

The Pharmaceutical Challenge of Cancer Research



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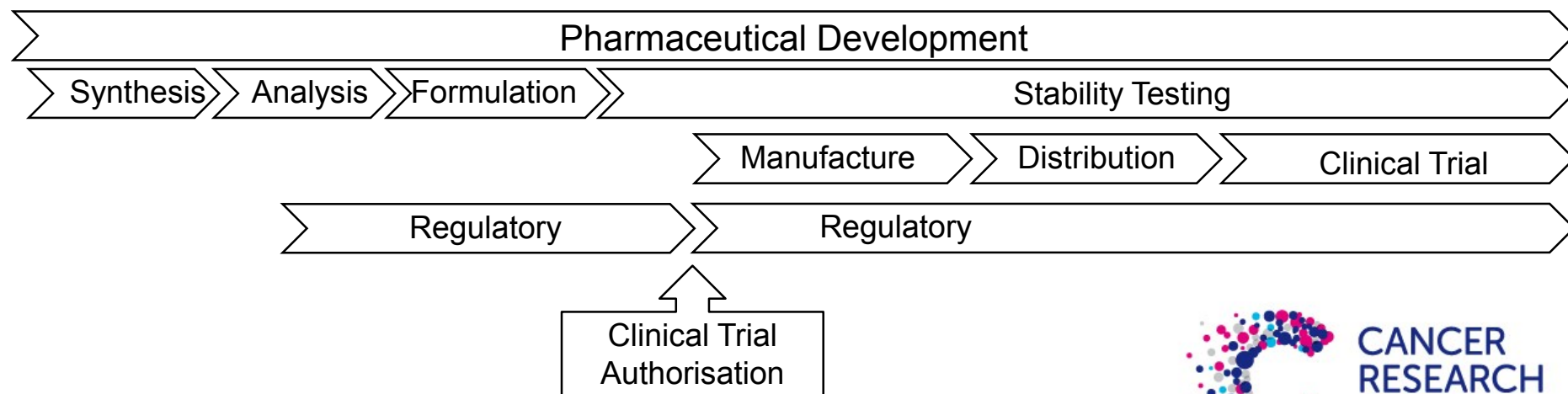
Formulation Unit

- 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

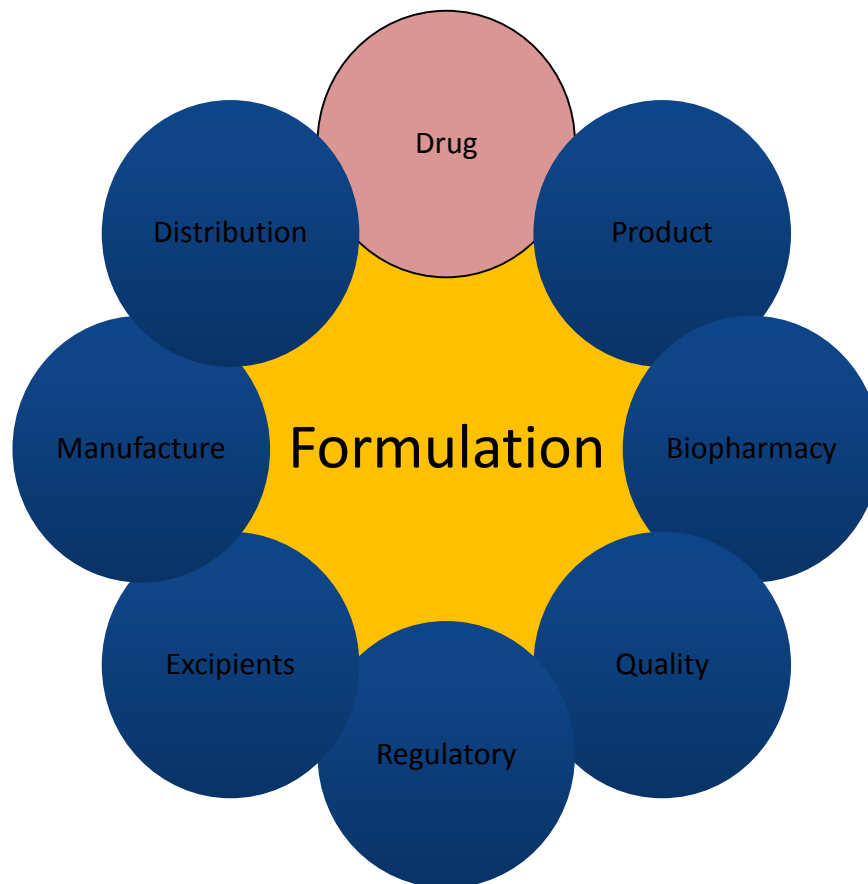
- Established in 1983

Bench to Bedside – Powder to Product – Molecule to Medicine



Formulation

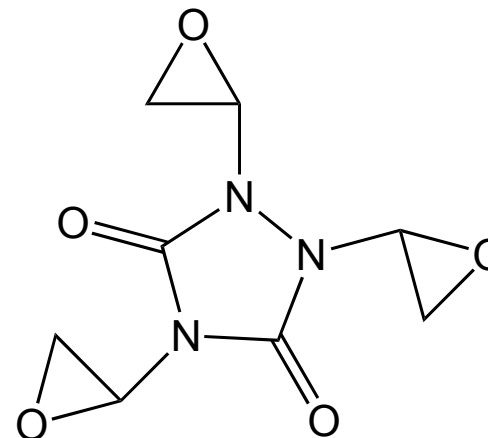
- Multiple factors
- One goal
- Limited
Knowledge
Resource
Time



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

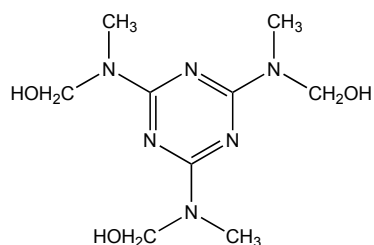
J. Welsh¹, J. F. B. Stuart^{1,2}, A. Setanoians¹, R. G. G. Blackie¹, P. Billiaert^{1,2}, G. Halbert¹, and K. C. Calman¹

