

The Pharmaceutical Challenge of Cancer Research



Gavin Halbert
Cancer Research UK Formulation Unit
Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde



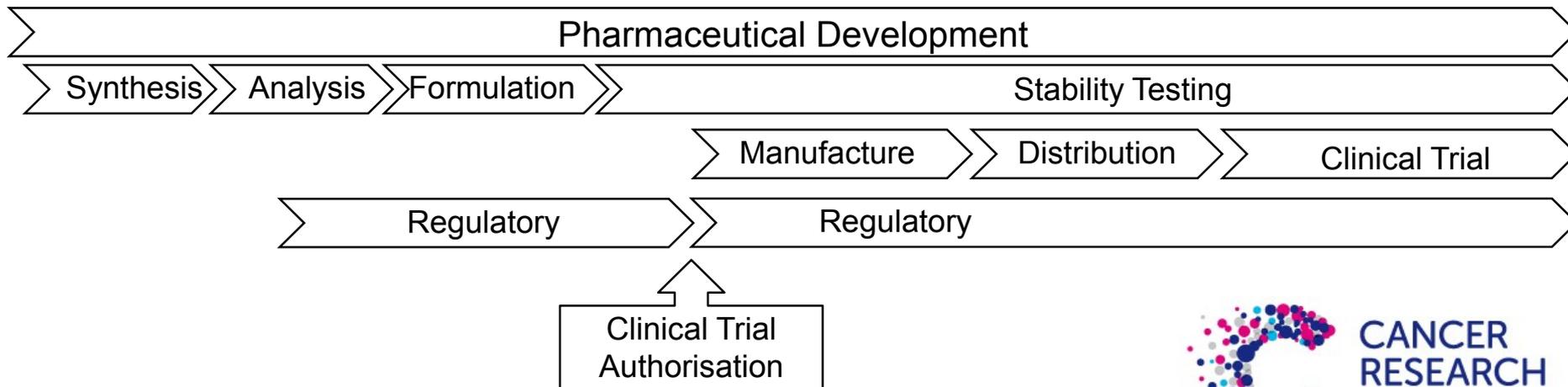
Formulation Unit

- Remit

To develop novel anti-cancer drugs selected by Cancer Research UK New Agents Committee for Phase I and II Clinical Trial
Pharmaceutical Translation Research

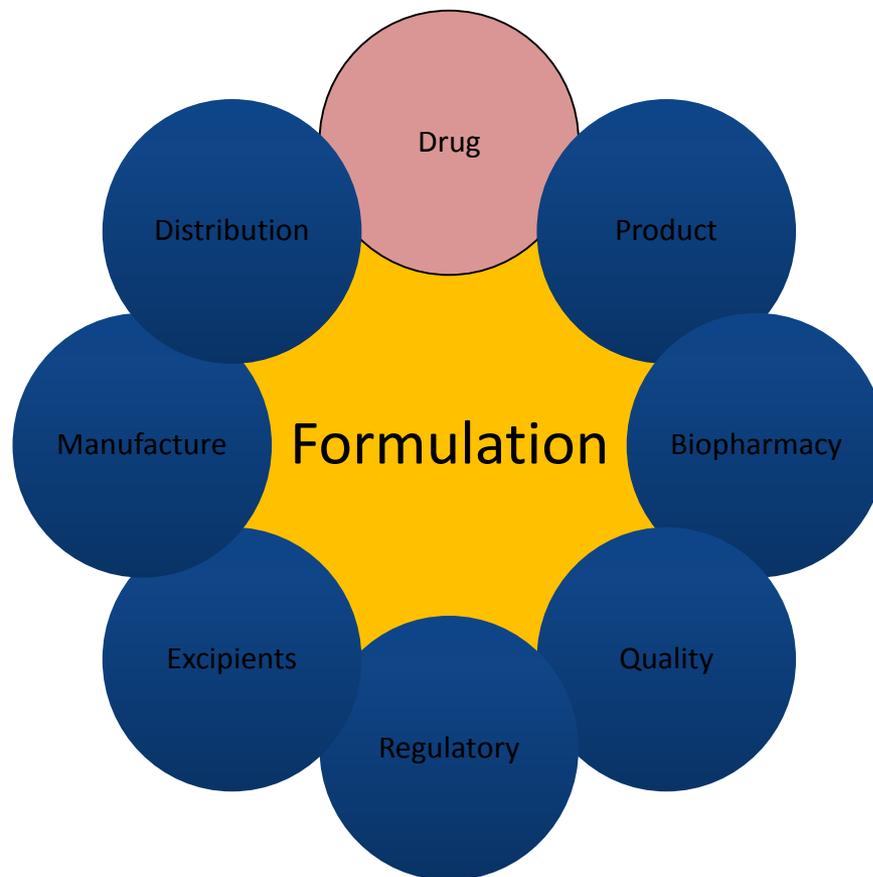
- Established in 1983

Bench to Bedside – Powder to Product – Molecule to Medicine



Formulation

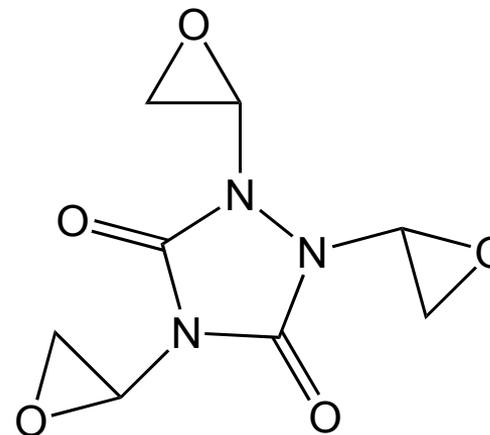
- Multiple factors
- One goal
- Limited
Knowledge
Resource
Time



- Early Projects
- Research Advances
- Recent Projects
- Currents Trends
- Potential Answers

Early Example - 1984

- 1, 2, 4-triglycidyl urazol -
Limited solubility & stability
- Reconstitution Fluid
Switch from dextrose to
NaCl



Cancer Chemother Pharmacol (1984) 12: 198–200

Cancer
Chemotherapy and
Parmacology
© Springer-Verlag 1984

The analysis and animal pharmacokinetics of 1,2,4, triglycidyl urazol using a high-pressure liquid chromatographic technique

