

DESIGN SPACE MODELLING FOR ROBUST DRUG PRODUCT TECHNOLOGY TRANSFERS

KILLIAN RYAN

PRINCIPAL ENGINEER, AMGEN, PROCESS DEVELOPMENT



Pioneering science delivers vital medicines™

AGENDA

- **Context**
- **Example of design space modelling – plunger depth**
 - What we used to do – “following our nose”
 - More accurate (and less precise)?
- **Strategies and Future Directions**

AGENDA

- **Context**
- Example of design space modelling – plunger depth
 - What we used to do – “following our nose”
 - More accurate (and less precise)?
- Strategies and Future Directions

CONTEXT: MANY TECHNOLOGY TRANSFERS SINCE 2011 SITE ACQUISITION

 **Repatha**[®]
(evolocumab) injection
140 mg/mL

 **Kyprolis**[™]
(carfilzomib) for injection


 **Aranesp**[®]
darbepoetin alfa
injection

 **Neulasta**[®]
(pegfilgrastim) injection

XGEVA[®]
(denosumab) injection

NEUPOGEN[®]
(FILGRASTIM)

 **prolia**[®]
(denosumab) injection

 **BLINCYTO**[®]
(blinatumomab) for injection
35 mcg single-use vial

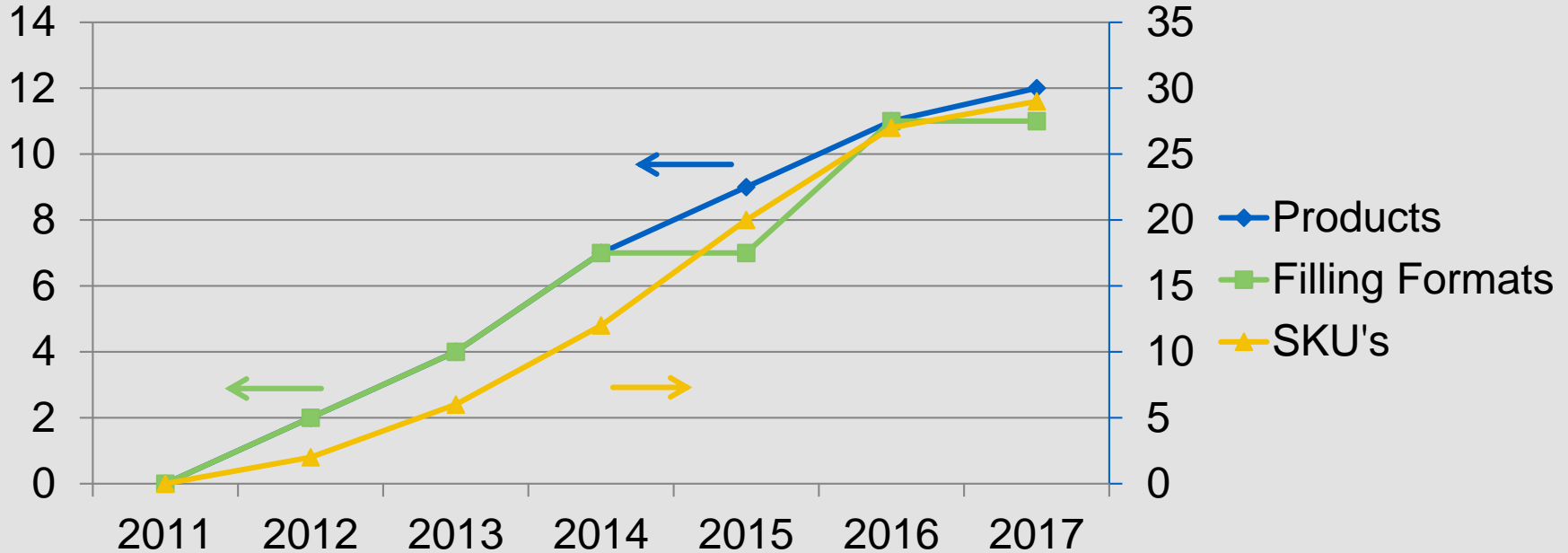
 **Enbrel**[®]
etanercept

 **Nplate**[®]
romiplostim injection

EPOGEN[®]
(EPOETIN ALFA)
RECOMBINANT
INJECTION

 **Vectibix**[®]
(panitumumab)
Injection for IV Infusion

CONTEXT: MANY TECHNOLOGY TRANSFERS SINCE 2011 SITE ACQUISITION



Provided October, 2016 as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.

