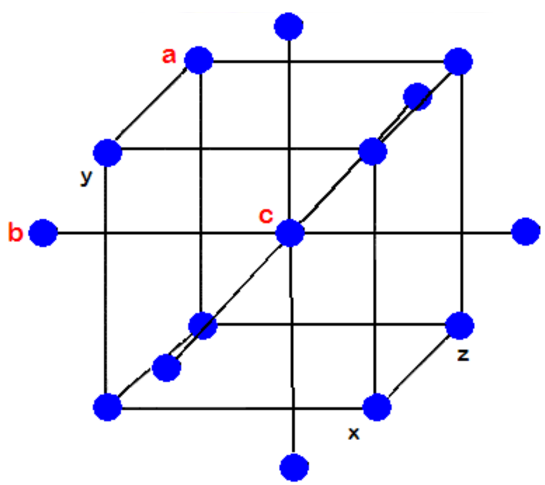
What is a Designed Experiment?

- A structured set of tests of a process or system



Experimental design

- Classical designs
  - Standard sets of designs for each number of parameters
  - Can have a resource constraint, leading to changing the problem to fit the design, often this is by dropping parameters to reduce number of runs

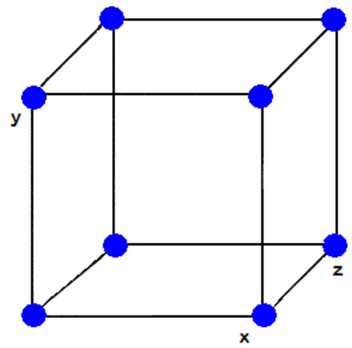


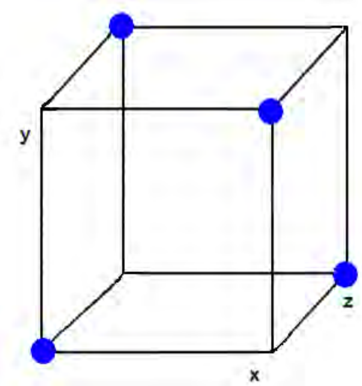
# of parameters

# of runs

	2	3	4	5	6	7
4	Full	1/2 Fract.				
8		Full	1/2 Fract.	1/4 Fract.	1/8 Fract.	1/16 Fract.
16			Full	1/2 Fract.	1/4 Fract.	1/8 Fract.
32				Full	1/2 Fract.	1/4 Fract.
64					Full	1/2 Fract.
128						Full

Aliasing





8 runs

Main effects and interactions can all be estimated

1. X
2. Y
3. Z
4. XY
5. XZ
6. YZ

4 runs, resolution 3 design

Main effects = Interactions

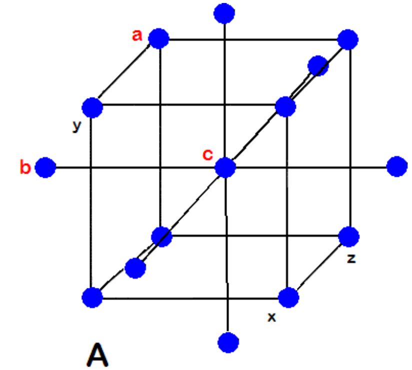
1. X = YZ
2. Y = XZ
3. Z = XY

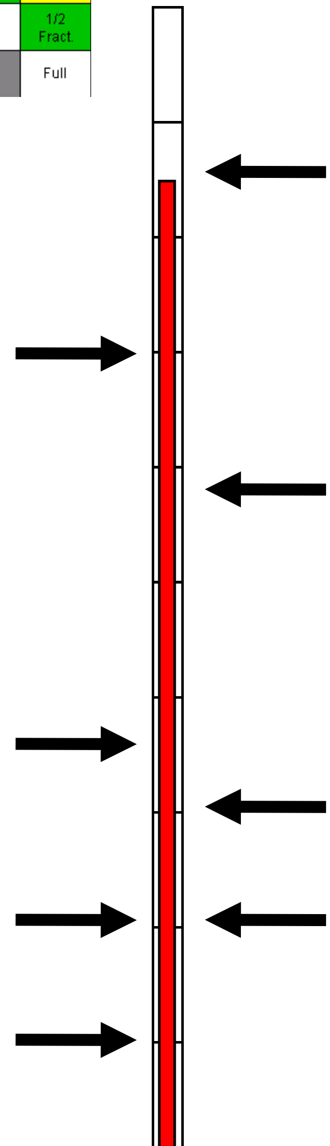
- We don’t have enough runs to estimate the effect of all the terms independently
- The result is some terms are “aliased”

Fractional factorial (6 factors)

	2	3	4	5	6	7
4	Full	1/2 Fract.				
8		Full	1/2 Fract.	1/4 Fract.	1/8 Fract.	1/16 Fract.
16			Full	1/2 Fract.	1/4 Fract.	1/8 Fract.
32				Full	1/2 Fract.	1/4 Fract.
64					Full	1/2 Fract.
128						Full

Response surface designs





6 factors (86 runs)

Full fraction (64 runs)

5 factors (50 runs)

Resolution 5 (32 runs)

