



Stability of Biopharmaceuticals: Past, Present and Future

Paul Varley,
Vice President,
Biopharmaceutical Development

Agenda

- 1 The last 20 years or so
- 2 Where we are now
- 3 The future

Progress

Early Process - THEN	Current Platform – NOW
75 mg/L fermenter yield	5-10+ g/L fermenter yield
50% purification yield with 9 step process	>75% purification yield with 4 step process
1 mg/mL formulation	100+ mg/mL formulation



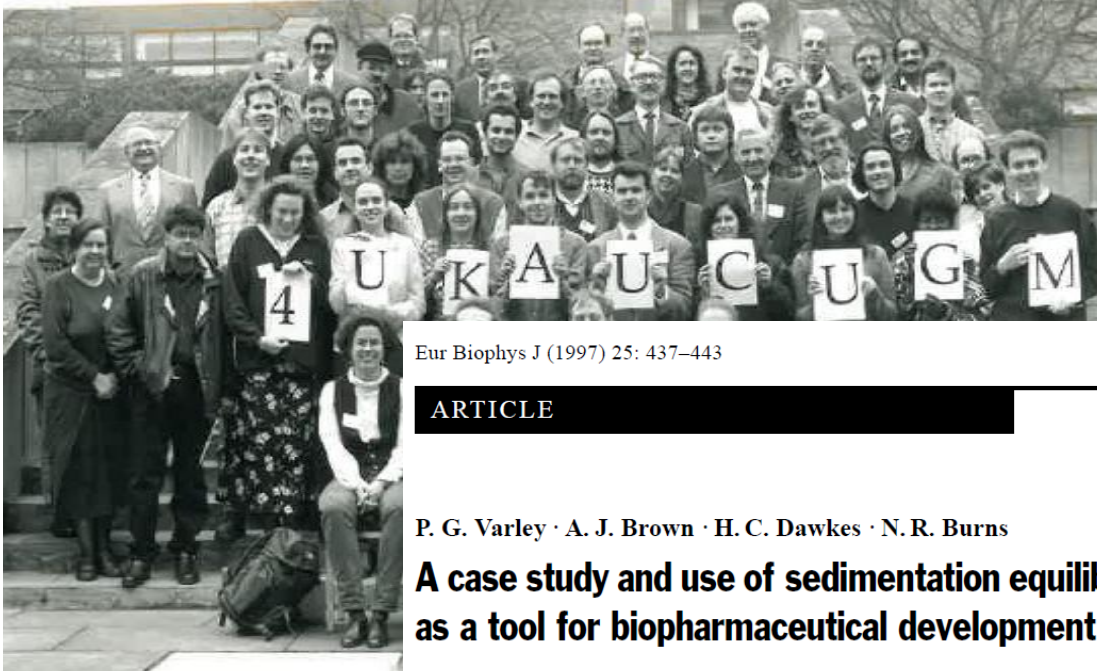
2014

Rank	Product	Company	Technology	WW Sales (\$m)
1	Avastin	Roche	Monoclonal antibody	9,232
2	Humira	Abbott & Eisai	Monoclonal antibody	9,134
3	Rituxan	Roche	Monoclonal antibody	7,815
4	Enbrel	Wyeth, Amgen & Takeda	Recombinant product	6,583
5	Lantus	Sanofi-Aventis	Recombinant product	6,386
6	Herceptin	Roche	Monoclonal antibody	5,796
7	Crestor	AstraZeneca	Small molecule chemistry	5,739
8	Spiriva	Boehringer Ingelheim	Small molecule chemistry	5,552
9	Remicade	SGP, J&J & Mitsubishi Tanabe	Monoclonal antibody	5,220
10	Gleevec/Glivec	Novartis	Small molecule chemistry	5,136

2008

Rank	Product	Company	Technology	WW Sales (\$m)
1	Lipitor	Pfizer, Astellas & Almirall	Chiral chemistry	13,507
2	Plavix	BMS & Sanofi-Aventis	Small molecule chemistry	9,447
3	Advair	GlaxoSmithKline	Small molecule chemistry	7,828
4	Enbrel	Wyeth, Amgen & Takeda	Recombinant product	6,455
5	Diovan	Novartis & Ipsen	Small molecule chemistry	5,825
6	Rituxan	Roche	Monoclonal antibody	5,481
7	Remicade	SGP, J&J & Mitsubishi Tanabe	Monoclonal antibody	5,293
8	Nexium	AstraZeneca	Chiral chemistry	5,200
9	Epogen/Procrit	J&J, Amgen & Kirin	Recombinant product	5,162
10	Avastin	Roche	Monoclonal antibody	4,818