J. Welsh¹, J. F. B. Stuart^{1,2}, A. Setanoians¹, R. G. G. Blackie¹, P. Billiaert^{1,2}, G. Halbert¹, and K. C. Calman¹

¹Department of Clinical Oncology, University of Glasgow, 1 Horselethill Road, Glasgow G12 9LY, Scotland

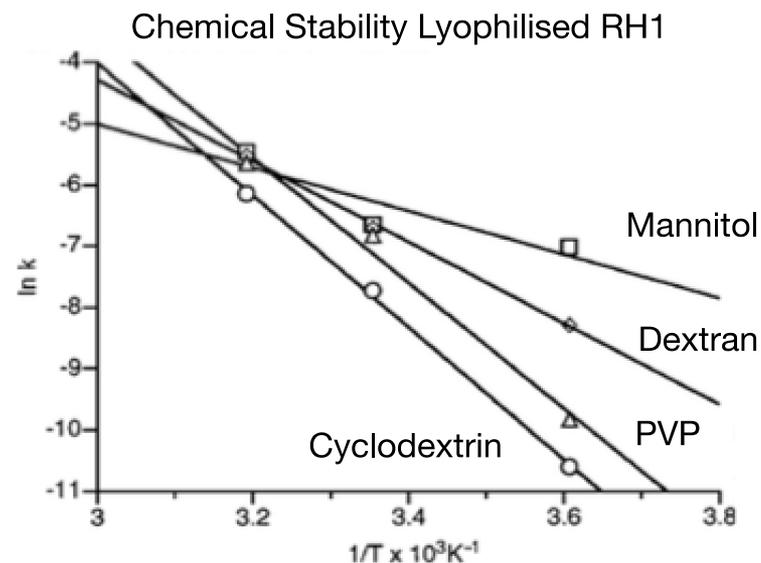
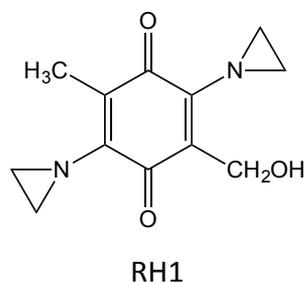
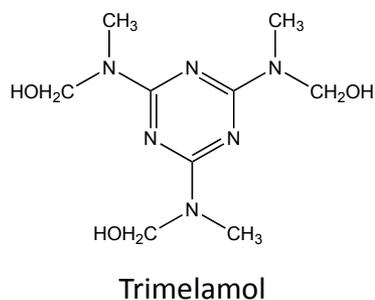
²Department of Pharmaceutics, University of Strathclyde, Glasgow, Scotland



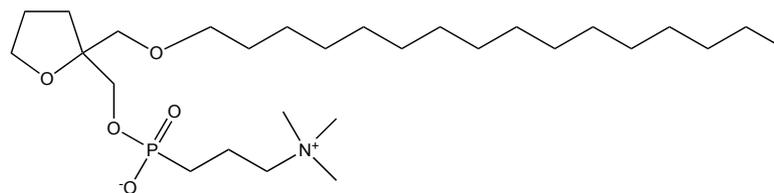
**CANCER
RESEARCH
UK**

Early Projects

- Many and varied
Exact number unknown
- Small molecules



Limonene





Clinical Trials

- 1, 2, 4-triglycidyl urazol
- Starting Dose
30mg/m² escalated to 900mg/m
- Toxicity
 - Myelosuppression, nausea, vomiting, phlebitis

- RH1
- Eligibility criteria
Proven cancer, refractory to treatment, no conventional therapy, >18 yrs, life expectancy >3 months

Tumour Type	No
Colorectal	8
Gastric	3
NSCLC	2
Melanoma	2
Merkel cell carcinoma	1
Pancreatic	1
Renal	1

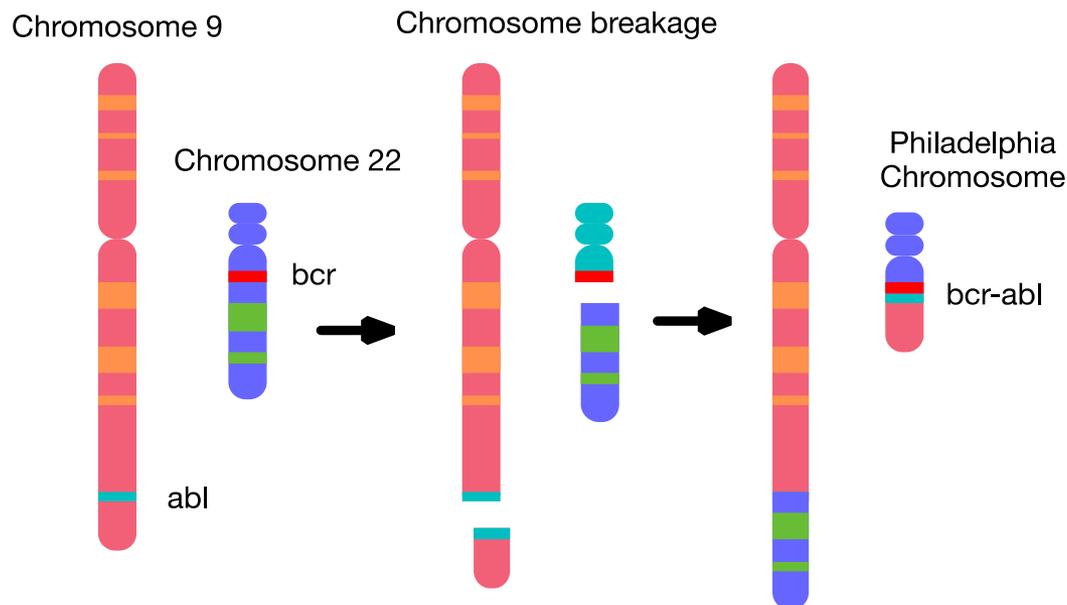


Common Issues

- Pharmacology
 - Cytotoxic chemotherapy
 - Limited administration
- Majority of formulations injections
- Drug solubility
 - Range of formulation techniques applied
- Drug stability
 - Hydrolytic – lyophilisation
 - Non-hydrolytic – physicochemistry
- General trials

