Example use of screening and analytical tools for secondary processing

E. Prasad, T. Islam, J. Robertson, G. Halbert

University of Strathclyde, Strathclyde Institute of Pharmacy and Biomedical Sciences, 99 George Street, Glasgow, G1 1RD, UK

CMAC FUTURE MANUFACTURING RESEARCH HUB

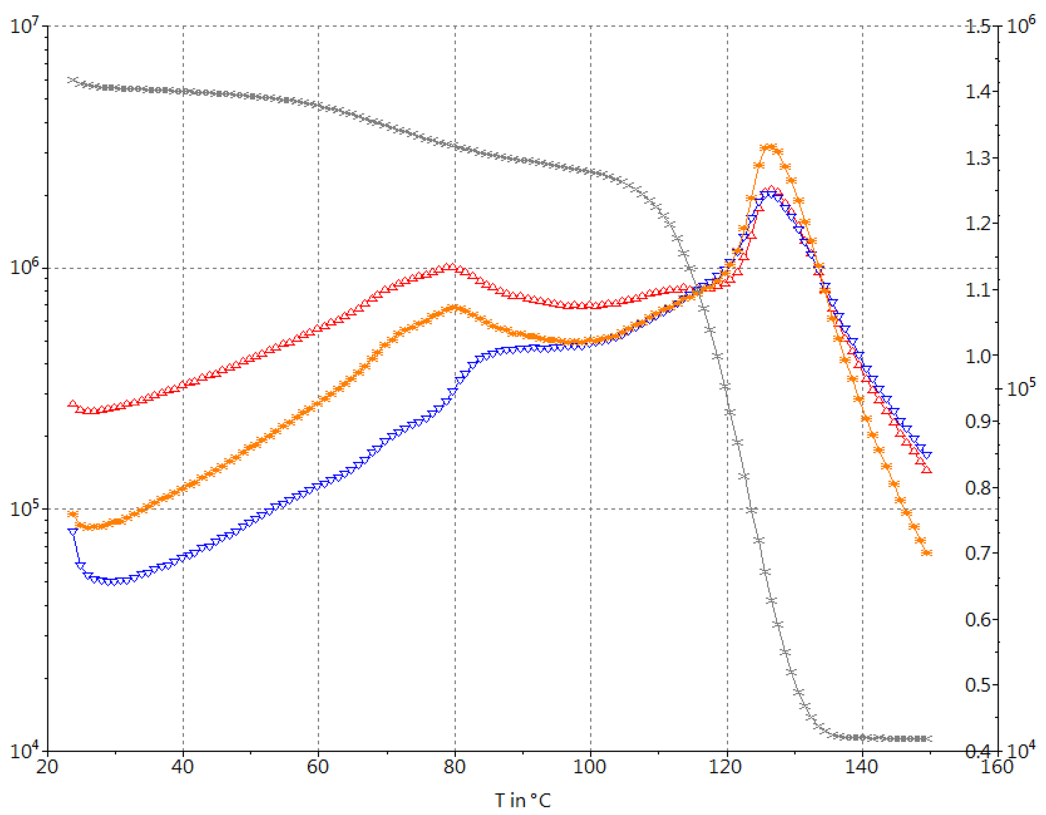
A number of process product archetypes are being targeted within the HUB program. For the finished product, Hot Melt Extrusion (HME) is one process type being explored for the formulation stage with either compression, moulding or 3DP being used to generate the dose form.