A Bit of Ancient History



Eur Biophys J (1997) 25: 437–443

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ARTICLE

P. G. Varley · A. J. Brown · H. C. Dawkes · N. R. Burns

A case study and use of sedimentation equilibrium analytical ultracentrifugation as a tool for biopharmaceutical development

Accepted: 6 October 1996

Abstract Analytical ultracentrifugation (AUC) has re-emerged as a powerful technique for protein characterisation. We report the pivotal role sedimentation equilibrium AUC has played in the development of macrophage inflammatory protein-1 α (MIP-1 α) as a protein therapeutic. MIP-1 α has potential clinical applications in cancer but its clinical use is limited, since it associates to form large insoluble aggregates in physiological buffers. Using AUC as

ufacture, formulation and quality control to provide information concerning aggregation and biologically important molecular interactions. This paper illustrates some of our work in the application of modern AUC in protein pharmaceutical development by highlighting the key role it has played in the development of BB-10010, a variant of the protein macrophage inflammatory protein-1 α (MIP-1 α).

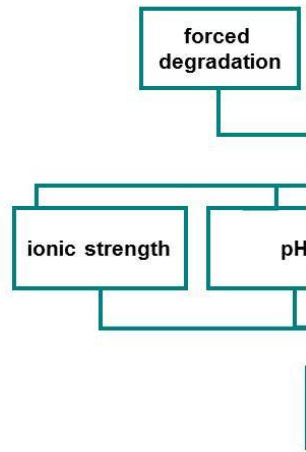
Macrophage inflammatory protein-1 α (MIP-1 α ,

More Ancient History

C a T

Boston, April, 2002

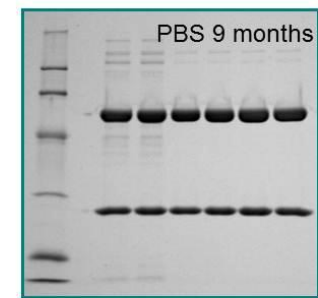
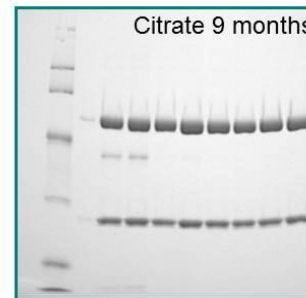
Generic Formulation Strategy



other data

Phosphate Free Formulations

- **Example: Enhanced stability of CAT-XYZ with citrate**



+25°C +5°C -20°C -70°C

+25°C +5°C -70°C

- Reduction in high Mw bands
- Stability at -20°C

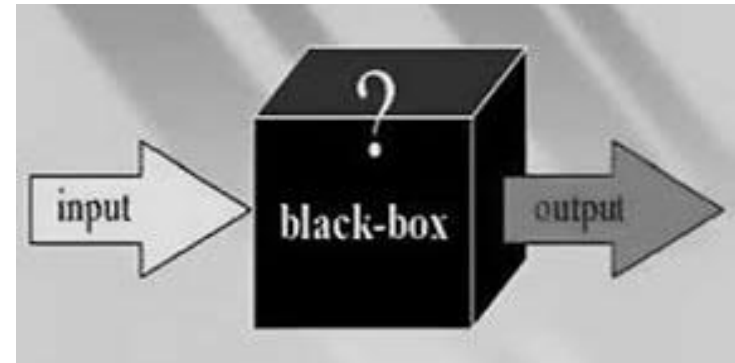
www.cambridgeantibody.com

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Where We Were

- ◆ Formulation is a “black box”
- ◆ Simple
 - PBS
 - Low concentrations
 - Frozen (-80°C)
- ◆ “Crude” analytical methods
 - Manual
 - Low throughput
 - Low resolution



Moving On.....