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

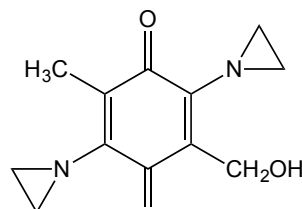
²Department of Pharmaceutics, University of Strathclyde, Glasgow, Scotland

Early Projects

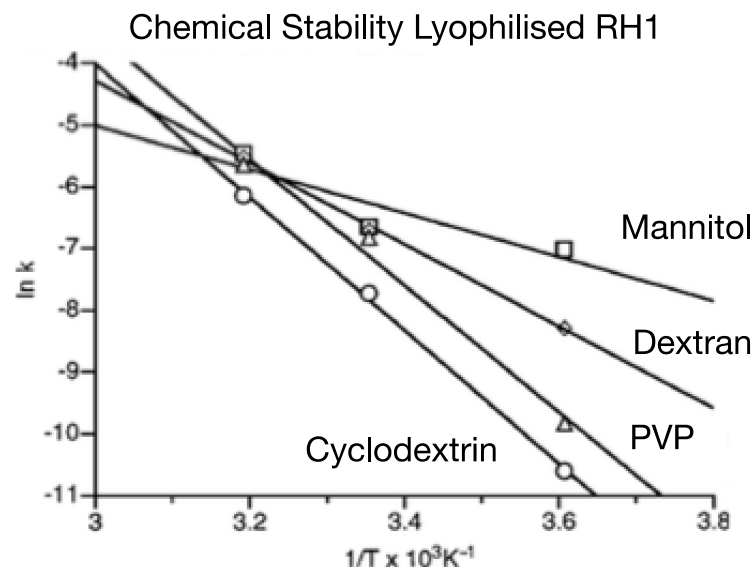
- Many and varied
Exact number unknown
- Small molecules



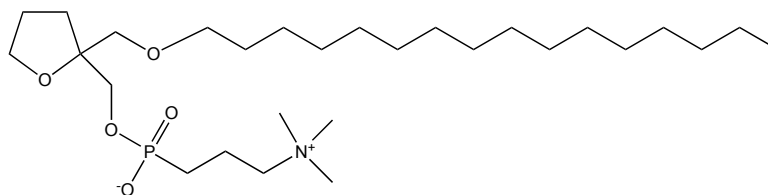
Trimelamol



RH1



Limonene



SRI 62 834

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

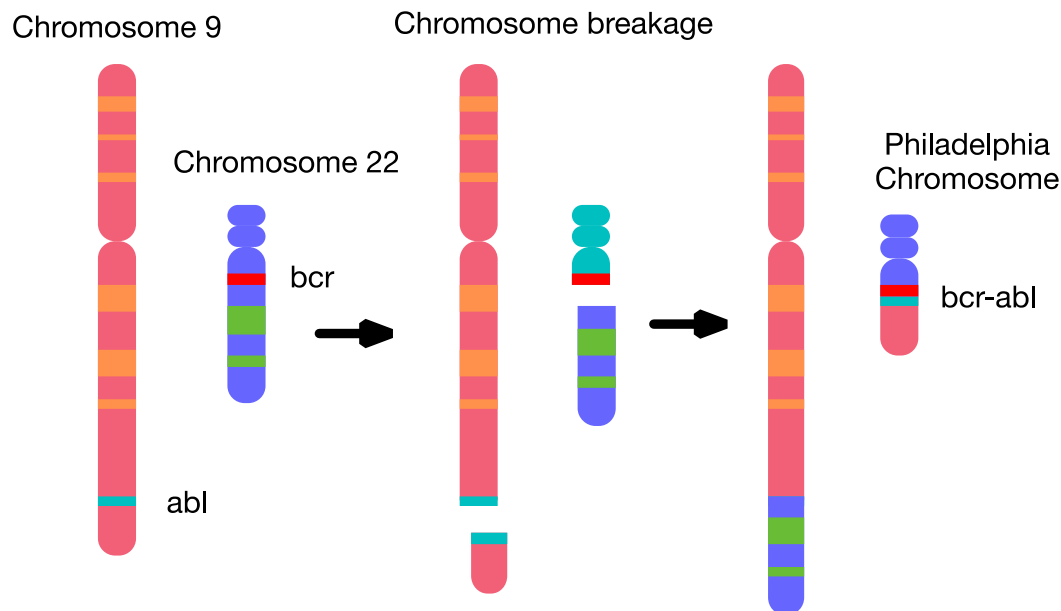
Tumour Type	No
Colorectal	8
Gastric	3
NSCLC	2
Melanoma	2
Merkel cell carcinoma	1
Pancreatic	1
Renal	1

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

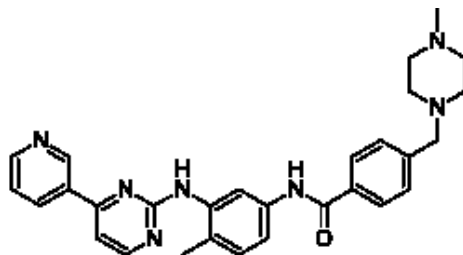
Research Advances

- Imatinib – 2001
“Dawn of targeted treatments”