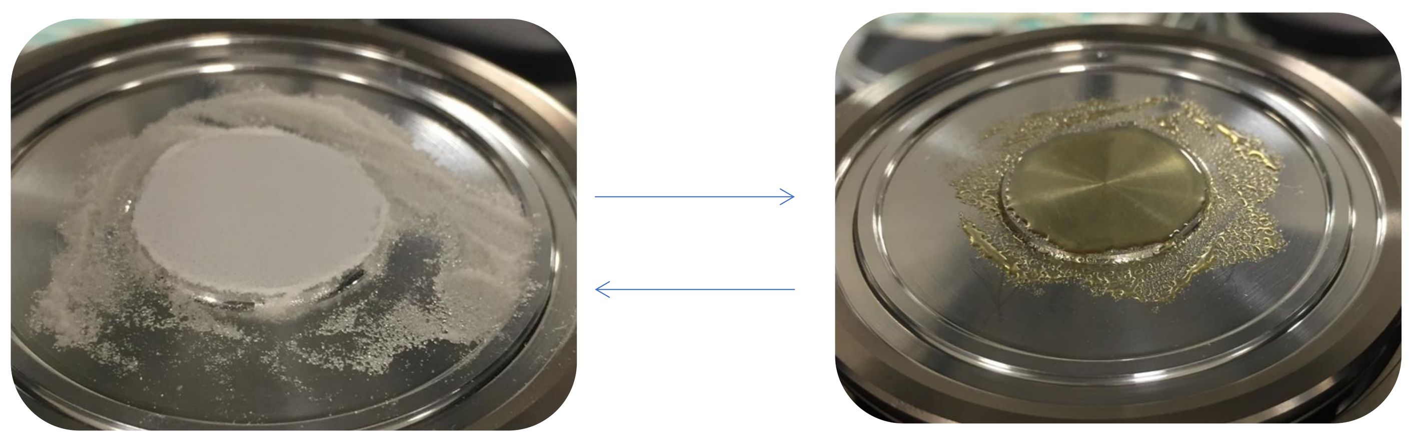
In order to support this activity a number of screening and analytical tools are being developed some of which are exemplified here:

1) Example screening tool for polymer processing by Hot-melt-extrusion – ***Fixed compressive load, constant deformation temperature sweep using a rotational rheometer.***

Screening a viable processing space for polymer formulations in HME is a time and labour intensive process. Processing conditions such as operating temperature are often based on a glass transition (Tg) or melting temperature of the drug. However, these values are not totally reflective of processes within the extruder, where not only temperature but also shear, compressive forces and tenacity affect the process. A Haake Mars Rheometer (ThermoFisher, DE) with a 25mm parallel plate geometry is being used to develop methods for screening the formulation characteristics prior to extrusion.