Research Advances

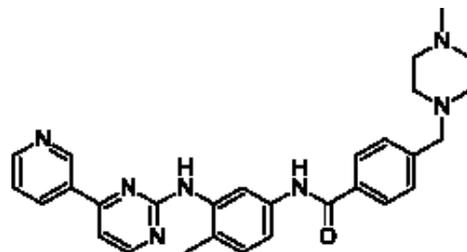
- Imatinib – 2001
“Dawn of targeted treatments”





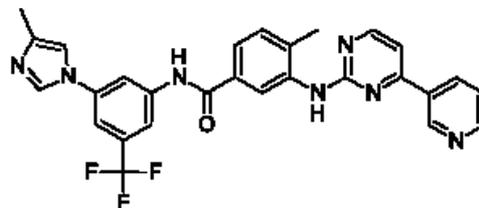
Very Different Drugs

imatinib



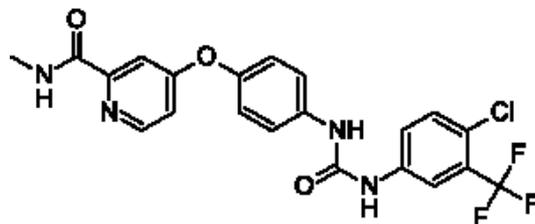
Solubility 200mg/ml
Oral Bioavailability 98%