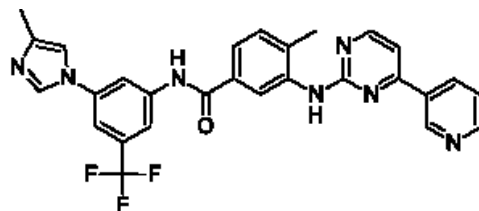
Very Different Drugs

imatinib



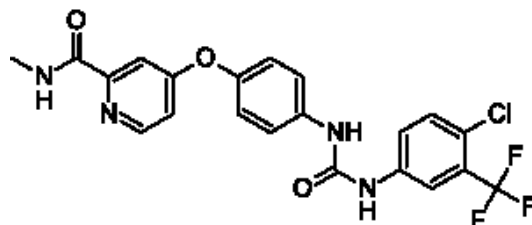
Solubility 200mg/ml
Oral Bioavailability 98%

nilotinib



Solubility sparingly
Oral Bioavailability 31%

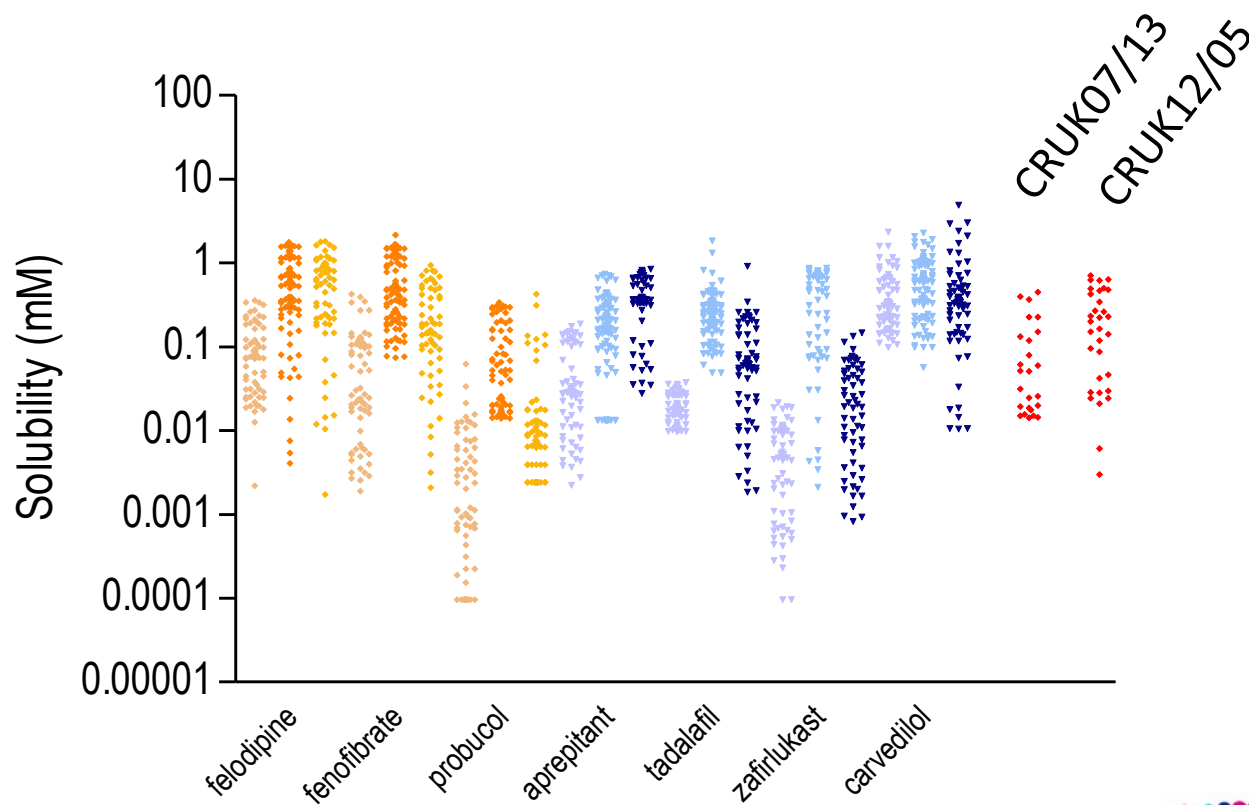
sorafenib



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

Intestinal Solubility Variation

- Impact of simulated gastrointestinal fluid composition



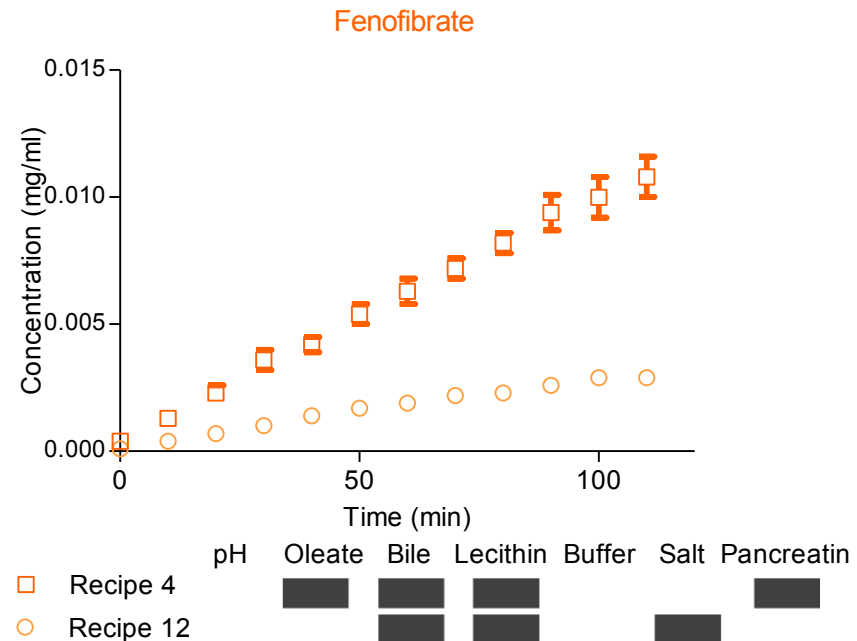
Khadra, I., et.al., (2015) Eur. J. Pharm. Sci., 67: 65-75 (Fasted data only)