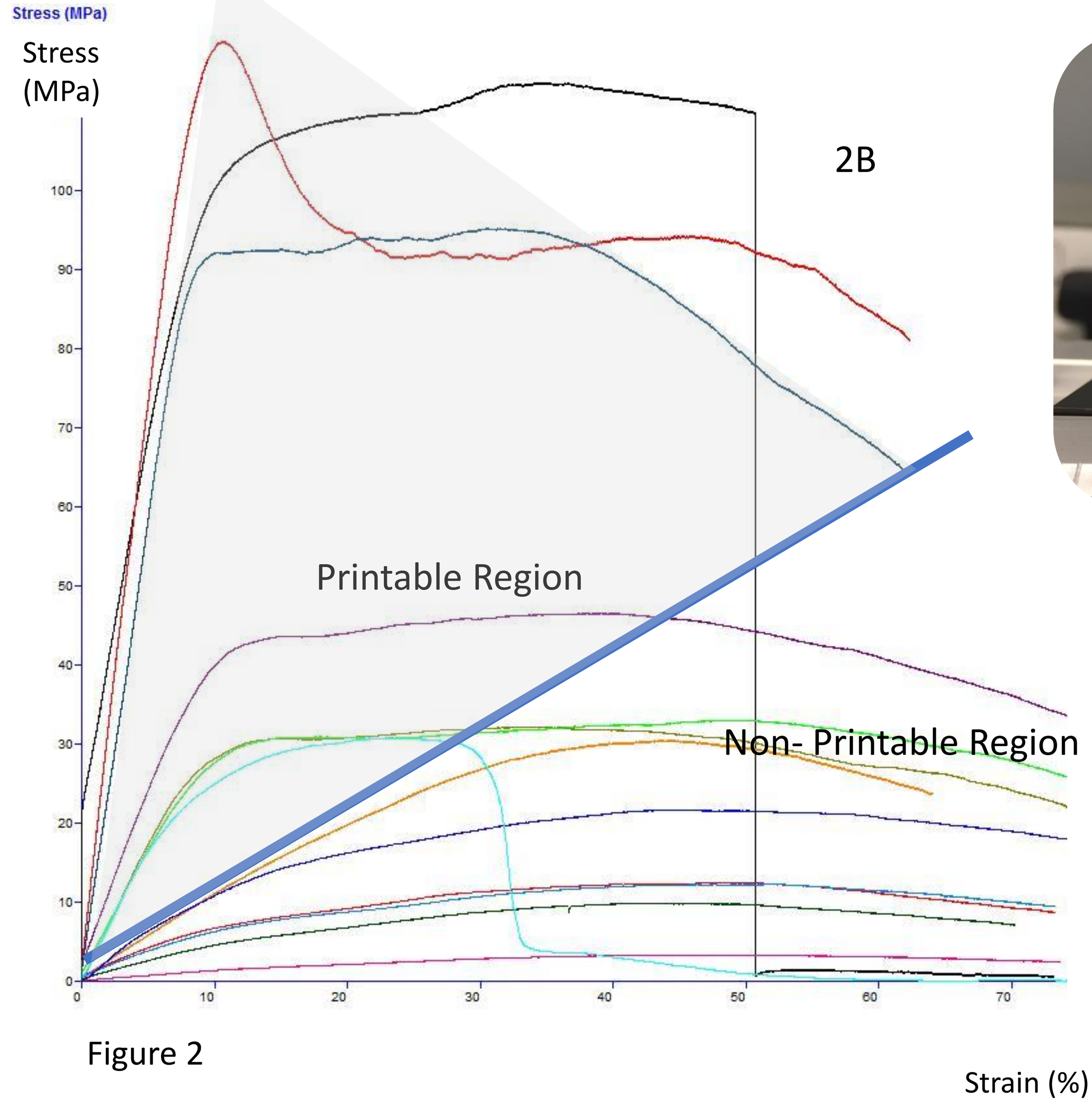
Figure 1

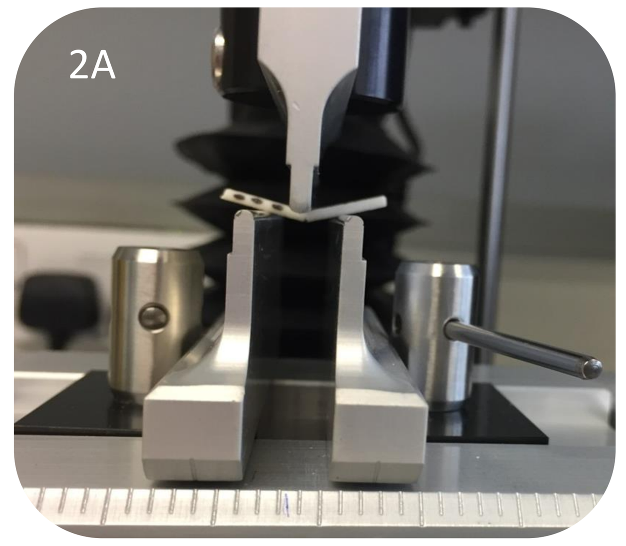




2) Example screening tool for extruded filament formulations for FFF-3D printing of OSD – ***Force displacement measurements to establish suitability for printing.***

In order to 3D print from a filament, the filament must have acceptable mechanical properties in order to allow feeding and transport within the printer. A TA-XT texture analyser (Stable Micro Systems, Godalming, UK) was modified to perform 3-point bend tests to derive stress-strain behaviour of the extrudates. The target was to establish a 'printable' region on the stress strain graph using commercial filaments as a basis.