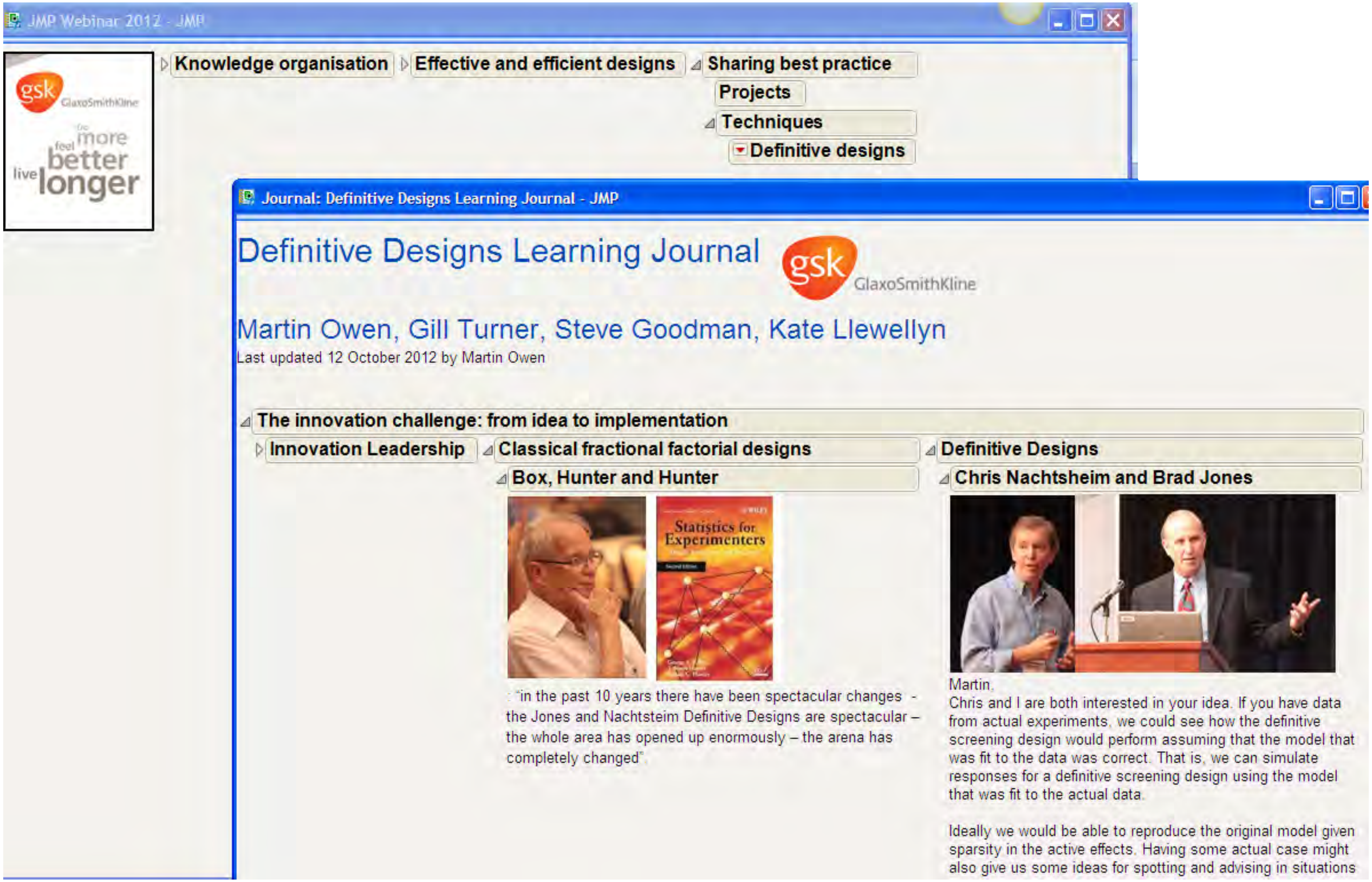
4 factors (30 runs)

Resolution 4 (16 runs)

3 factors (16 runs)

Resolution 3 (8 runs)

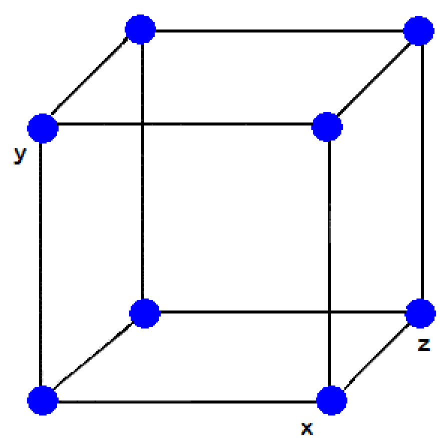
Custom designs

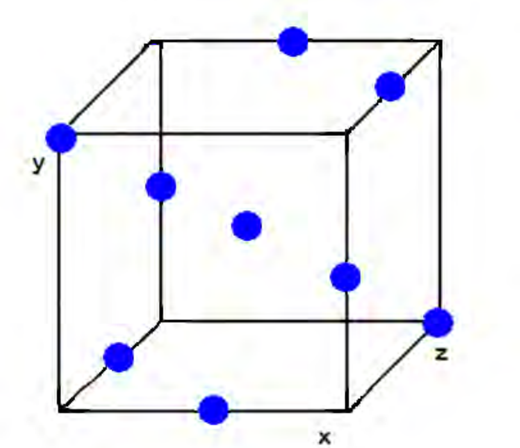


Custom designs

- Classical fractional factorial designs are orthogonal and require the # of runs to be a power of 2
- Custom designs are computer generated optimal designs
- Optimal designs are generally nonorthogonal and hence have fewer resource constraints

	2	3	4	5	6	7
4	Full	1/2 Fract.				
8		Full	1/2 Fract.	1/4 Fract.	1/8 Fract.	1/16 Fract.
16			Full	1/2 Fract.	1/4 Fract.	1/8 Fract.
32				Full	1/2 Fract.	1/4 Fract.
64					Full	1/2 Fract.
128						Full