CONTEXT: MANY TECHNOLOGY TRANSFERS SINCE 2011 SITE ACQUISITION

| Product | Syringe Presentations |
|-----------|--------------------------------------|
| Neulasta® | Pre-Filled Syringe |
| Aranesp® | Pre-Filled Syringe Dose A |
| | Pre-Filled Syringe Dose B |
| | Pre-Filled Syringe Dose C |
| | Pre-Filled Syringe for Auto-Injector |
| NEUPOGEN® | Pre-Filled Syringe Dose A |
| | Pre-Filled Syringe Dose B |
| Prolia® | Pre-Filled Syringe |
| ENBREL® | Pre-Filled Syringe for Auto-Injector |
| | Pre-Filled Syringe Dose A |
| | Pre-Filled Syringe Dose B |
| Repatha® | Pre-Filled Syringe |
| | Pre-Filled Syringe for Auto-Injector |

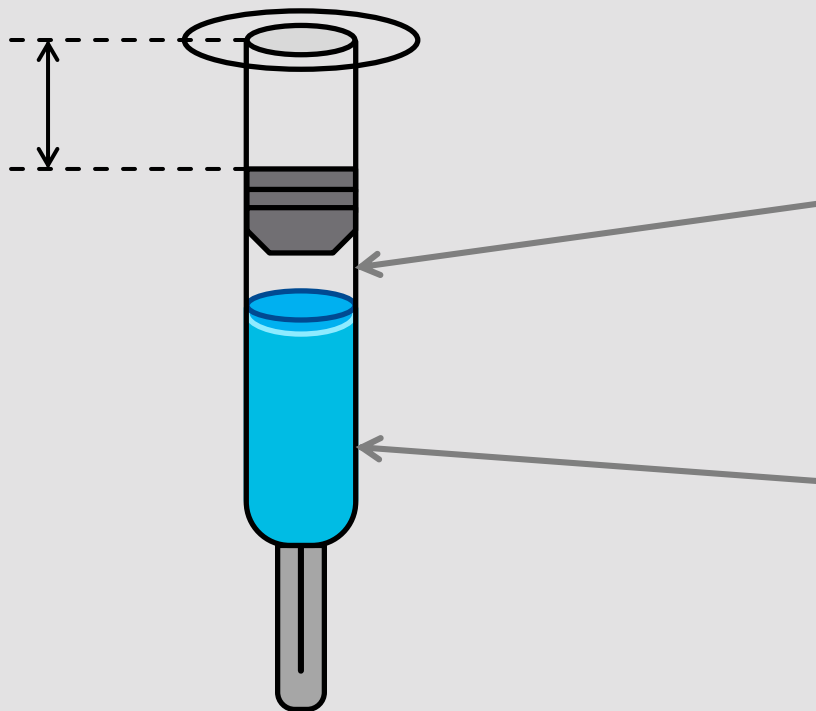
| Product | Lyo Vial Presentations |
|-----------|------------------------------|
| Enbrel® | 4 cc Lyophilised Vial |
| Nplate® | 6 cc Lyophilised Vial Dose A |
| | 6 cc Lyophilised Vial Dose B |
| Kyprolis® | 50 cc Lyophilised Vial |
| | 30 cc Lyophilised Vial |
| BLINCYTO® | 4 cc Lyophilised Vial |

| Product | Liquid Vial Presentations |
|------------|---------------------------|
| NEUPOGEN® | 3 cc Liquid Vial Dose A |
| | 3 cc Liquid Vial Dose B |
| EPOGEN® | 3 cc Liquid Vial |
| Vectibix® | 20 cc Liquid Vial |
| | 5 cc Liquid Vial |
| XGEVA® | 3 cc Liquid Vial |
| Stabiliser | 10 cc Liquid Vial |

AGENDA

- Context
- **Example of design space modelling – plunger depth**
 - What we used to do – “following our nose”
 - More accurate (and less precise)?
- Strategies and Future Directions