nilotinib



Solubility sparingly
Oral Bioavailability 31%

sorafenib

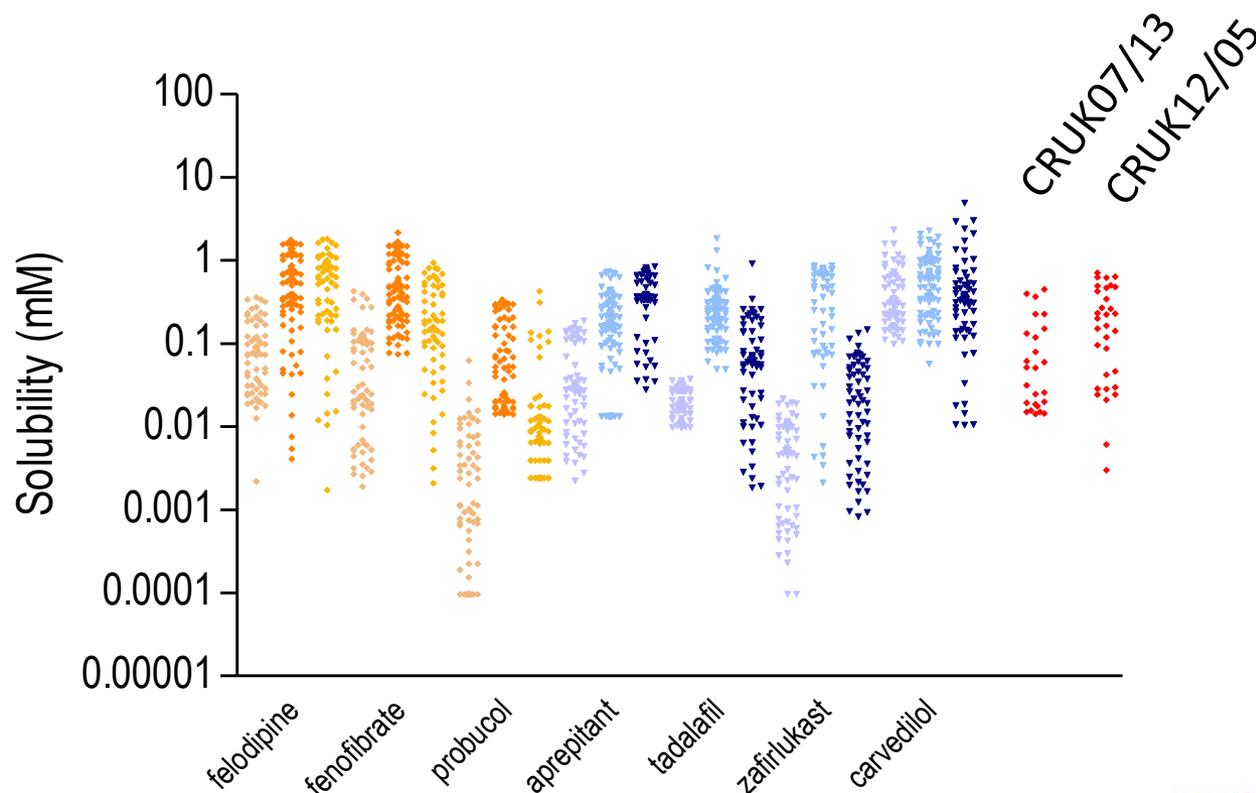


Solubility (1:2 DMSO:PBS) 0.3mg/ml
Oral Bioavailability 50%



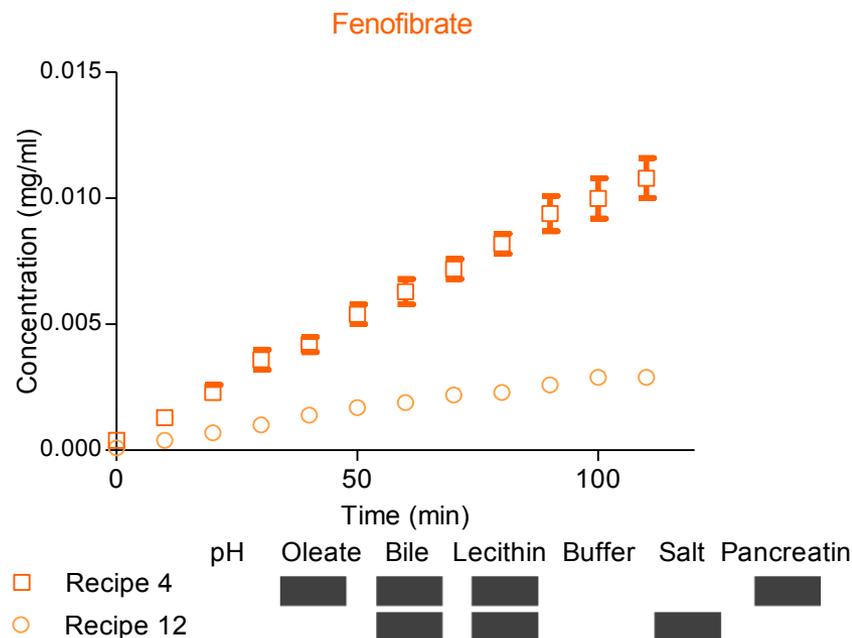
Intestinal Solubility Variation

- Impact of simulated gastrointestinal fluid composition



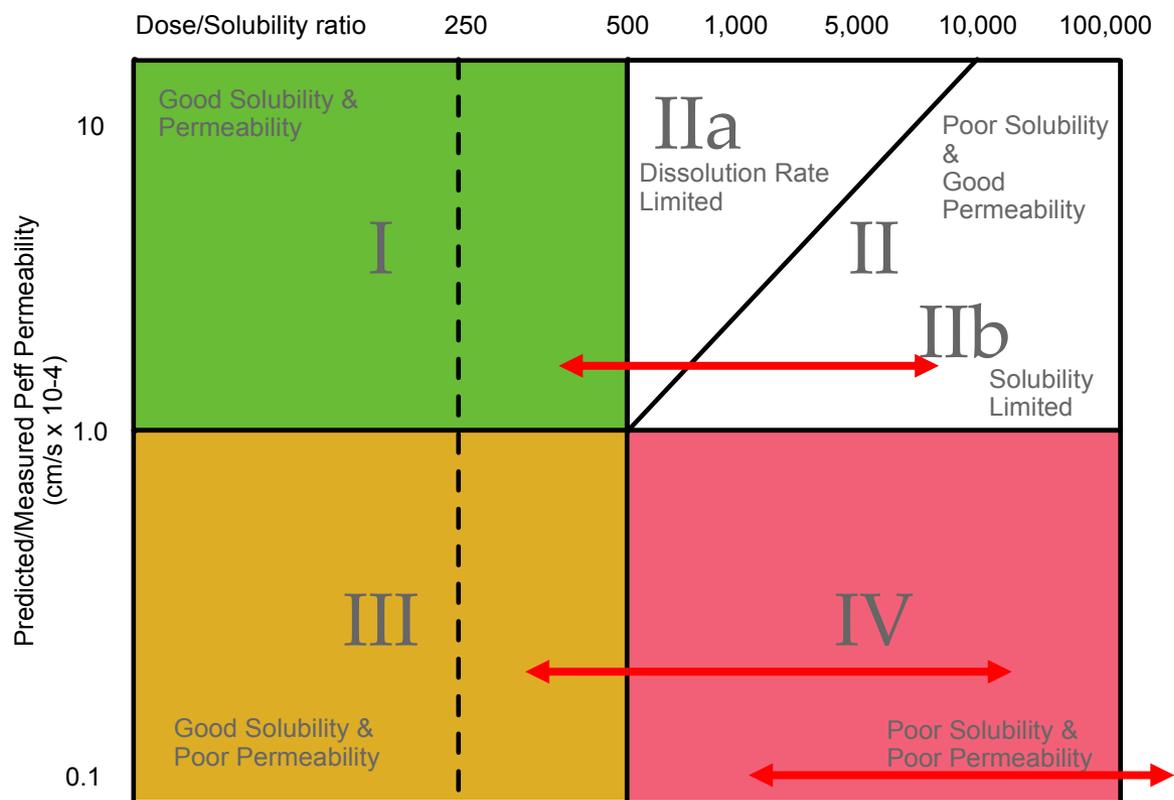
Impact on Dissolution

- Low solubility
 - Slower dissolution
 - Natural GIT variation
 - Not applicable
 - Amorphous
 - Bioenhanced
- But does it stay in solution?