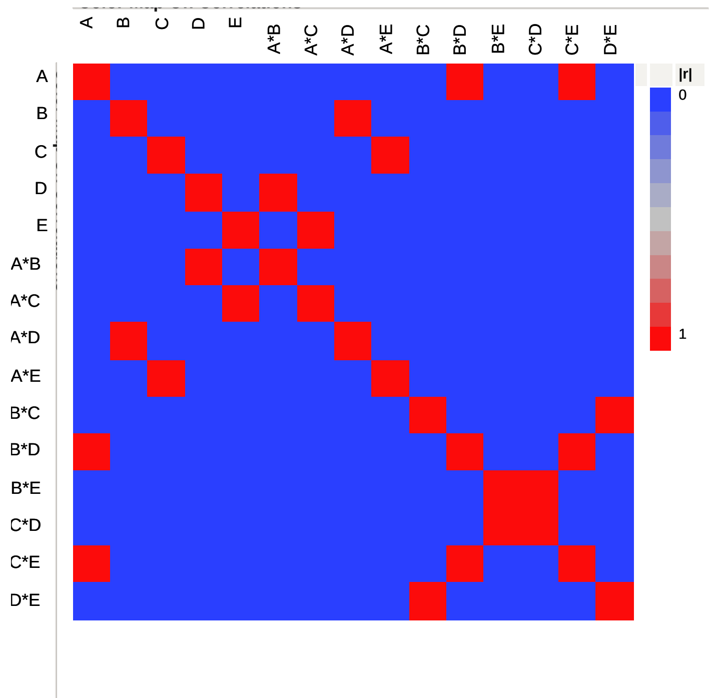




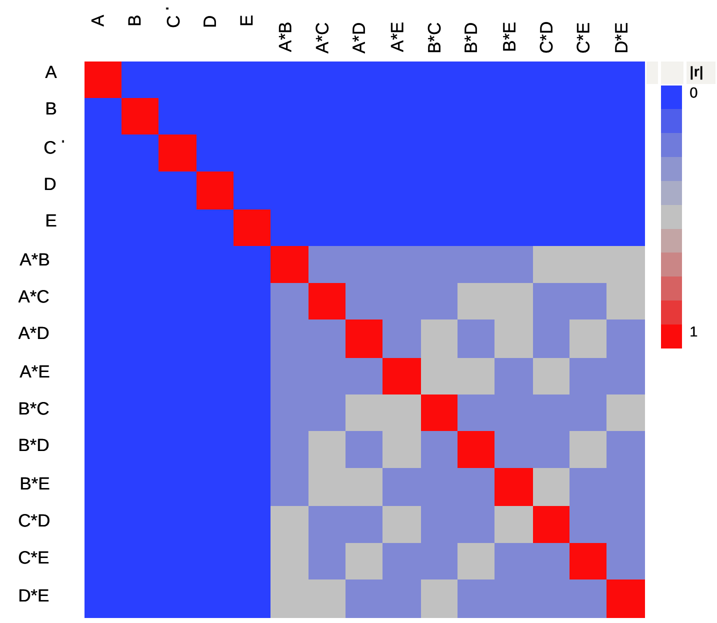
Flexible resource designs

- Classical designs are complemented by newer custom design technologies in the form of optimal designs
  - Optimal designs (e.g. definitive screening designs, supersaturated designs) offer greater flexibility in decision making (risk vs. resource)
  - Require clear prior information and risk caveats

Fractional factorial



Definitive screening design



What is Quality by Design?

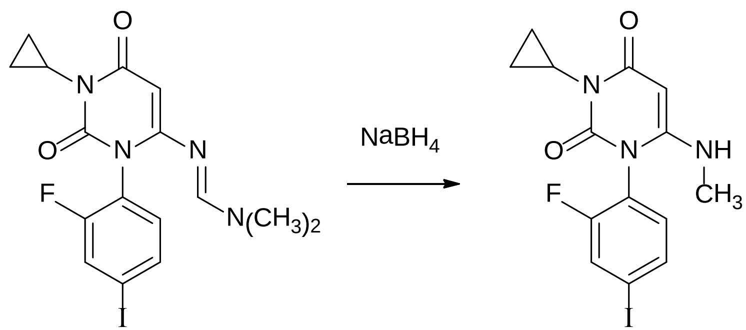
- Process and product understanding
  - Critical parameters
  - Critical impurities

- Risk assessment
  - Identify risks
  - Mitigate risks through further work

- Control strategy
  - Ensure patient safety through robust manufacturing

"Focus on the patient"

Stage 2

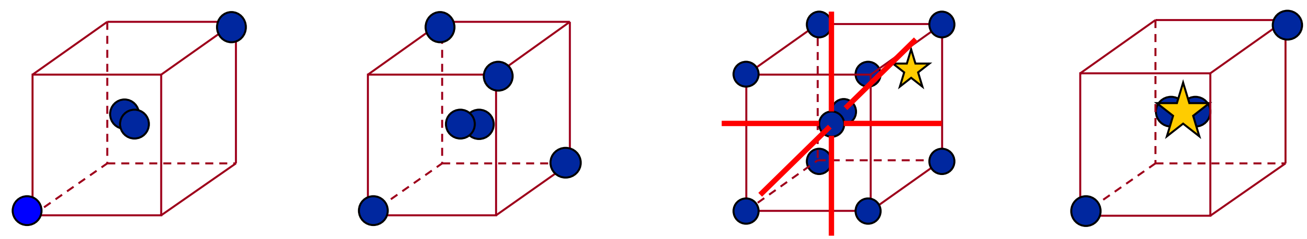


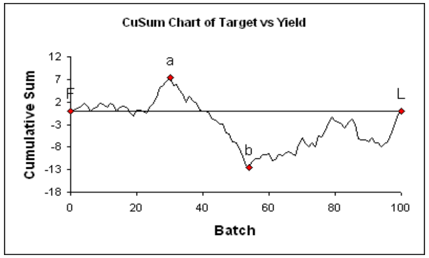
- Key de-iodinated impurity formed under reaction conditions
- This is a critical impurity that can be present in the API given to patients
  - Identify critical parameters controlling formation
  - Control parameters to ranges that ensure quality of the intermediate
- Demonstrate sequential experimental design workflow