Stability and Formulation

Boston, Nov, 2010

- Biggest single source of issues for IND enabling (Early assessment selection)

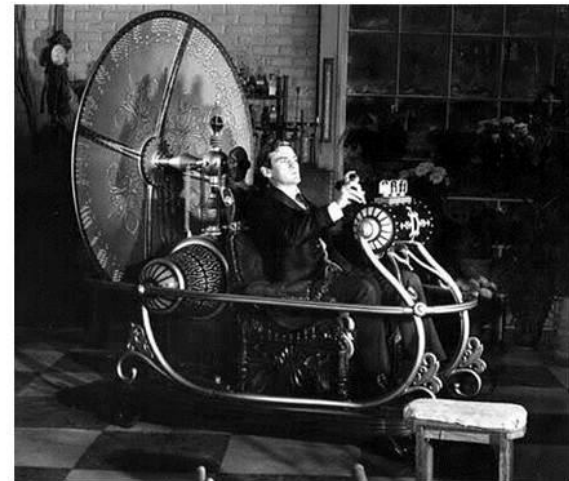
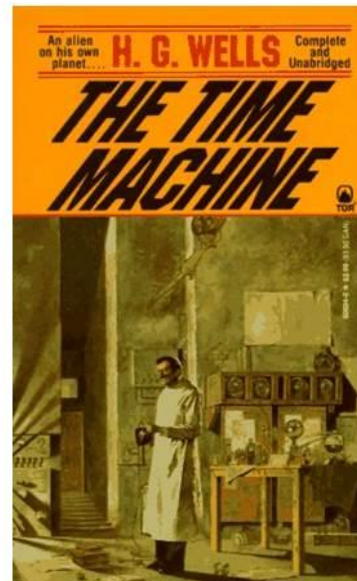


Stability and Formulation

- Standard formulation development strategy for all products

- We do not have a time machine

- Selection of IND formulation
 - ◆ Depends on
 - > molecules behavior
 - > requirements for formulation
 - > on attitude to risk
 - > *Experience etc*



Agenda

1

The last 20 years or so

2

Where we are now

3

The future

Trends

- ◆ Higher concentrations required
- ◆ More complex molecules
- ◆ Novel delivery devices
- ◆ Need for speed

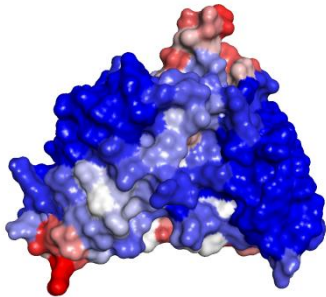
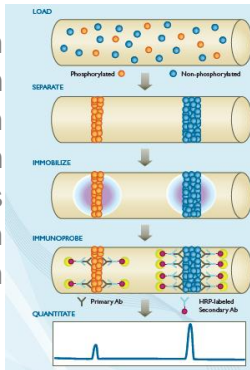
Where We Are Now

- ◆ Developability
- ◆ Systematic and statistical approaches
- ◆ Analytical Advances
- ◆ Automation
- ◆ Novel molecules
- ◆ Delivery and devices

Lead Selection with Developability Focus

High throughput cIEF

- Fragmentation
 - Deamidation
 - Oxidation
- Asp isomerization
- Sequence variants
 - O-glycosylation
 - Glycation



Chemical Stability & PTMs

Solution Properties

Target clones

In silico prediction tools

Differential static light scattering

- StarGazer 384-well
- Determine aggregation transition (Tagg)

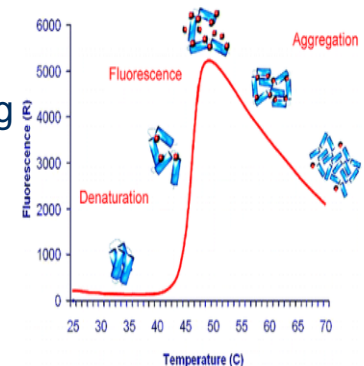


StarGazer-384™ system

- Conformational stability
- Colloidal stability
- Interfacial stability
- pI
- Aggregation

Differential scanning fluorimetry (DSF)