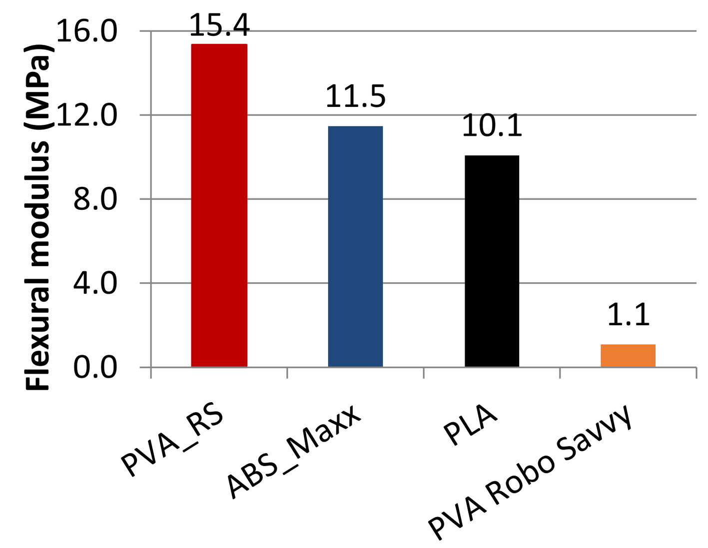
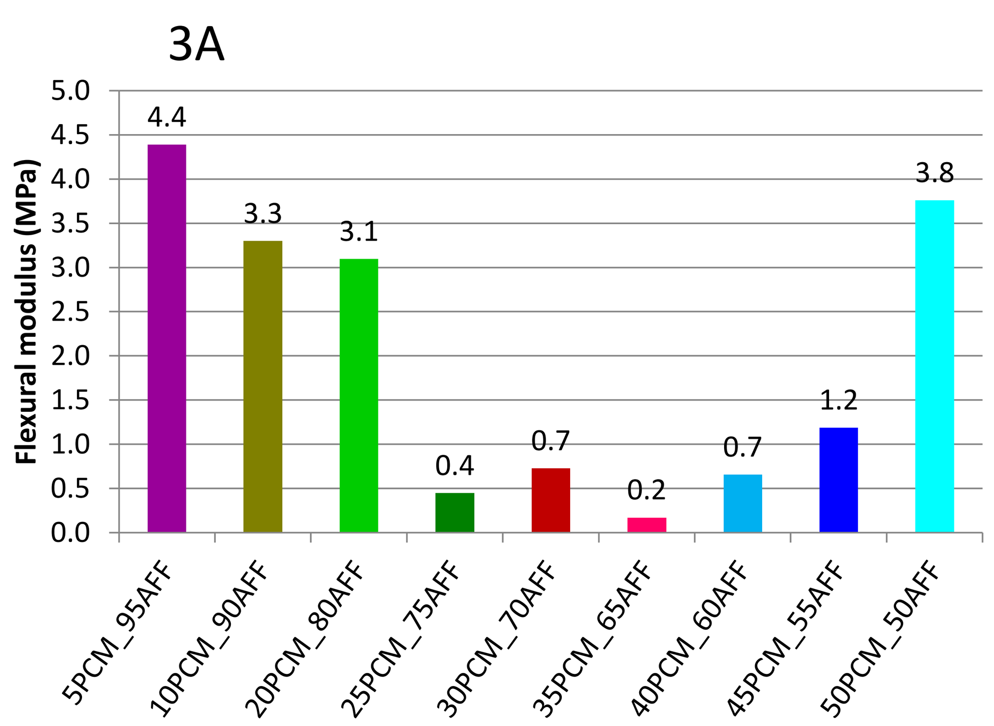
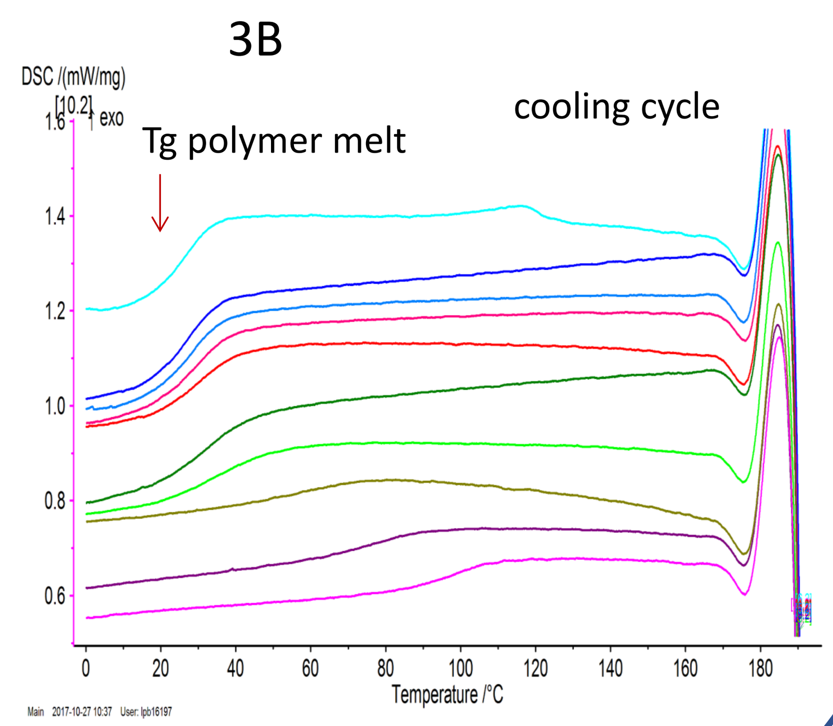