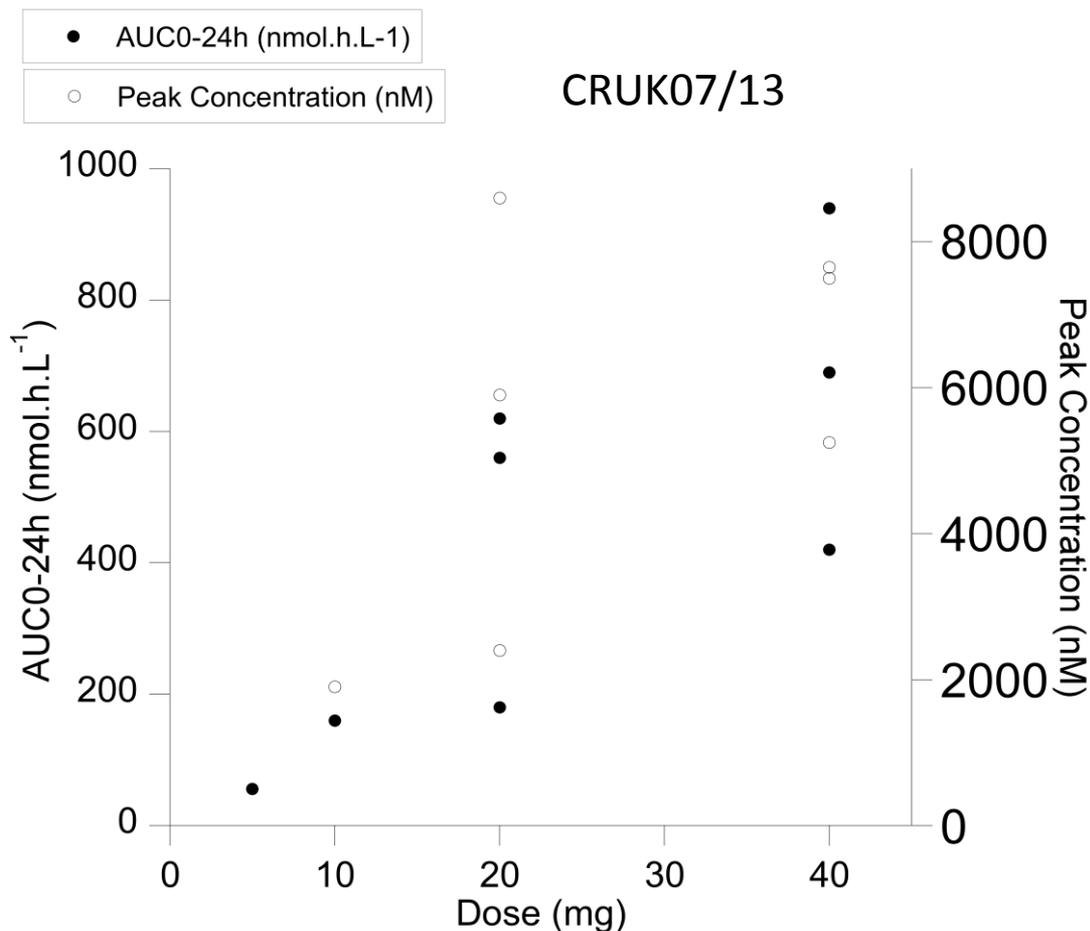


Biopharmaceutics Classification System



Impact on pharmacokinetics

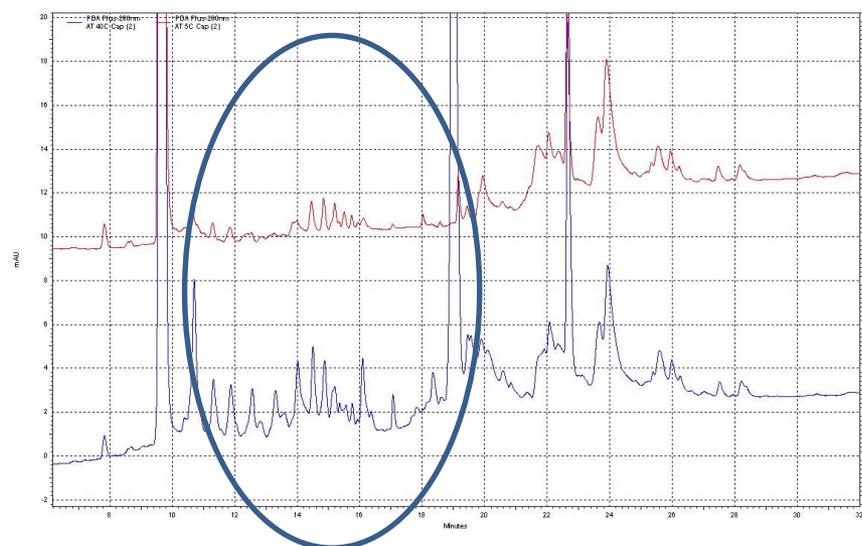
- Phase 1 Dose escalation studies – BCS I to BCS II



Impacts receptor exposure

Bioenhanced Formulations

- Improve dissolution
 - Amorphous
 - Solid solutions
- Spring and parachute effect
- Stability
 - Chemical & Physical
- Solid solution
 - Drug/Excipient
 - Intimate contact
- Excipient Quality



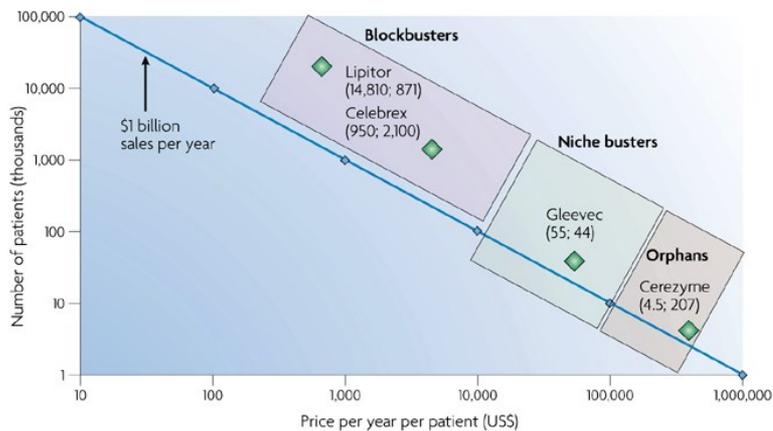


Common Issues

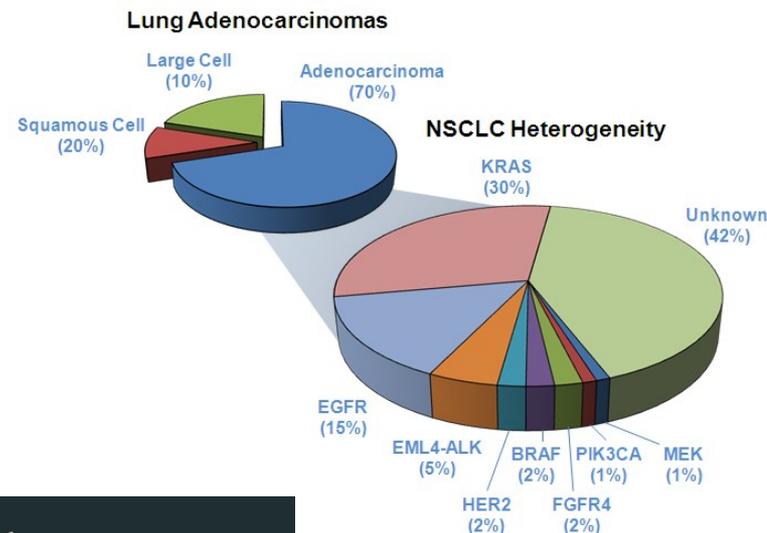
- Pharmacology
 - Targeted chemotherapy
 - Single pathway
 - Continuous administration
- Majority of formulations oral
- Drug solubility – impacts on drug absorption
- Bioenhanced formulations
 - Stability problems
- Targeted trials

Current Trends I

- Smaller patient numbers
 - Therapy cost increases
 - Combination therapies
 - Agile therapy
- Rapid changes