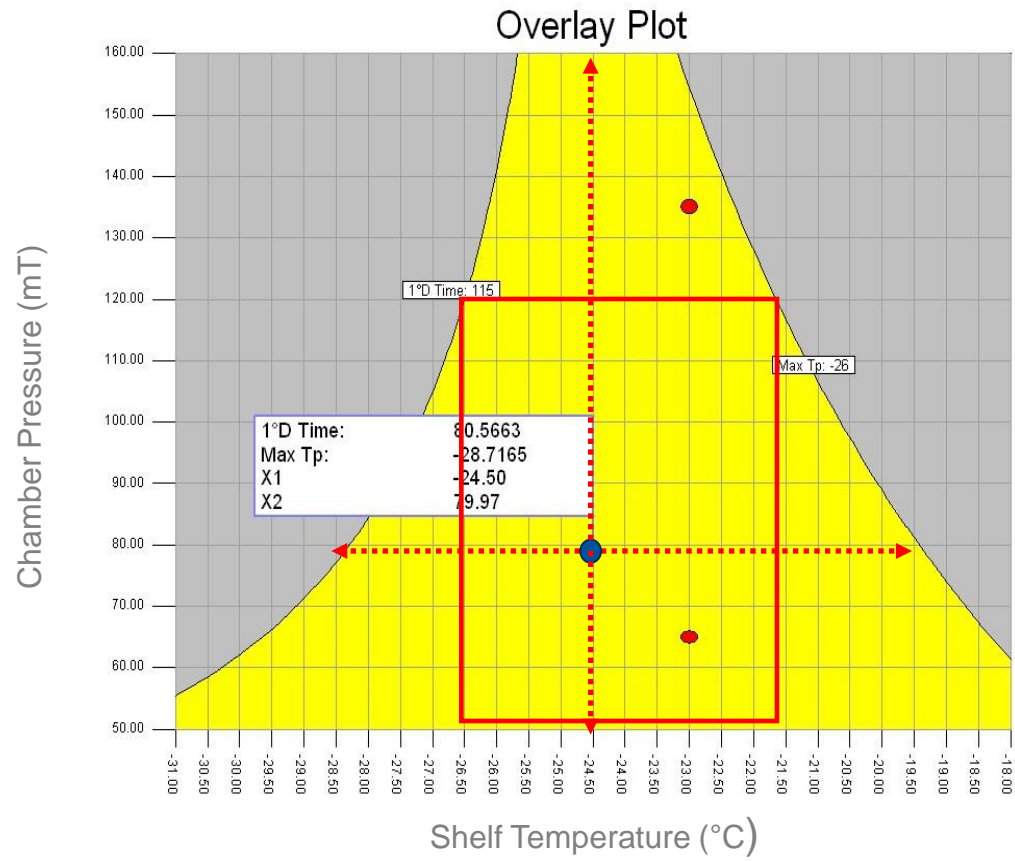
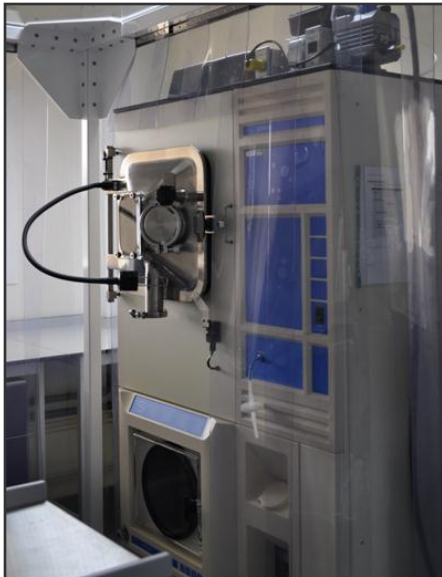
- Sypro-Orange dye
- Determine unfolding transition (T_m)



◆ Selective pressure for favourable Development & Manufacturing Properties, e.g:

- Stability & resistance to degradation (in culture, in process, in vial, in vivo)
- Structure-function (identify key attributes)
- (Expression)

Systematic and Statistical Approaches Design Space For Lyo Cycle



Evolution of analytical technologies – from “black-and-white TV” to “3D high definition TV”