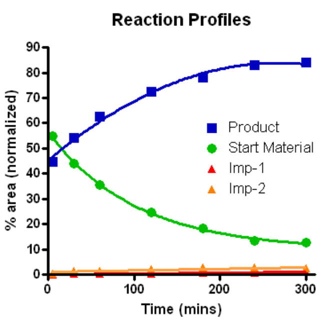
Sequential Workflow

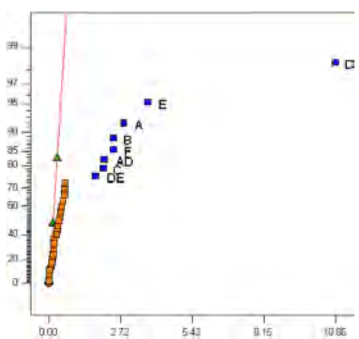
Identify parameters & ranges → Parameter investigation → Robustness & verification → Process performance

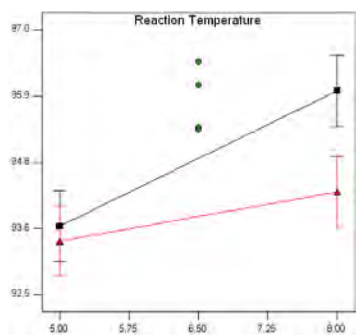
Scope	Screen	Optimise	Robustness	Trending