Nature Reviews | Drug Discovery



HOME NEWS TECHNOLOGY SPACE PHYSICS HEALTH EARTH HUMANS LIFE TOPICS EVENTS JOBS

Home | Features | Health | Human

INTERVIEW 19 October 2016

The price of my life: \$1.6 million and counting

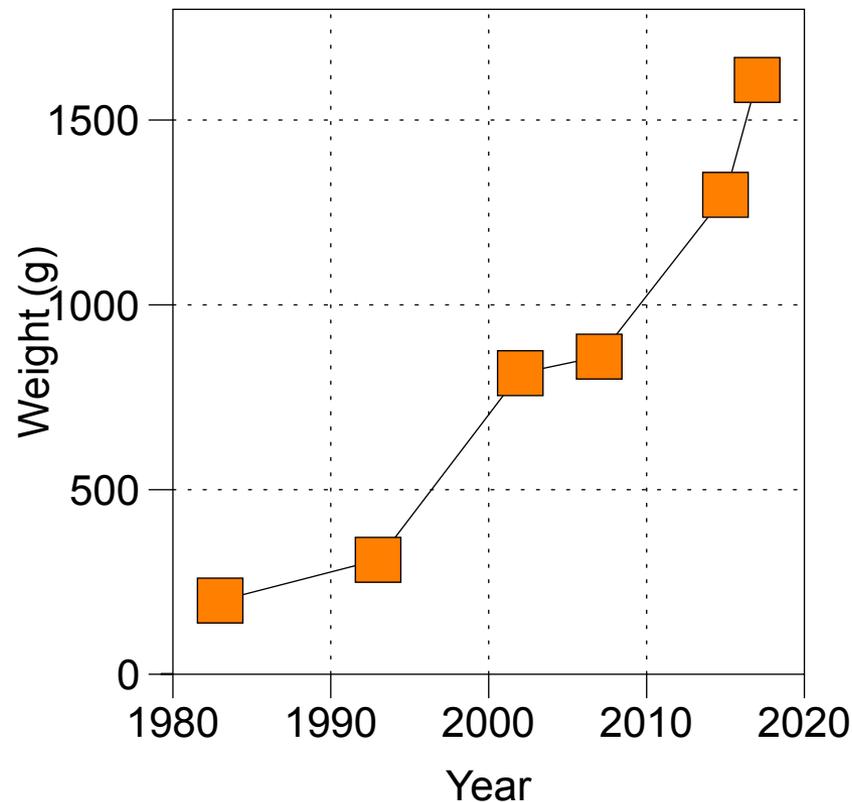
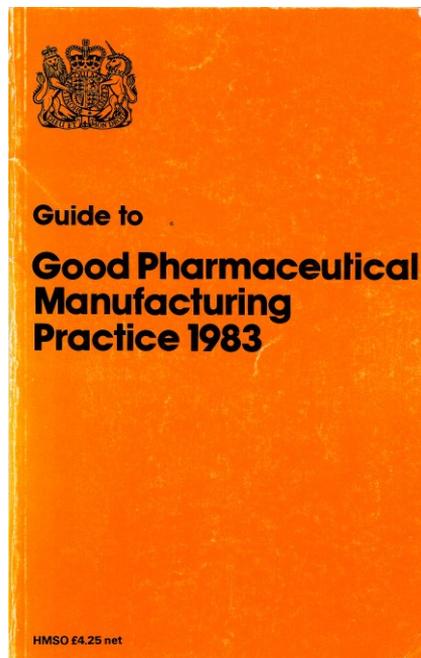
Six years ago, **Randy Hillard** was diagnosed with terminal gastric cancer and given less than a year to live. But then he responded extraordinarily well to the drug trastuzumab (Herceptin) – originally meant to extend his life by two months. Six years later, he is still having \$17,000 infusions every three weeks. His survival has cost \$1.6 million – and counting. A professor of psychiatry at Michigan State University and a hospice doctor, Hillard knows it is a high price to pay. He spoke to New Scientist during his 95th Herceptin infusion.



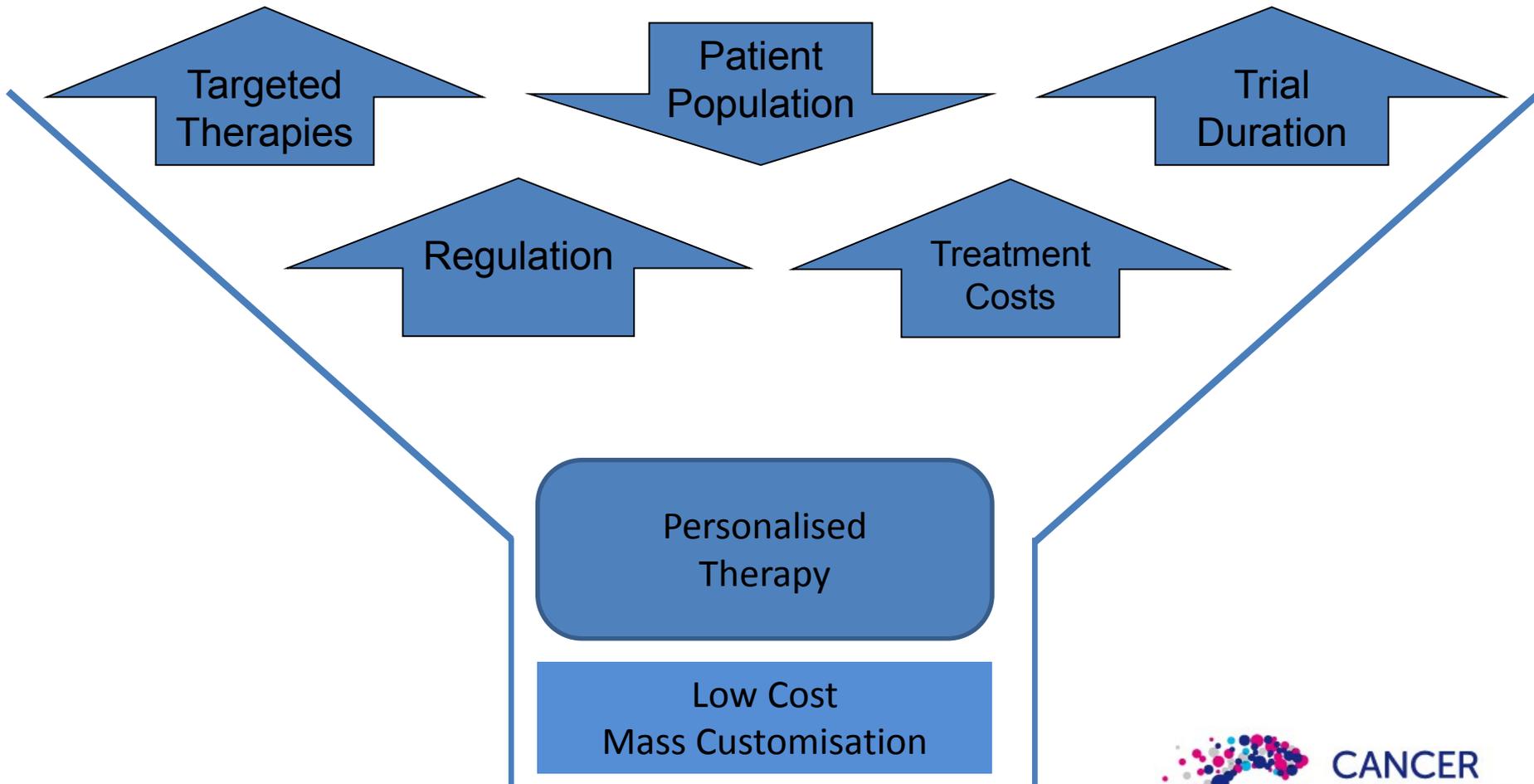
Photo: Richard Heine / The Washington Post via Getty Images