Synagis approval

Today

Future



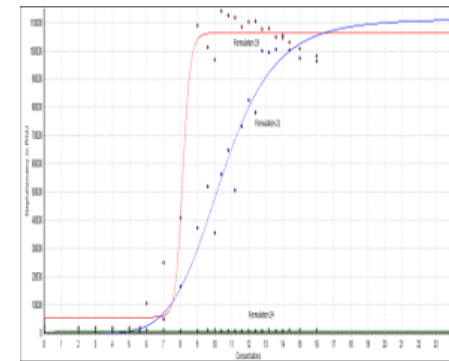
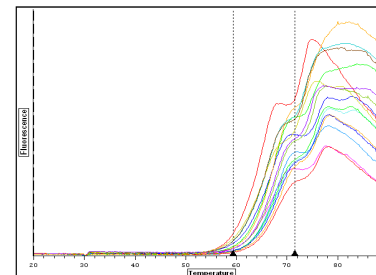
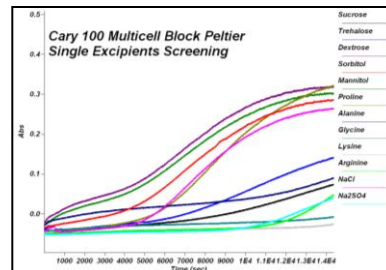
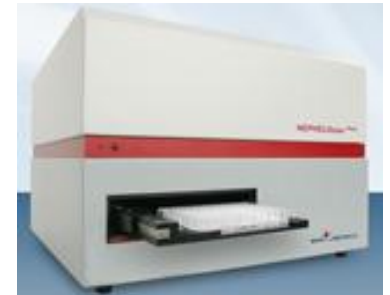
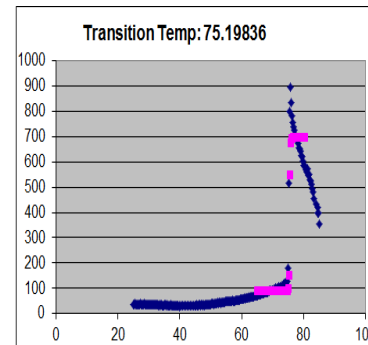
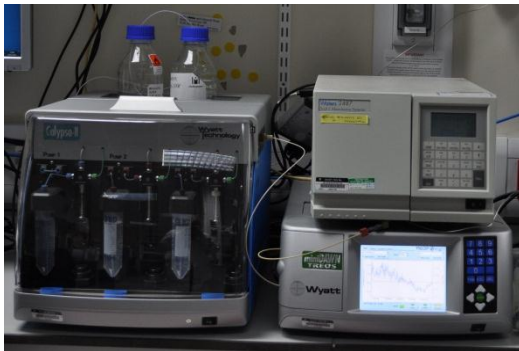
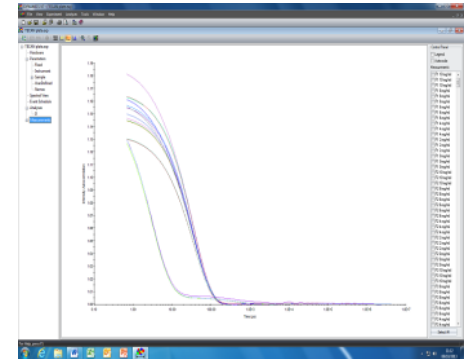
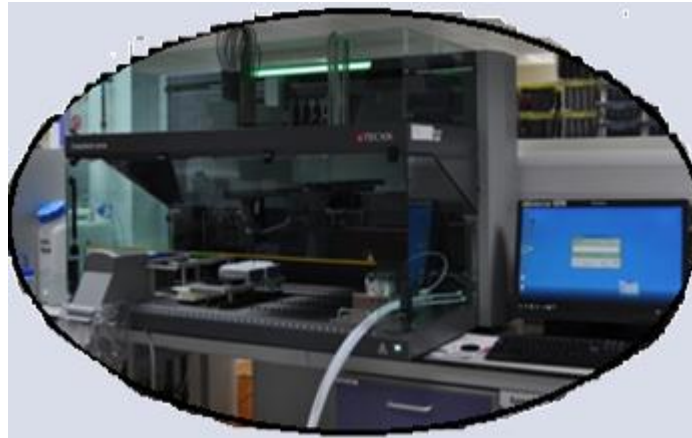
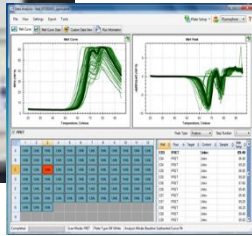
“State-of-the-Art” analytical capabilities are the backbone of Formulation Development.