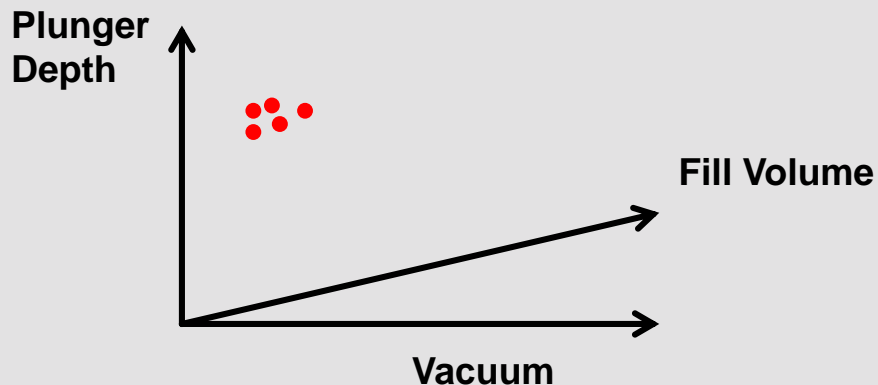
PLUNGER DEPTH EXAMPLE



**More Vacuum =
Plunger Lower
Down**

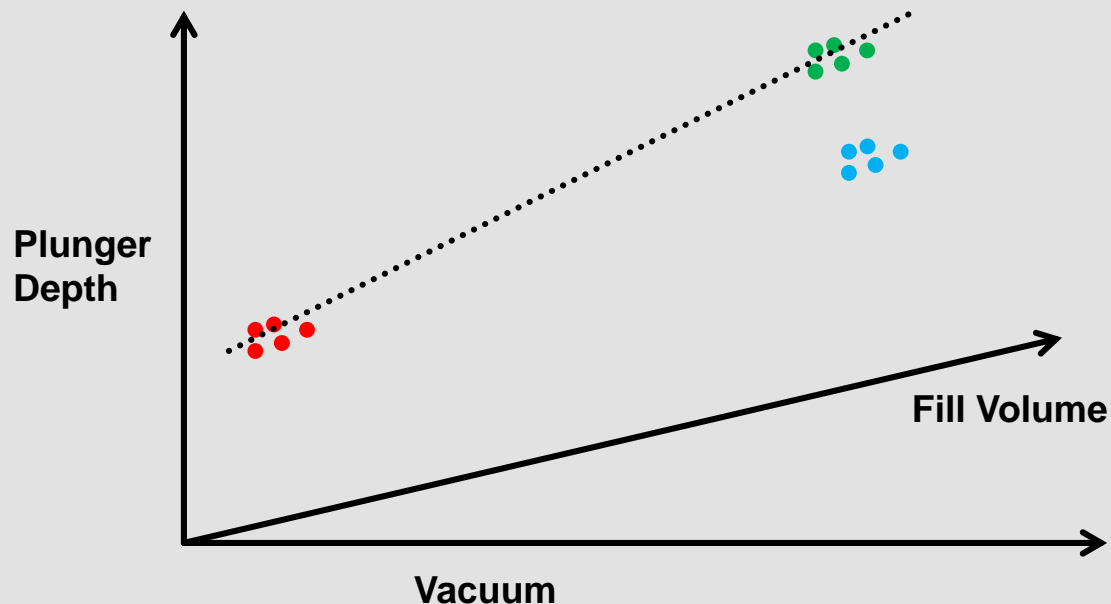
**More Liquid =
Plunger Higher Up**

PLUNGER DEPTH EXPERIMENTATION



**Commercial Line
Time,
Components,
Cost**

PLUNGER DEPTH EQUIPMENT EXPERIMENTATION

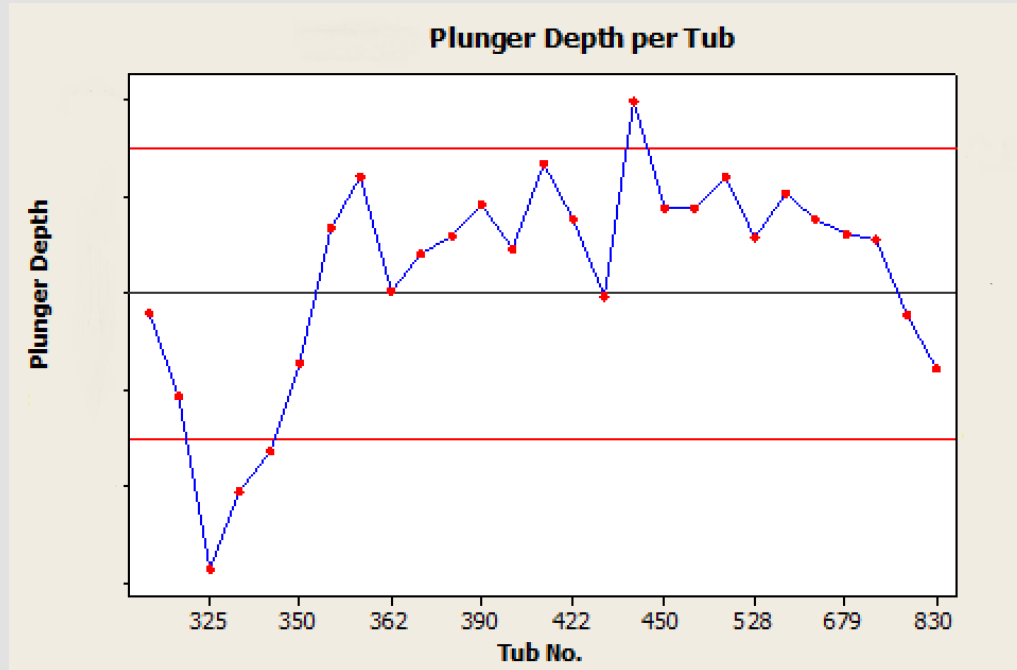


Commercial Line
Time,
Components,