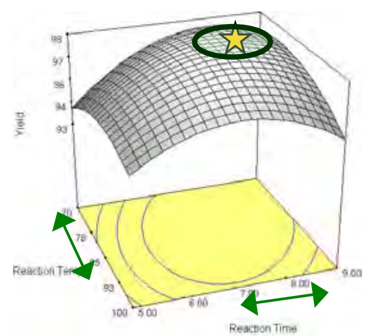












Trending on scale-up of process conditions

Explore mildest to most forcing conditions

Identify key parameters and interactions

Estimate any curvature around optimum conditions

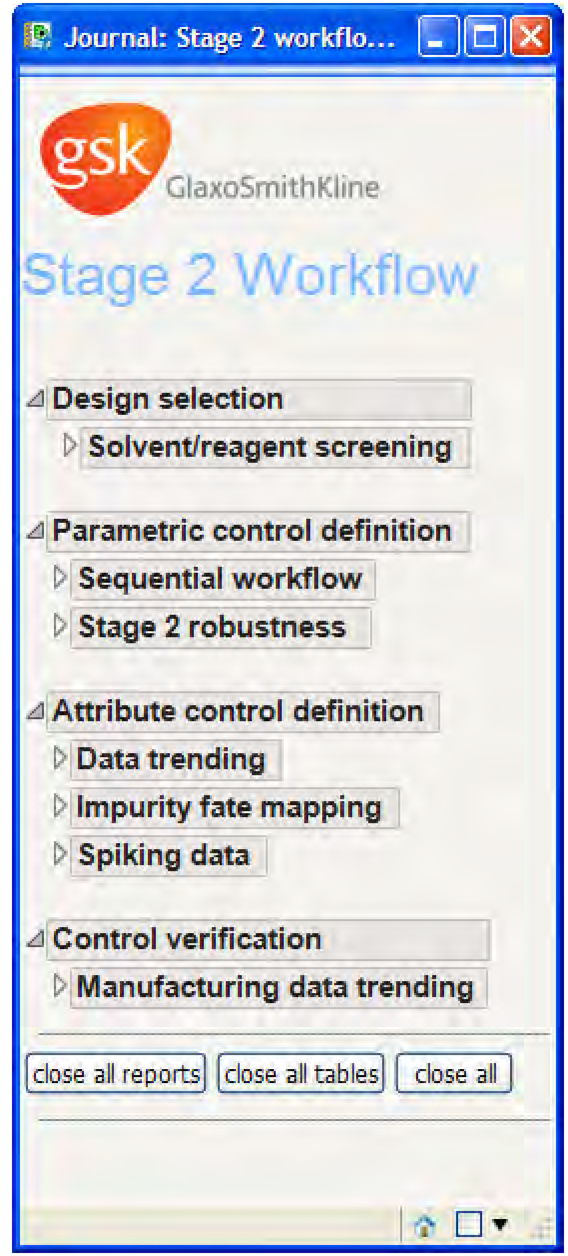
Test out process ranges

TECHNICAL DEMO

Stage 2

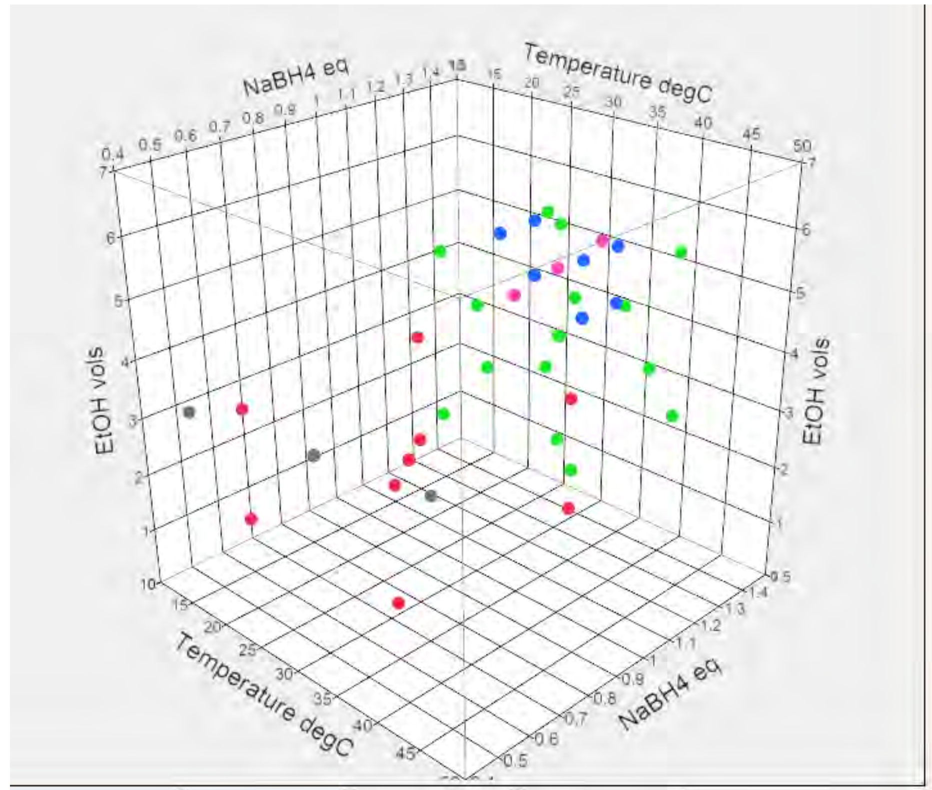
Overview of Stage 2

- High level overview of control strategy
- Details on demand
- Rest of my talk will take a deeper dive into Stage 2
  - Control strategy for the key impurity in Stage 2
  - Implementation of innovative experimental designs



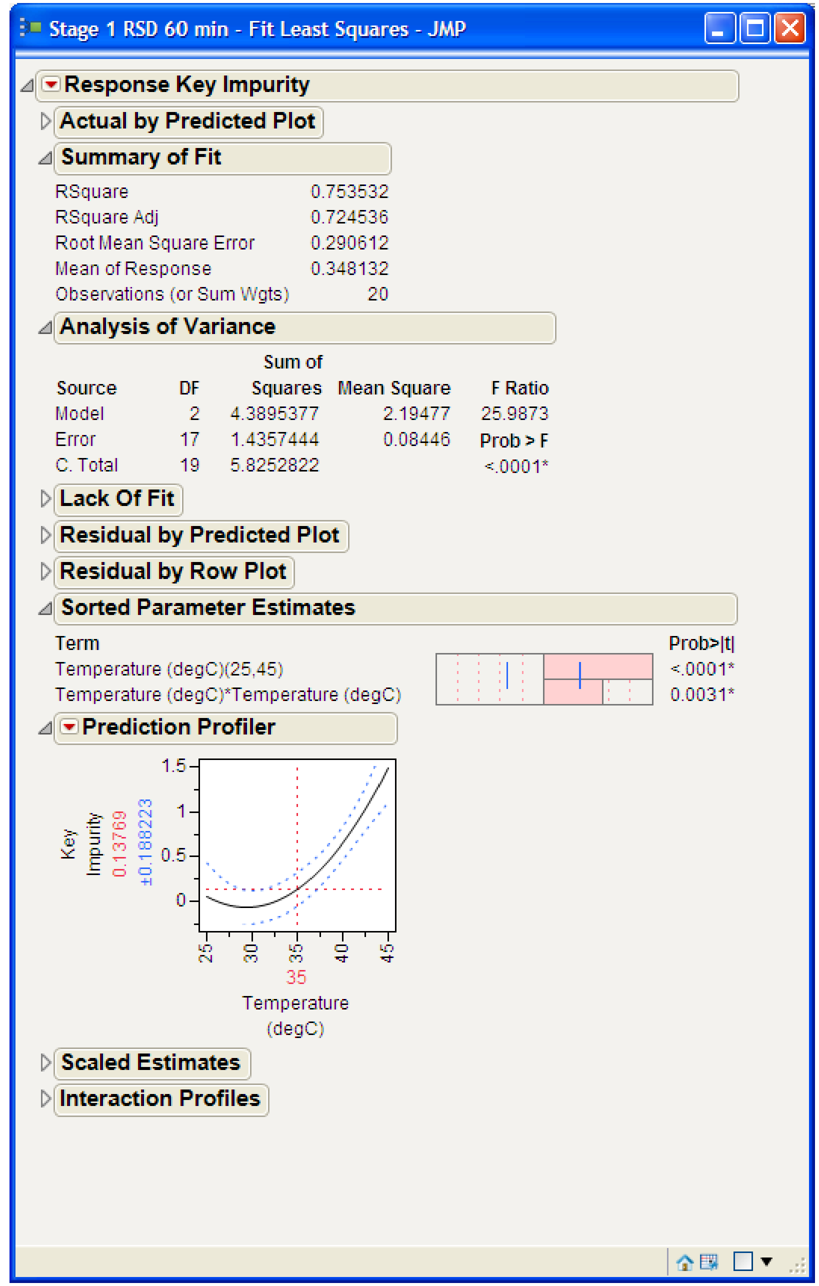
Workpackages

- Sequential workflow
- Impact of each workpackage
- Use visuals in JMP to communicate the workflow