- Peptide map with simple MS
- Simple bioassay (microneut)
- SDS-PAGE
- ELISAs

- Peptide map with high resolution MS
- Reporter gene, cytotoxicity and other bioassays
- Extensive particle characterization
- Platform based assays
- Automation

- Deuterium exchange MS for higher order structure/function
- 2D LC/MS and CE/MS for HCP characterization
- CE-MS for product characterization
- Chip-based glycan and peptide analysis
- Multi-functional bioassays, cell migration; complete assay sets for Fc effector functions
- in silico* predictive technologies

Automation



New Challenges

◆ Beyond antibodies – Novel molecules

1	Peptides
2	ADC
3	mAb Combos
4	Fusion proteins
5	Vaccines
6	Therapeutic Proteins
7	Virus Technologies
8	ADCC
9	Novel Scaffolds
10	Blood Brain Barrier
11	Bispecifics
12	Fab
13	mRNA



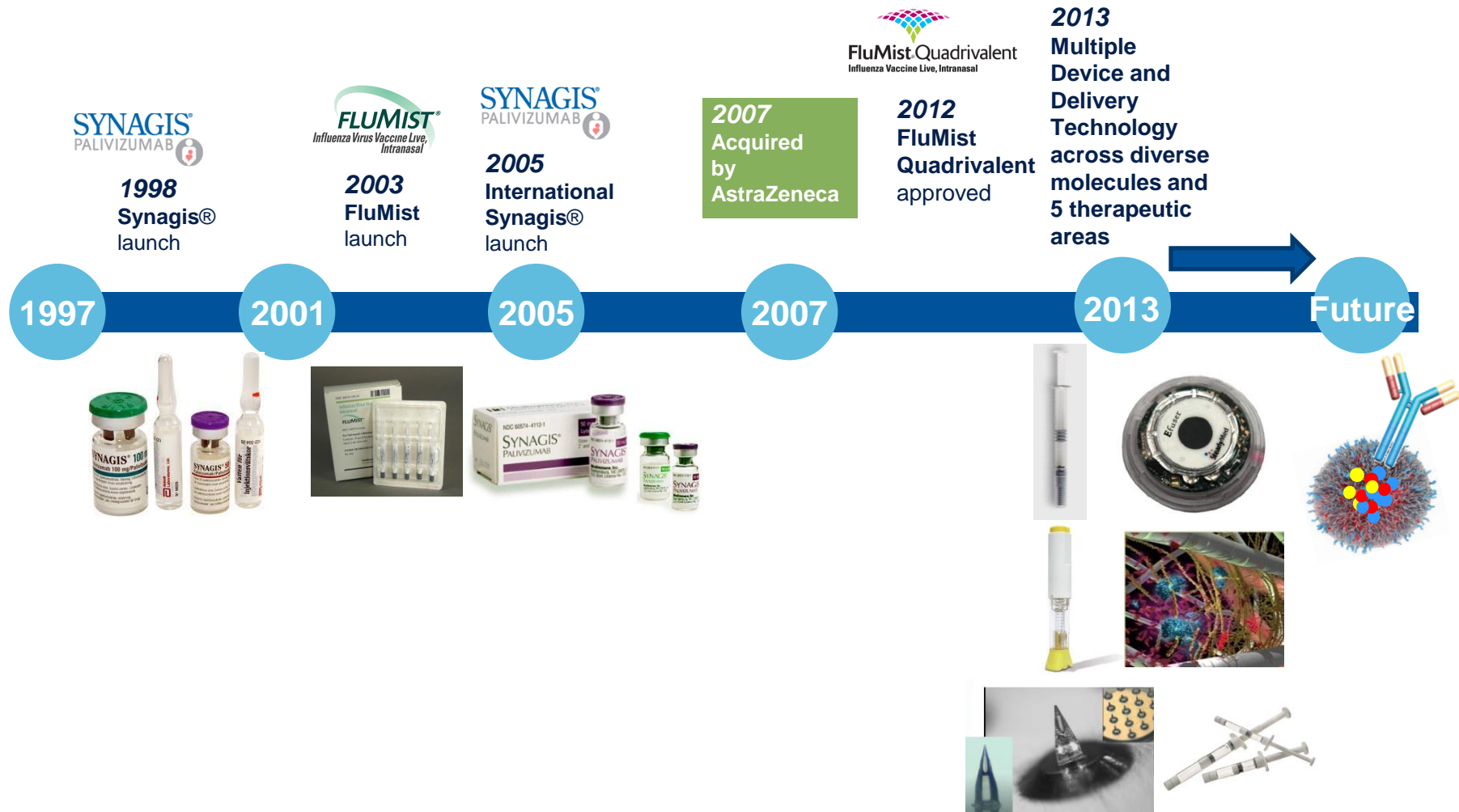
THE GOOD THE BAD AND THE UGLY

New Molecules
/Mechanisms