Cost
Experimental Error
Inefficient

WHAT WE'VE LEARNED FROM THE CHARTS....

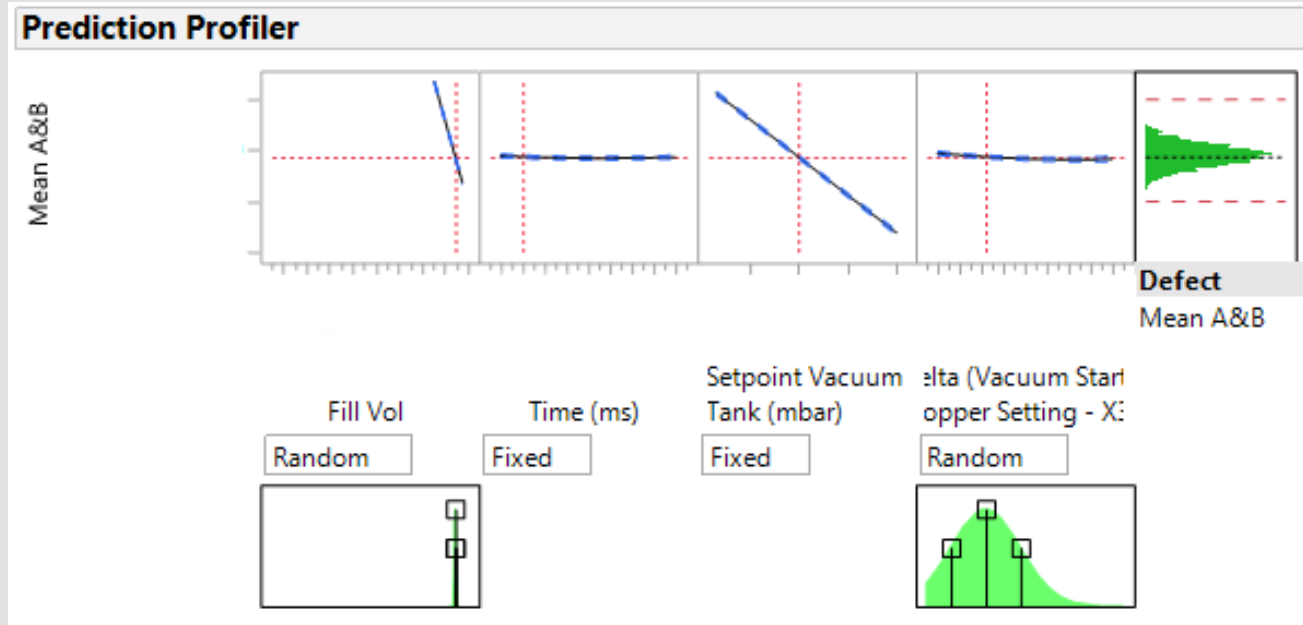
- **Small Region**
 - Vacuum Vs. Plunger Depth for a single product
 - Following our nose
- **Chart 2 Vacuum Vs. Plunger Depth for Design Space**
 - Separating noise from true response
 - Precision and the illusion of accuracy

NOISE OR TRUE RESPONSE?