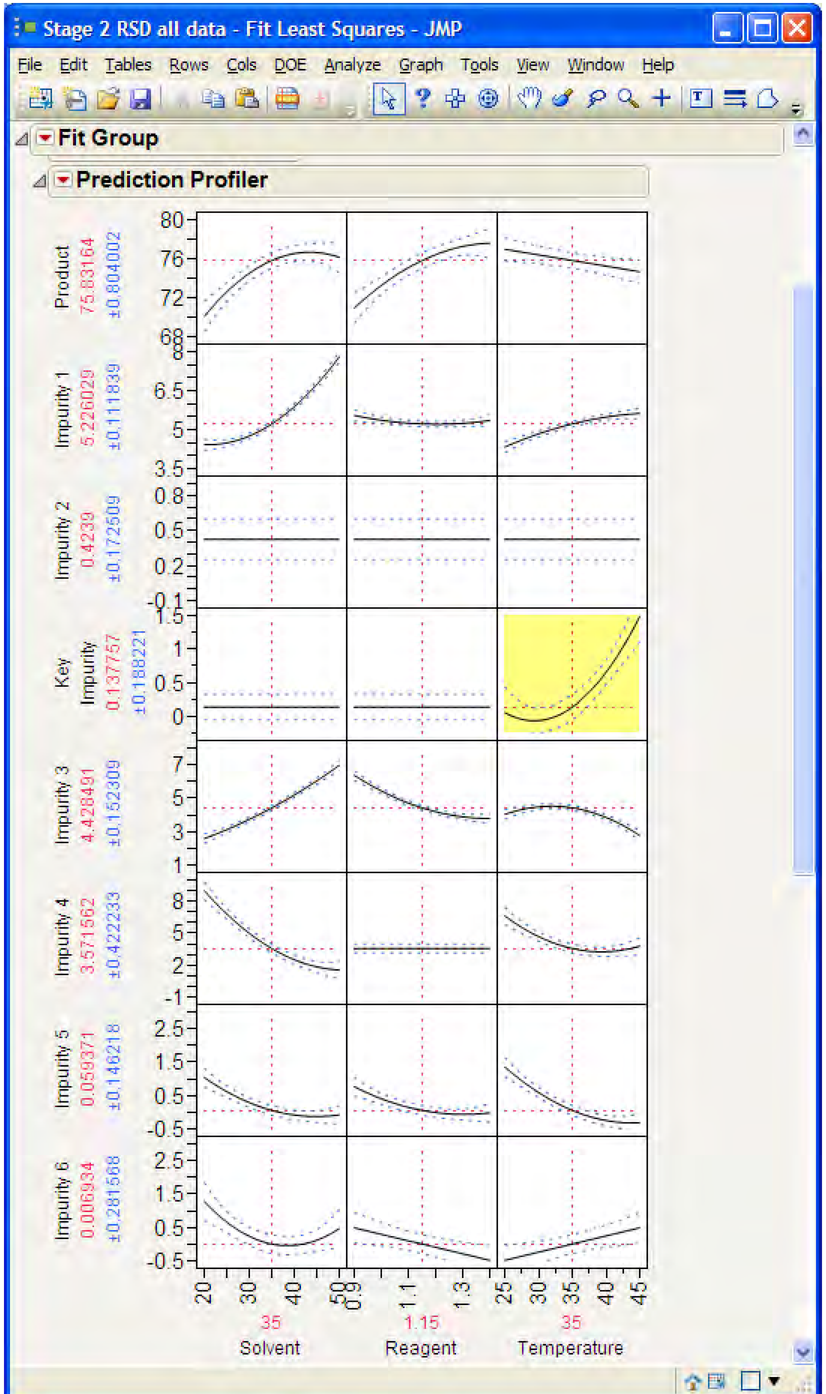
Details of key parameter

- Key impurity discussed here
- Using profiler to visualise the cause & effect relationships
- A simple message shown here
  - The real picture is much more complex



Multiple responses

- Actually the real picture is more complex
- No chemical problem has a single response
- We need to be able to visualise our multivariate world



Supersaturated design

- Collaboration with University of Southampton
- Significant prior knowledge from sequential DoE
- Simulation study to assess candidate designs
- Analysis using Gauss-Dantzig Selector

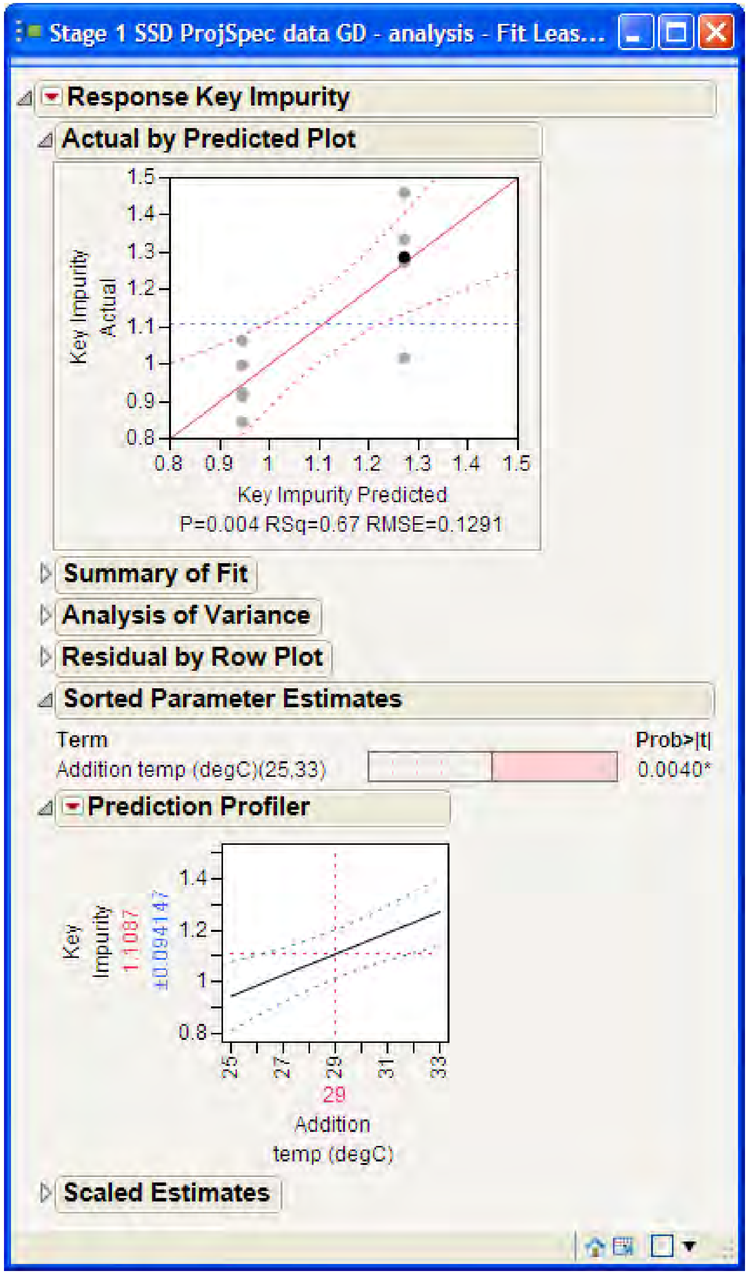
Table 4: Design for 16 factors in 10 runs