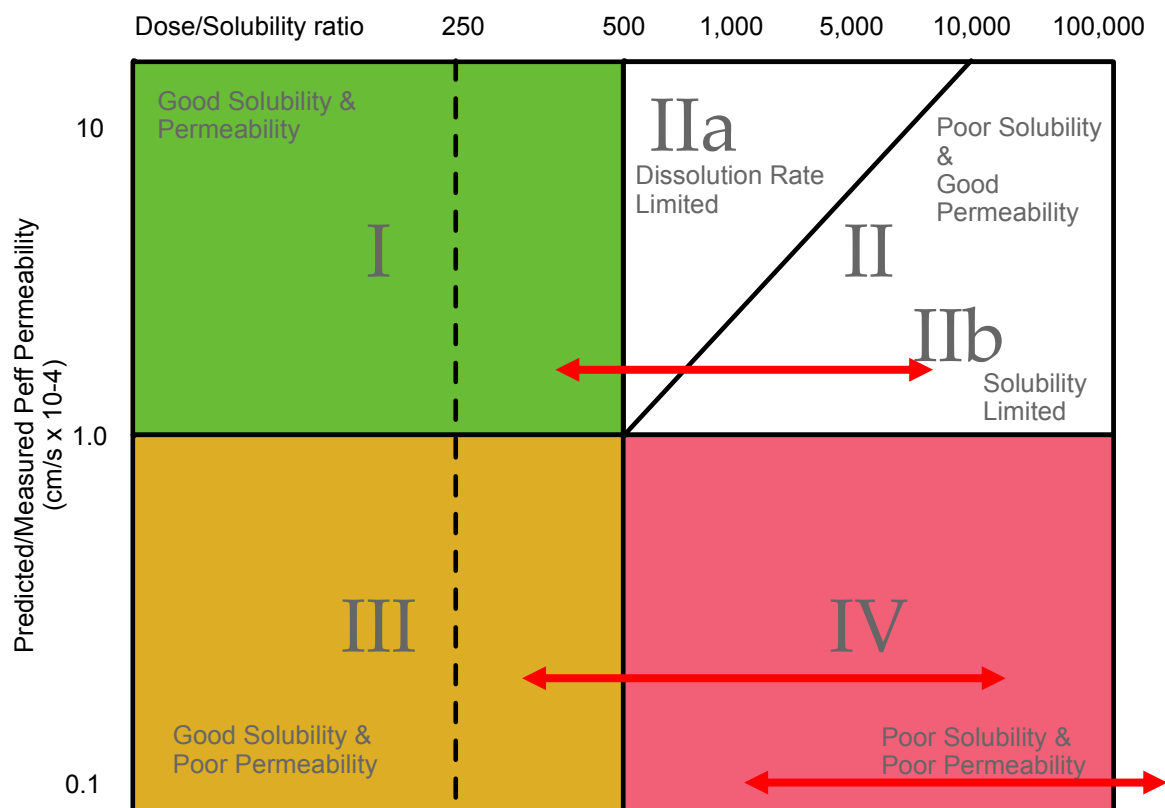
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Impact on Dissolution