Provided October, 2016 as part of an oral presentation and is qualified by such, contains forward-looking statements, actual results may vary materially; Amgen disclaims any duty to update.

THIS IS WHAT IT LOOKS LIKE WITH FOUR PARAMETERS...



AGENDA

- Context
- Example of design space modelling – plunger depth
 - What we used to do – “following our nose”
 - More accurate (and less precise)?
- **Strategies and Future Directions**

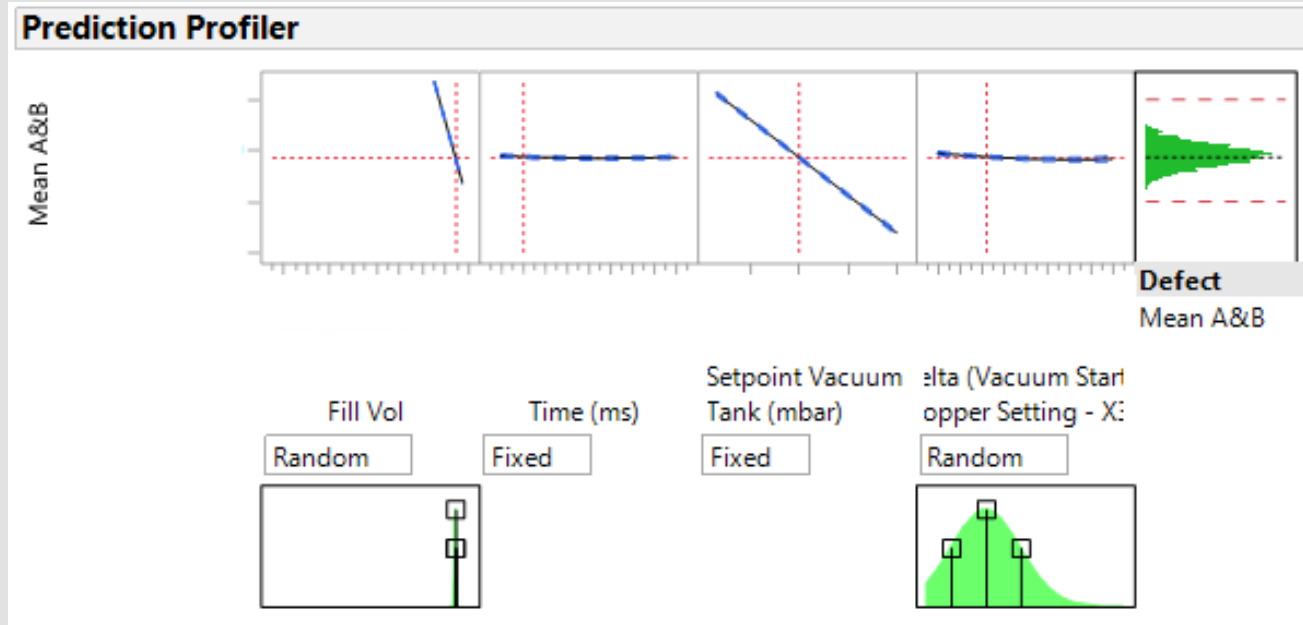
HOW IS THIS A STRATEGY FOR TRANSFER?

- **More speed and continuous improvement in performance**
 - Faster: No and Yes
 - Saves line time
 - Worth the effort to be able to say what is system capability Vs. noise
 - Demonstrate better understanding of our equipment
- **Apply to other areas**
 - **Liquid Inspection**
 - Fill volume, viscosity, surface tension, spin speeds, spin directions, bubbles etc.
 - Using historical data first, before proceeding with trials on production equipment
 - **Freeze Dryer Modelling**
 - Heat transfer and primary drying: separating small scale cake effects from large scale freeze dryer effects
- **Strategic Goal**
 - Zero line time - straight to flawless engineering run or PPQ

AGENDA

- Context
- Example of design space modelling – plunger depth
 - What we used to do – “following our nose”
 - More accurate (and less precise)?
- Strategies and Future Directions

CHARTS LIKE THIS ARE VERY CONVINCING BUT DON'T LET THE STATISTICS BLIND YOU TO THE SCIENCE



THANK YOU FOR YOUR ATTENTION

Questions?