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
-1	1	1	1	1	-1	-1	1	-1	-1	1	-1	-1	-1	-1	-1
1	1	-1	1	1	-1	-1	-1	-1	-1	-1	1	1	1	1	1
-1	-1	-1	-1	-1	1	-1	1	1	-1	-1	-1	-1	-1	1	1
1	1	1	-1	1	1	-1	1	1	1	1	1	1	1	1	-1
-1	-1	1	-1	1	-1	1	-1	-1	1	-1	-1	-1	1	1	-1
-1	-1	1	1	-1	-1	1	-1	1	-1	1	1	1	-1	1	-1
1	-1	-1	1	1	1	1	1	-1	1	-1	1	1	-1	-1	-1
-1	1	-1	1	-1	1	1	-1	1	1	1	-1	-1	1	-1	1
1	1	1	-1	-1	-1	-1	-1	1	1	-1	-1	1	-1	-1	1
1	-1	1	-1	-1	-1	1	1	-1	-1	1	1	-1	1	-1	1

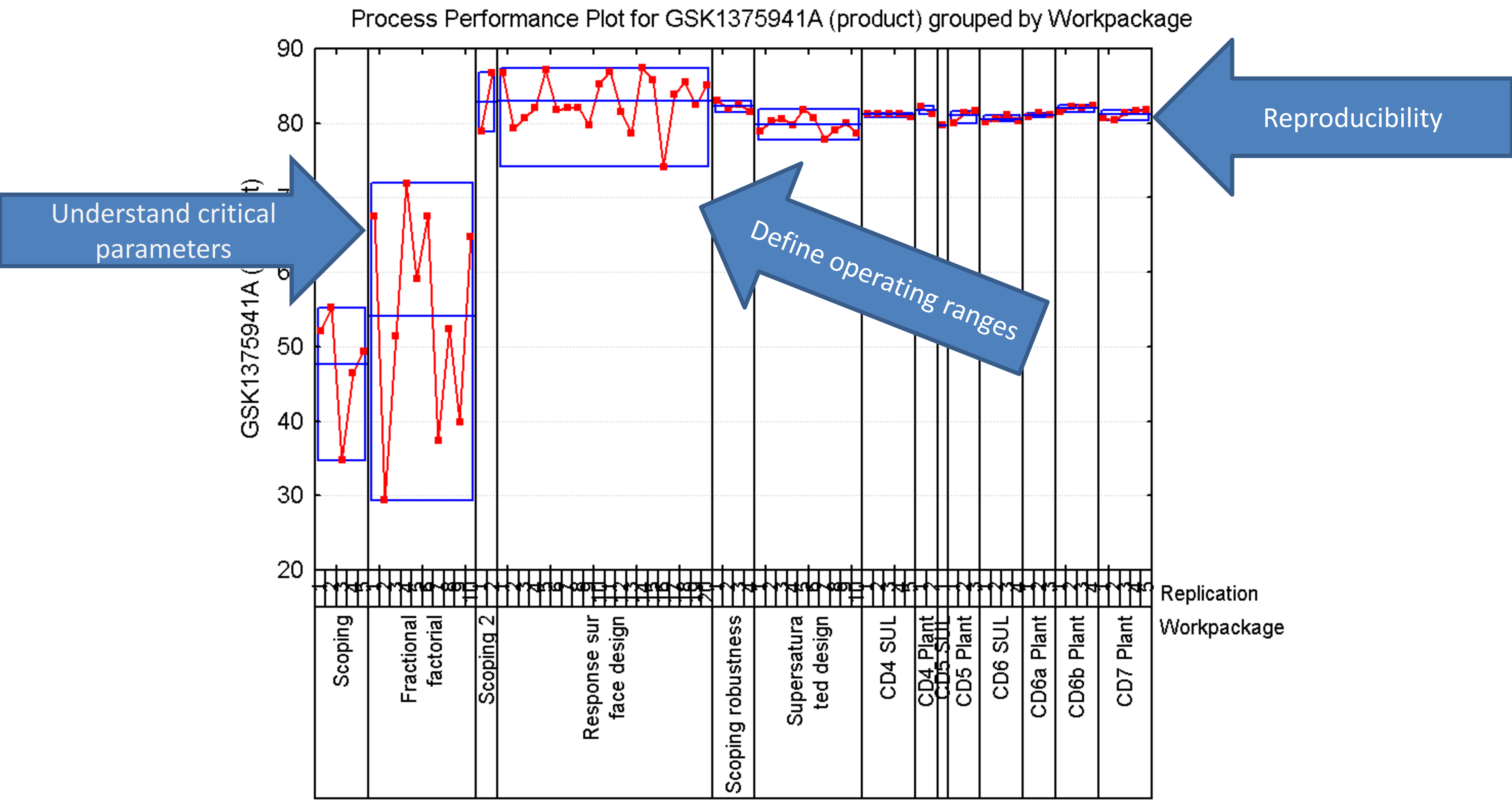
Outcome of supersaturated design

Simple message

- Key pictures for the big picture people
- Detail for the modellers and statisticians
- Here we see the active effect of temperature again