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

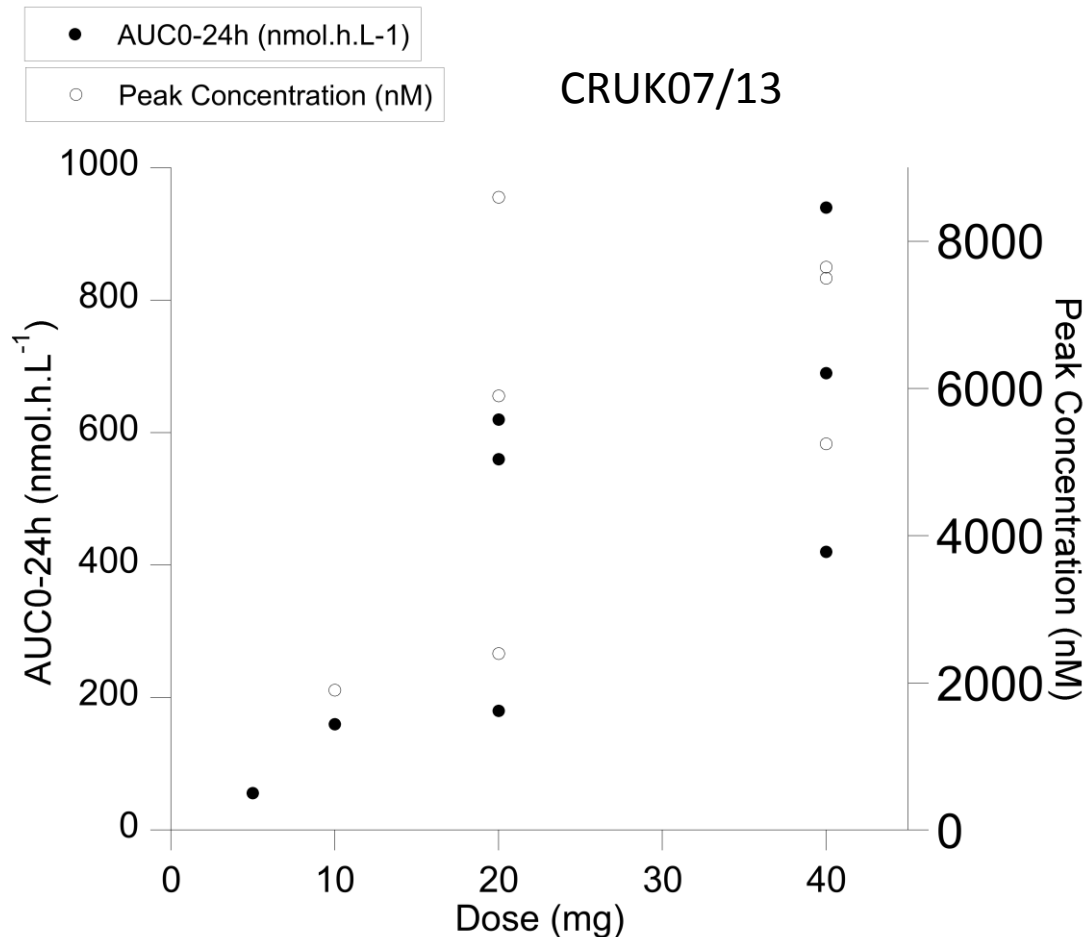


Biopharmaceutics Classification System



Impact on pharmacokinetics

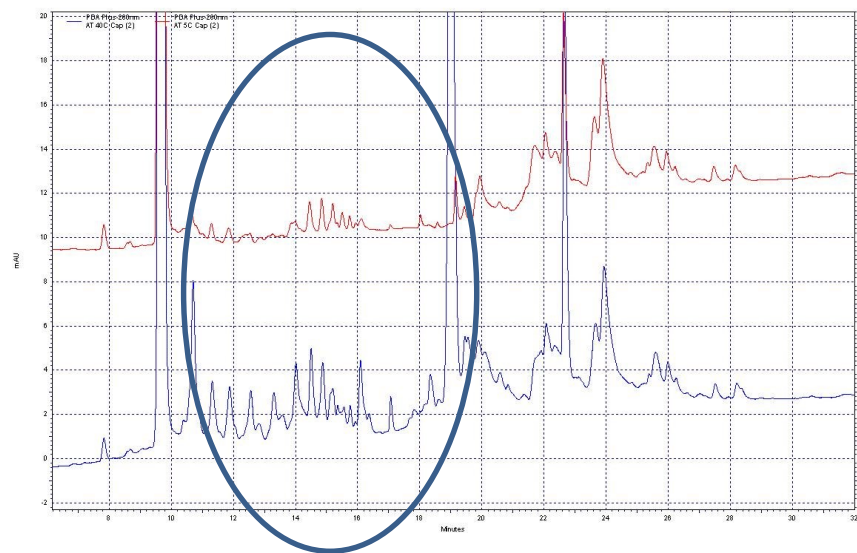
- Phase 1 Dose escalation studies – BCS I to BCS II



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

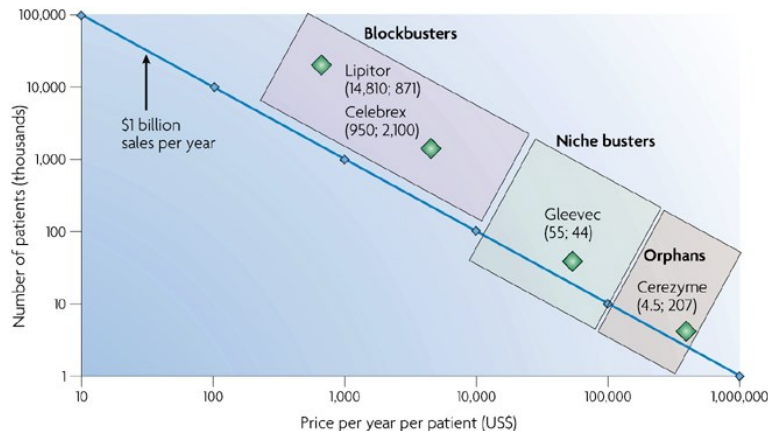


Common Issues

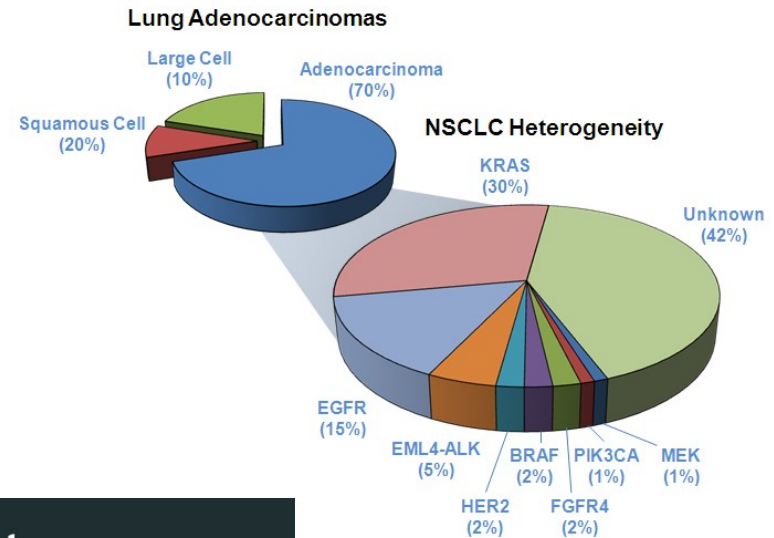
- Pharmacology
 - Targeted chemotherapy
 - Single pathway
 - Continuous administration
- Majority of formulations oral
- Drug solubility – impacts on drug absorption
- Bioenhanced formulations
 - Stability problems
- Targeted trials

Current Trends I

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



Nature Reviews | Drug Discovery



New Scientist

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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.