Figure 2

The example above demonstrates the capability of differentiating between different formulations. In this case an HPMC-Paracetamol system is shown vs commercial filament. The flexural properties of the 5-50% API loaded filaments were in agreement with the printability of these formulations. Additionally thermal analysis of these formulations aligned with the broad groupings observed from this mechanical testing. This may be indicative of the distribution of components and subsequent micro-structure within the filaments. E.g glass transition temperatures and melting point suppression are in agreement with the flexural properties.

Figure 3





An additional example with a brittle-hygroscopic polymer-API system is shown below. Here not only is the printability aspects shown but also an exemplification of the mechanical test to assess stability due to the uptake of moisture (4A vs 4B).

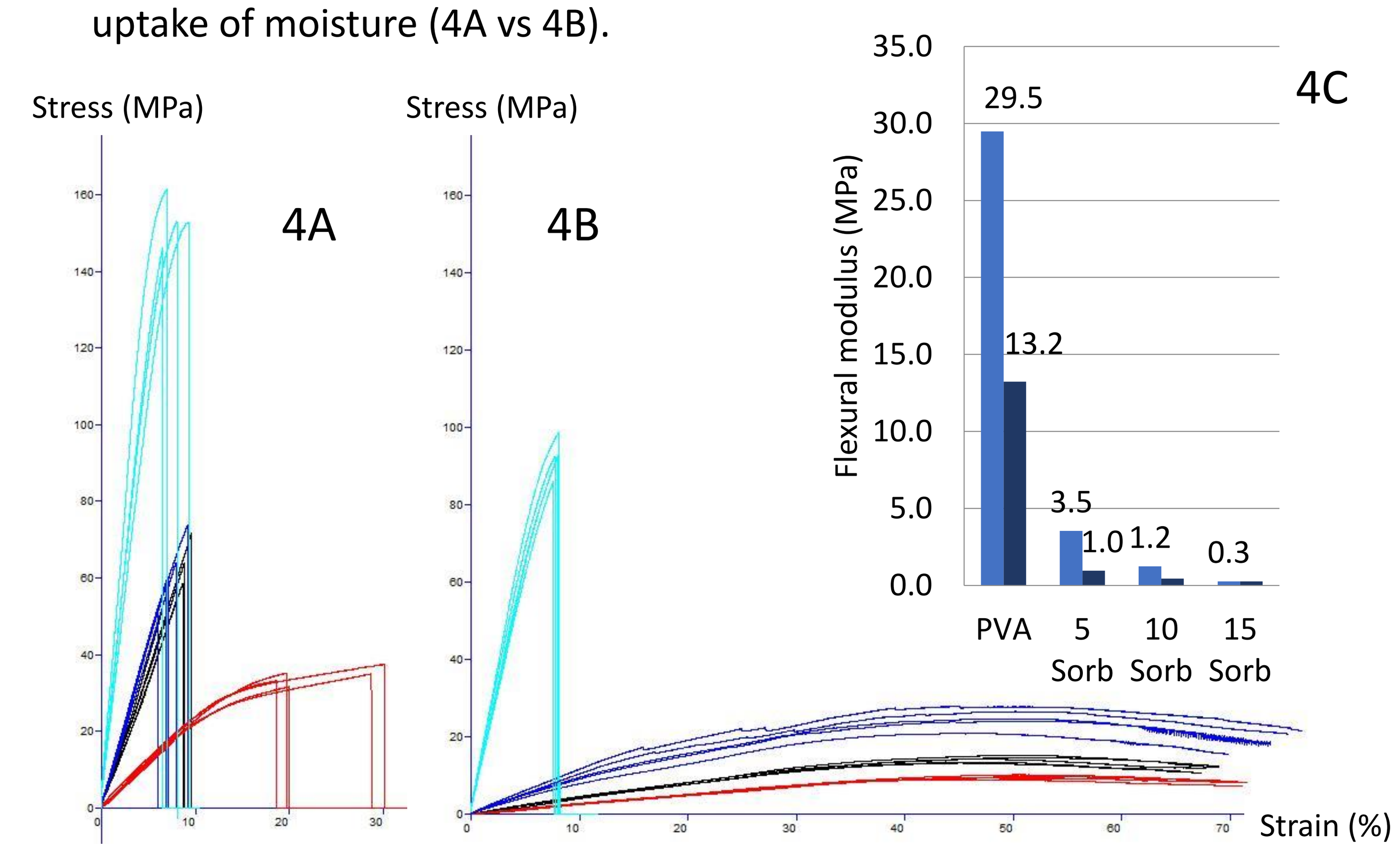


Figure 4

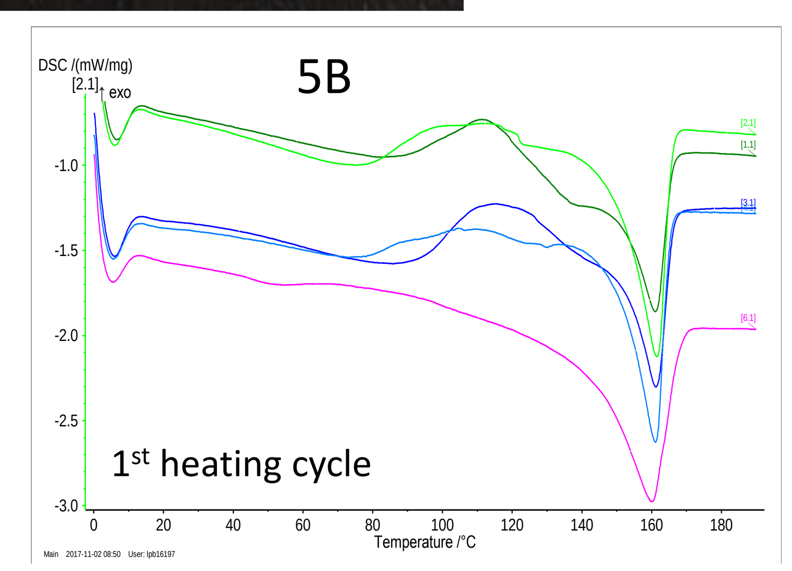
3) Example techniques for understanding polymer-API interactions- ***Solid solutions, solid dispersions, Inhomogeneity of solid form and thermal history.***

Within 3D printed dose forms the solid solution may be supersaturated at high API loadings. Upon storage, this can often be seen as changes in visual appearance resulting from crystallisation of API. Additionally as a result of the print process the thermal history is altered versus post HME extrudate. Thermal analysis is one technique used at CMAC to assess this. We are also combining this with other analytical techniques such as PDF, RAMAN and THz supported with modelling through PhD programs to determine phase equilibria of API-Polymer systems.

Figure 5

5A

DSC with thermal history



For further information please contact elke.prasad@strath.ac.uk

EPSRC · University of Strathclyde Glasgow · University of Bath · University of Cambridge · The University of Sheffield · Imperial College London · University of Leeds · Loughborough University · gsk · AstraZeneca · Novartis · Bayer · Lilly · Takeda · Roche