Current Trends II



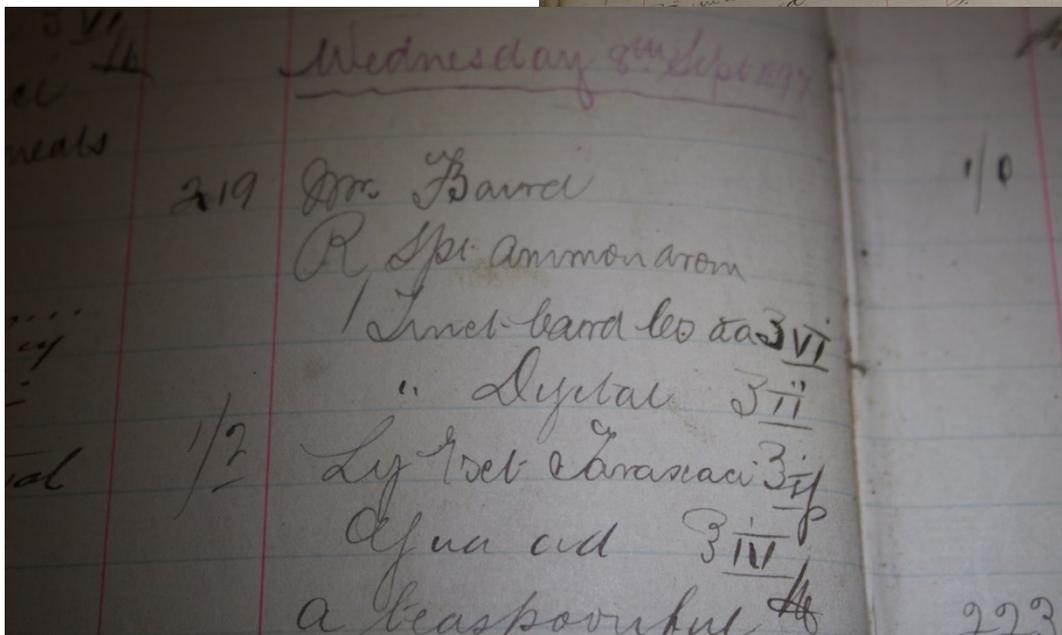
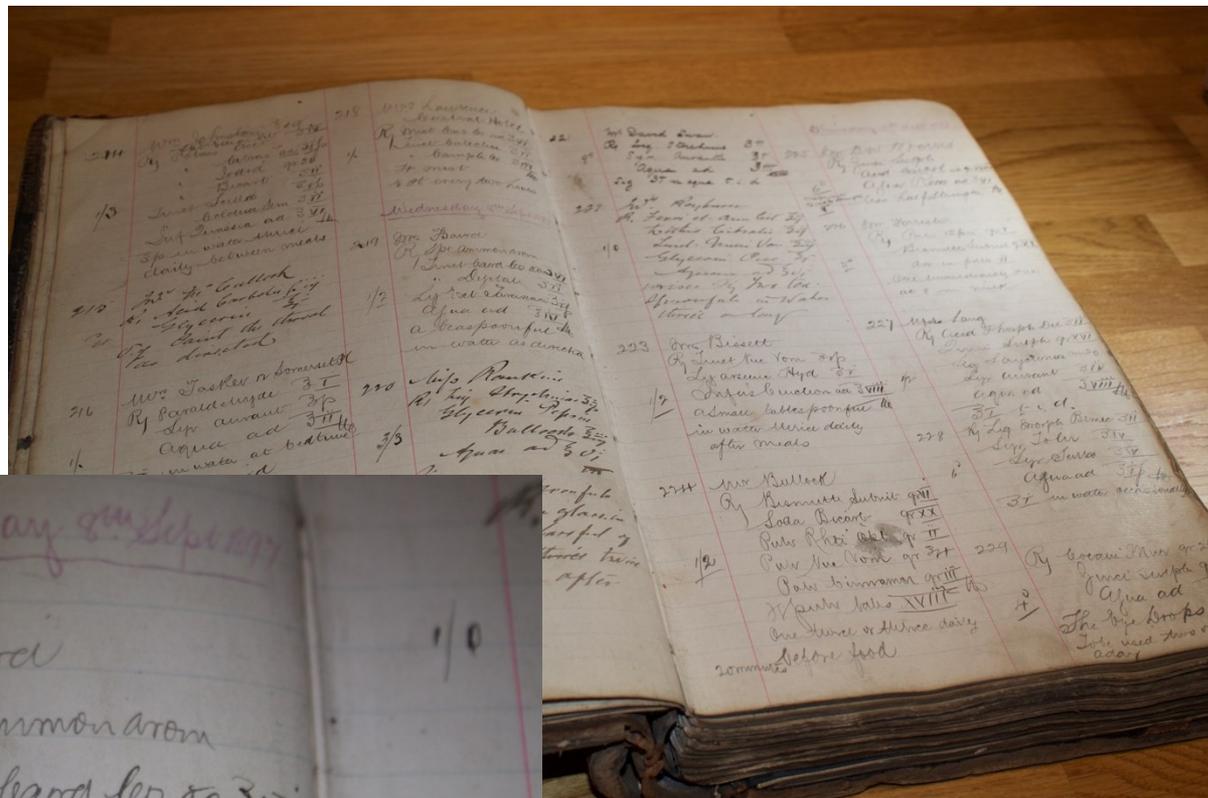
Pharmaceutical Hockey Stick





Mass Customisation

- This is not new!