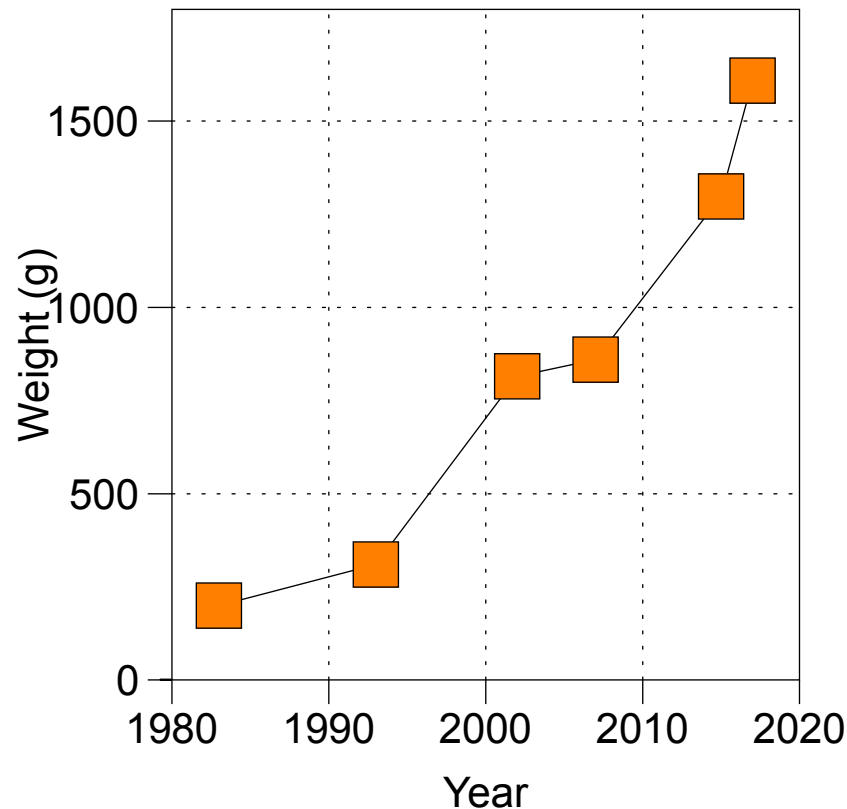
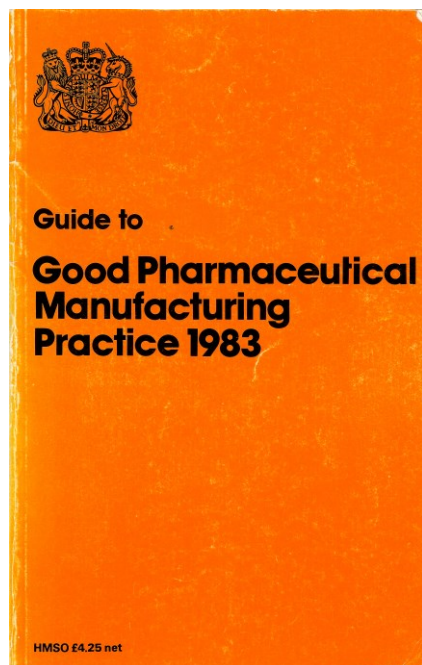
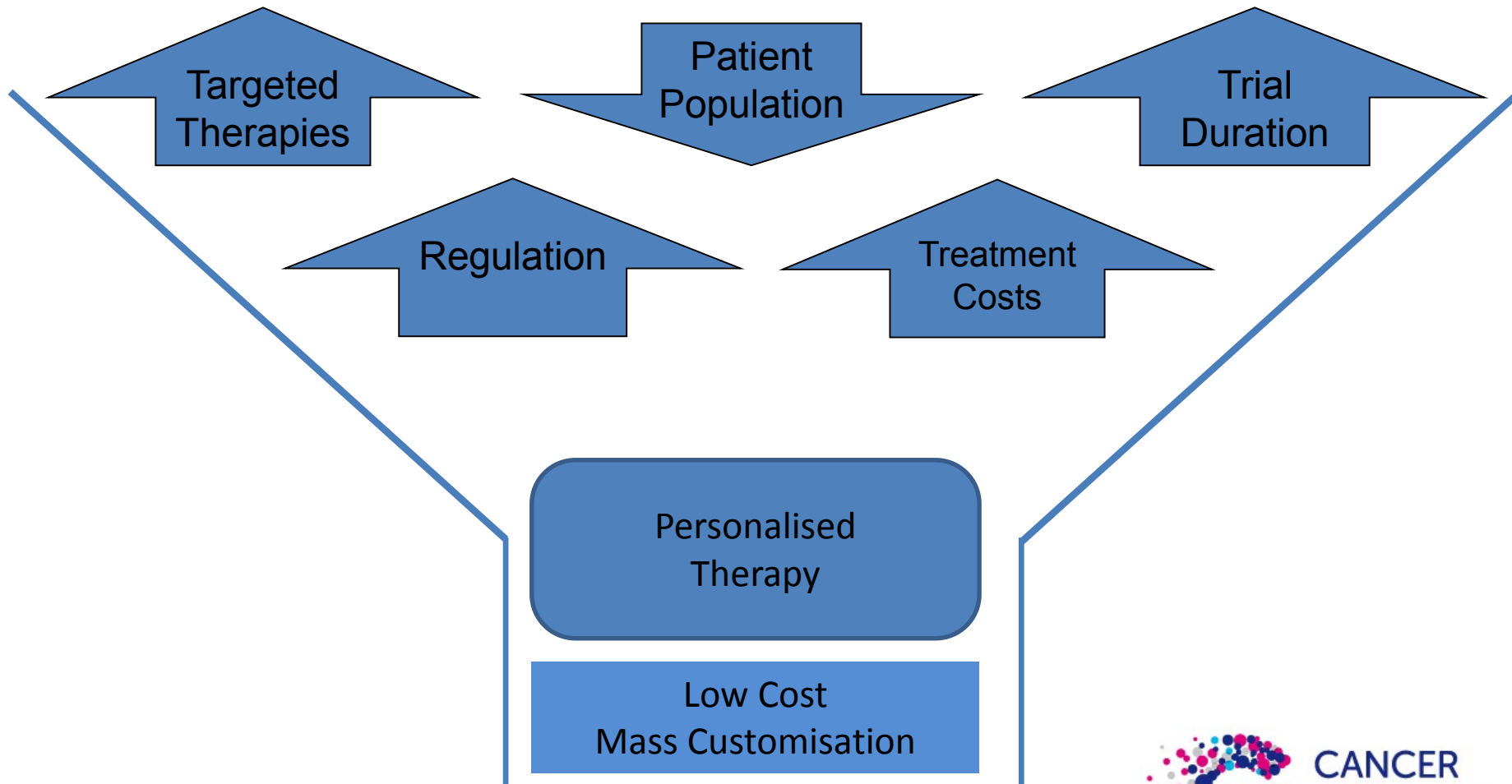