Benefits of modelling



Definitive screening designs

No aliasing of main effects

Assign curvature to specific factors

20 factors (41 runs)

15 factors (33 runs)

10 factors (21 runs)

8 factors (17 runs)

6 factors (13 runs)

4 factors (9 runs)

Fractional factorial

(half or quarter fractions)

Complete aliasing of some terms

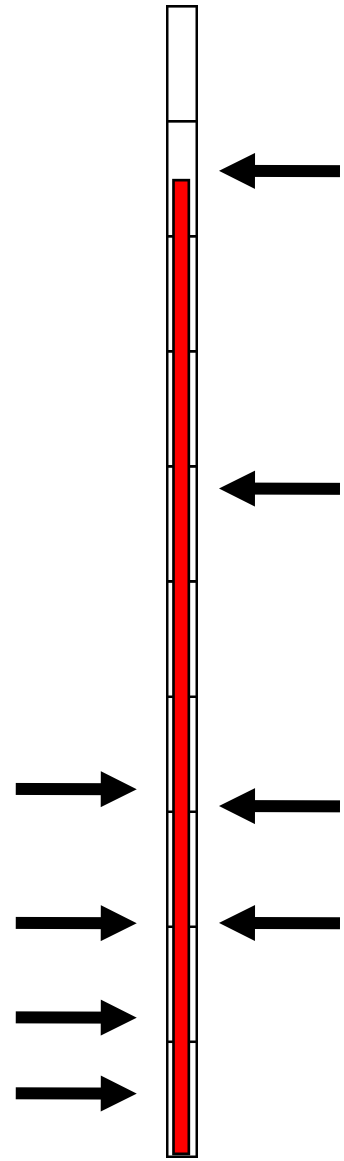
Omnibus curvature detection

8 factors (32 runs)

6 factors (16 runs)

4 factors (8 runs)

3 factors (4 runs)



Response surface designs

6 factors (86 runs)

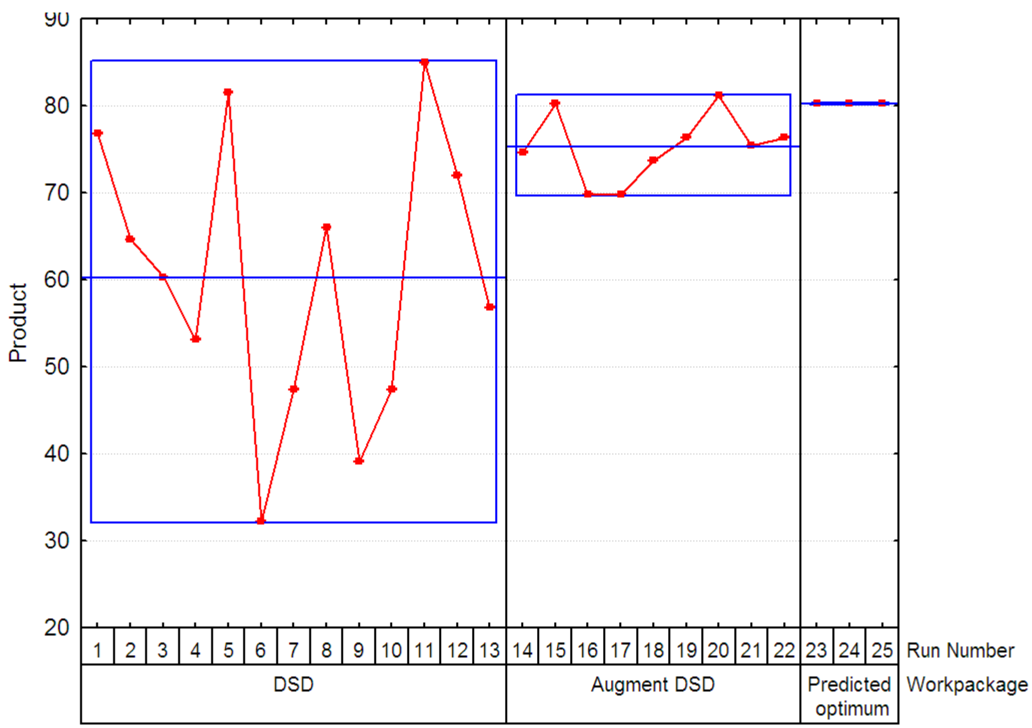
5 factors (50 runs)

4 factors (30 runs)

3 factors (16 runs)

What would the workflow look like?

1. 9 run DSD on 5 factors
2. Augment key factors with revised ranges in a further 9 runs
3. Predicted optimal conditions



Actual workflow	Predicted workflow
> 30 runs	> 22 runs

In reality – I'd have included more parameters in the initial design!

Acknowledgements

- Gill Turner & Martin Owen
  - GSK
- Trametinib Team
  - GSK
- Dave Woods, Chris Marley & Daniel Tray
  - SSD collaboration
- Bradley Jones
  - JMP

QUESTIONS?