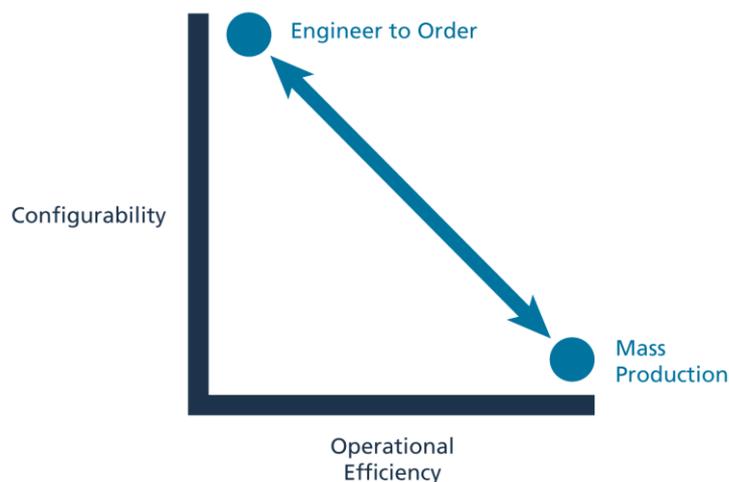
Future Pharmaceutical Challenge

Solutions – scaleable, quick, agile, low cost, GMP compliant, patient friendly

Does one formulation and manufacturing technology fit all?

Are there other aspects that can change?

Basic and applied research required

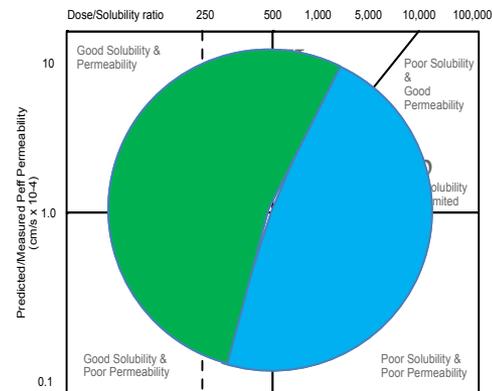
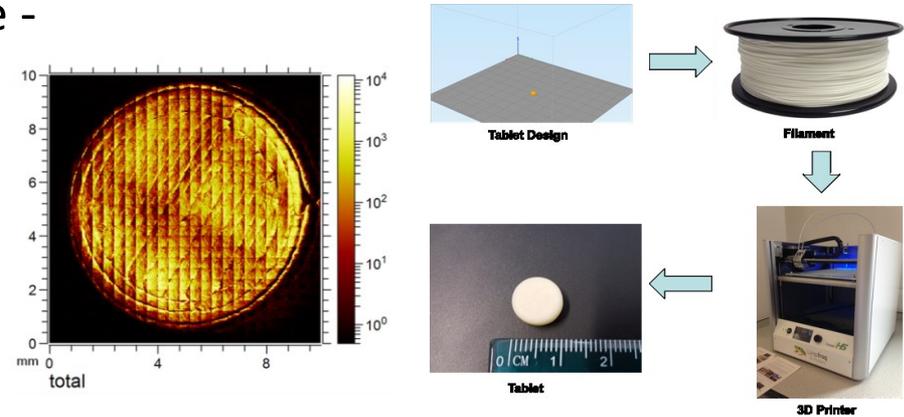


3D Printing
Just in time manufacture
Small scale development
Individual patient trials



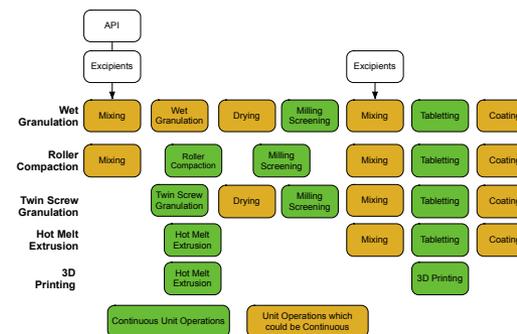
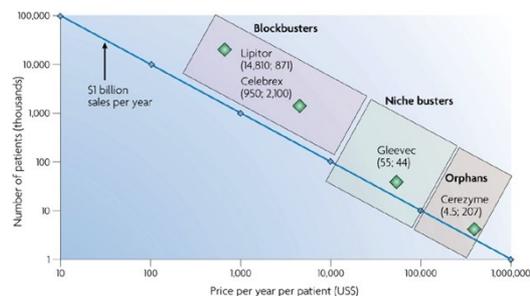
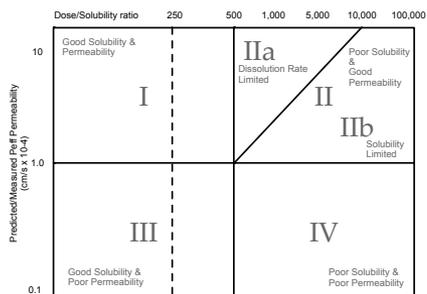
3D Printing & Injection Moulding

- Hot topic – a la mode
 - Multiple groups UK and world-wide - multiple approaches
- Marketed product
 - New field
- Multiple areas of research
 - Equipment, process, parameters, formulation, product
- Future
 - Wide open

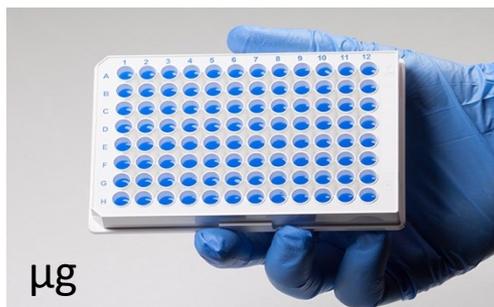




Predictive Pharmaceuticals



Nature Reviews | Drug Discovery



µg

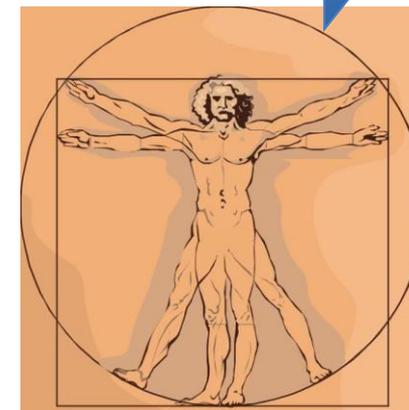
Discovery



mg

Development

g(?)





Acknowledgements

- You for listening
- Collaborators
 - Many and varied
 - Local, national and international
- Cancer Research UK Funding
 - EPSRC, EU FP7, MRC





Thank you

Gavin Halbert