Photo: Michael H. The Washington Post/Getty Images

Current Trends II

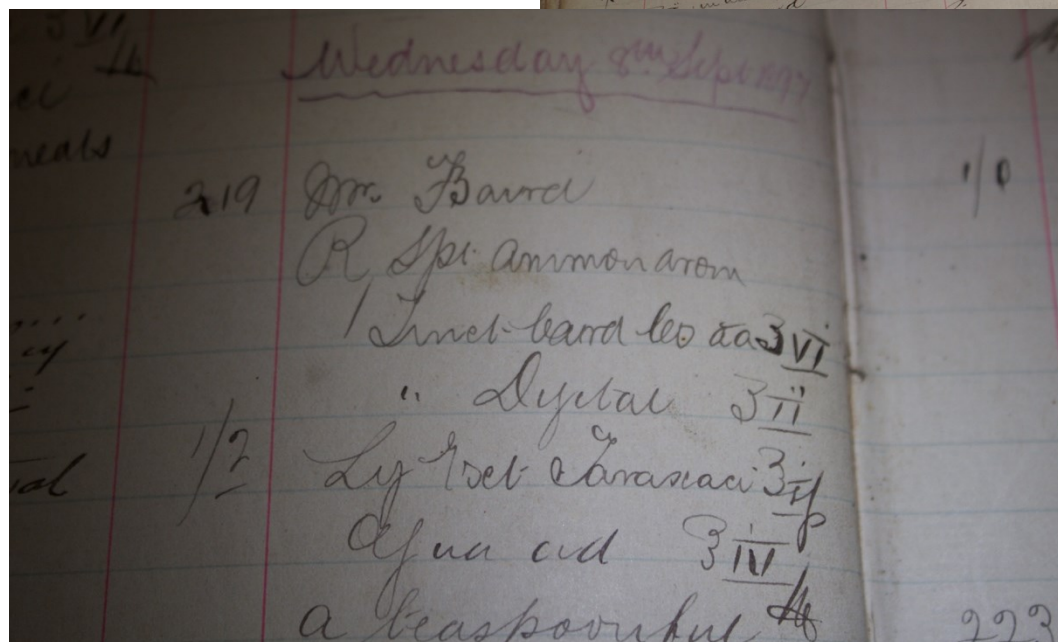
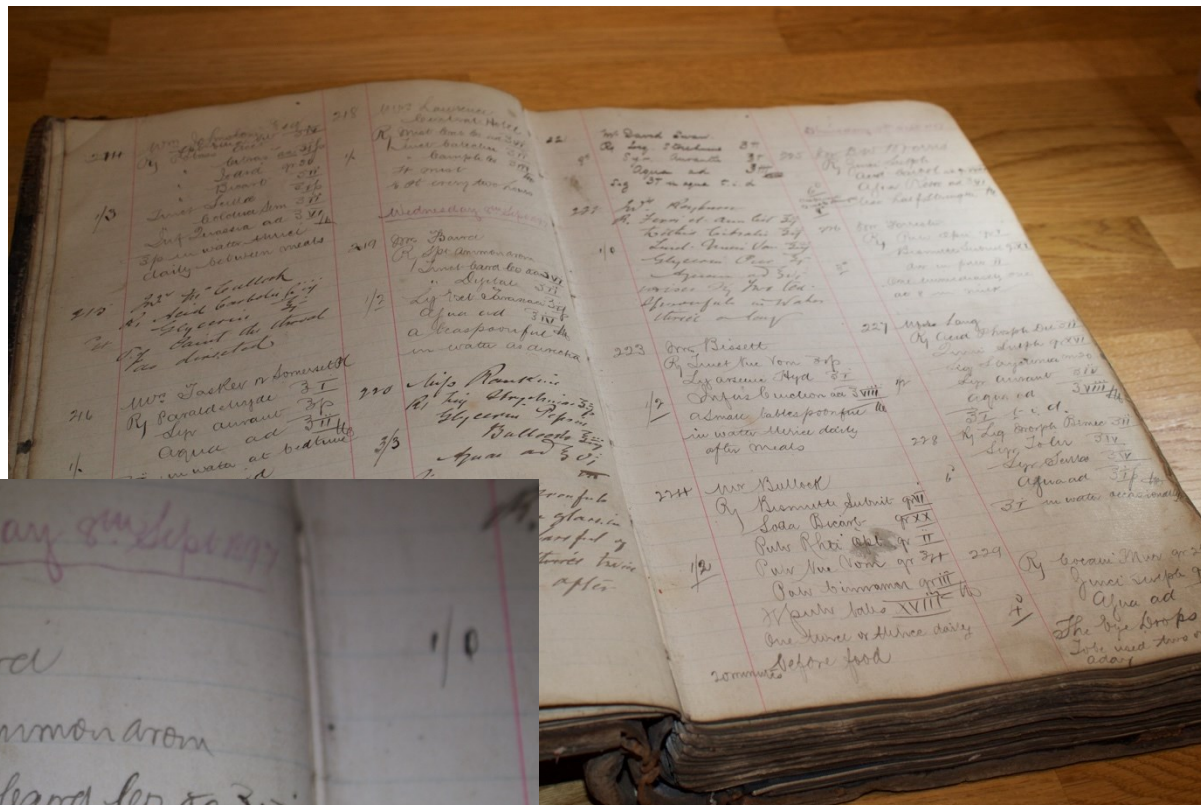


Pharmaceutical Hockey Stick



Mass Customisation

- This is not new!



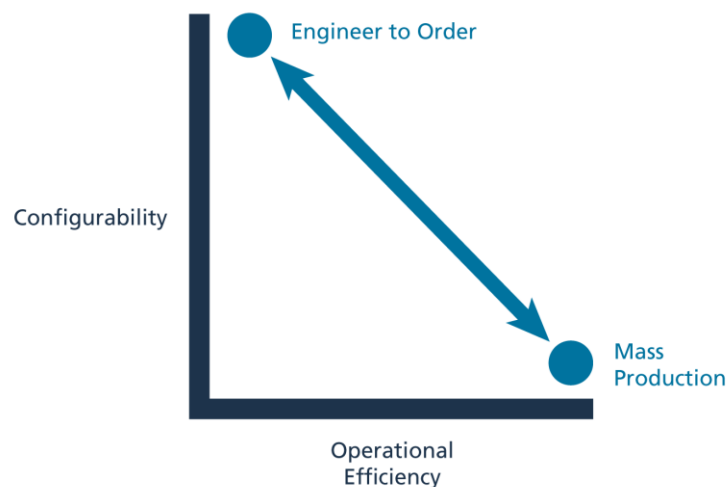
Future Pharmaceutical Challenge

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



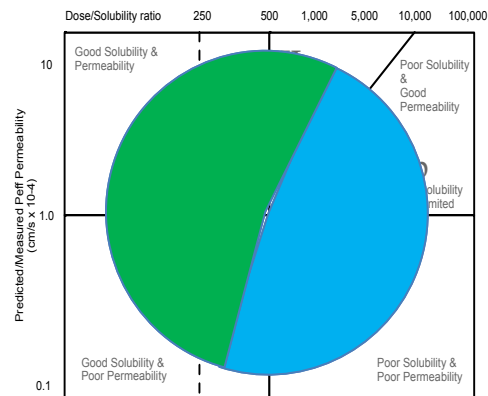
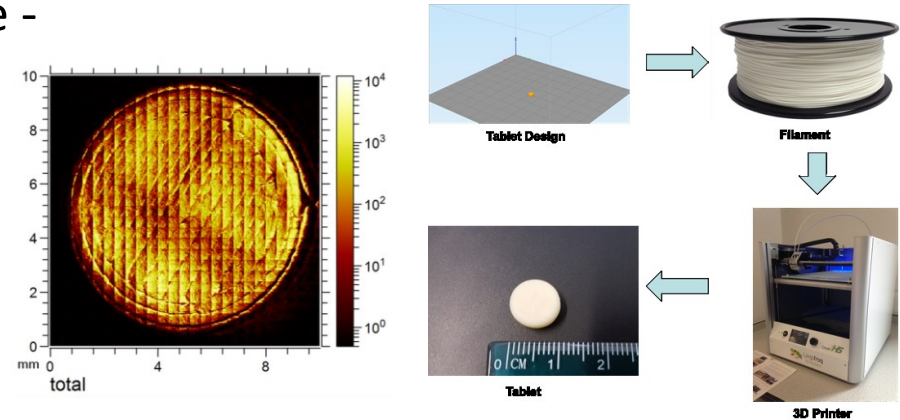
3D Printing
Just in time manufacture
Small scale development
Individual patient trials



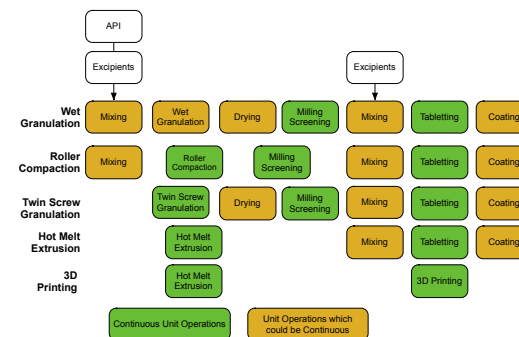
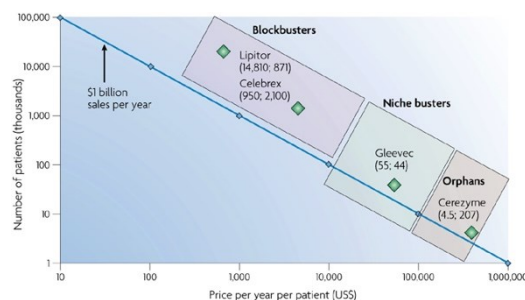
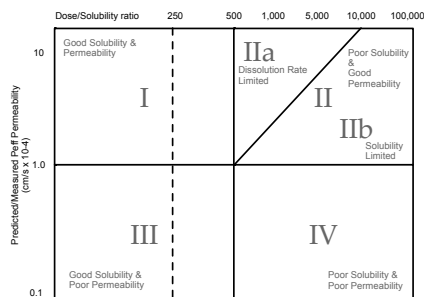
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3D Printing & Injection Moulding

- 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

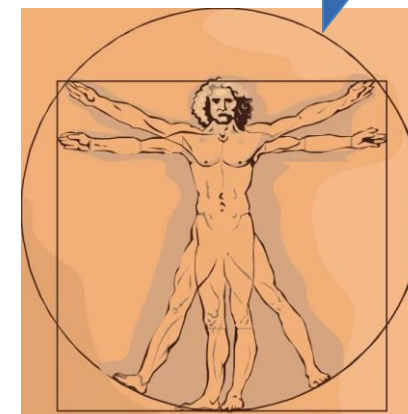
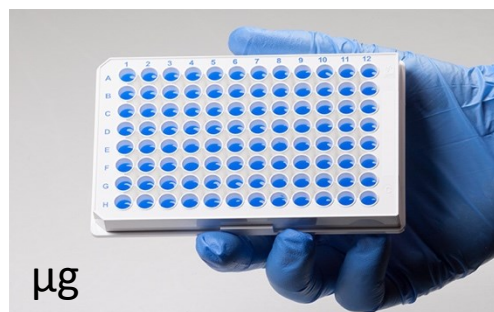


Predictive Pharmaceuticals



Nature Reviews | Drug Discovery

Predict, Integrate, Design, Test



Acknowledgements

- You for listening
- Collaborators
 - Many and varied
 - Local, national and international
- Cancer Research UK Funding
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Thank you

Gavin Halbert