& Medicines

“Expressability”
& Consistency

Drug stability &
Heterogeneity

Evolution of Delivery and Device Technology at MedImmune



Agenda

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Future needs

◆ Mab platform

- Ultra high concentrations
- More complex devices
- Combinations and mixtures

◆ New formats and modalities

- Increasing diversity & complexity (=challenge)
- Devices

◆ Commercial drivers

- ◆ Speed, competition

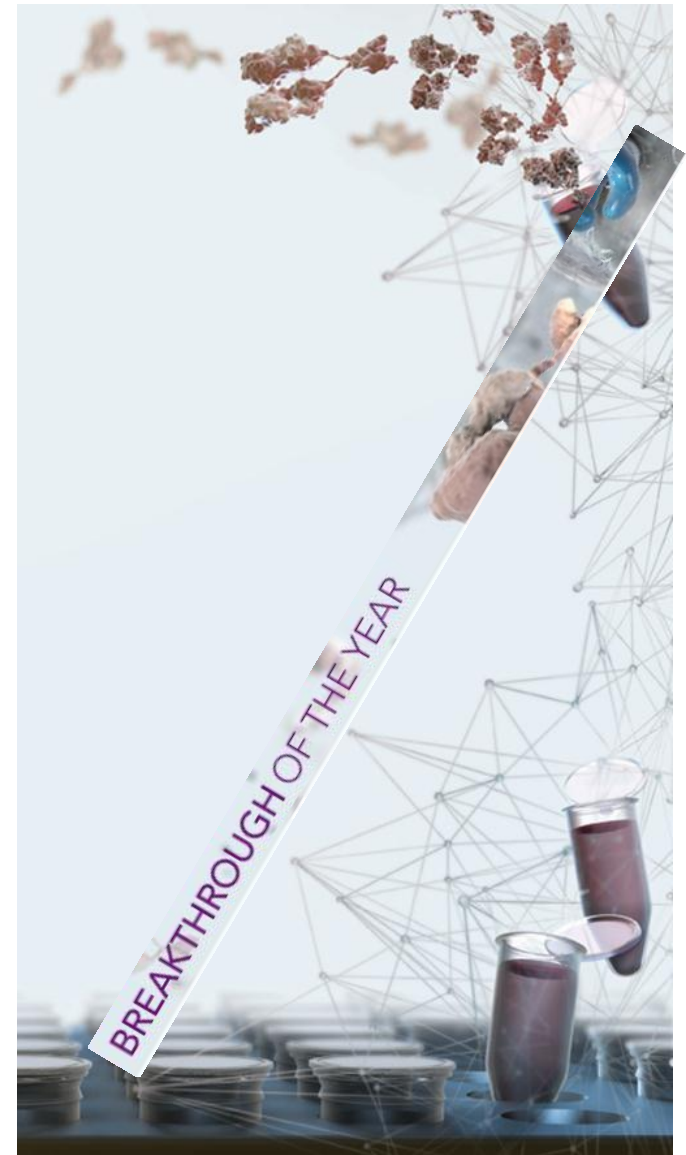
◆ Predictability – desired stability designed in

- ◆ Automation/HTS
- ◆ *In silico* modelling
- ◆ Analytical technology
- ◆ Experience

◆ Informed risk taking

Stability and Formulation

- ◆ Unprecedented opportunities for the development of Biological medicines
- ◆ Stability and formulation sciences more important than ever to deliver this promise
- ◆ Recent developments in the science will continue to enable this to happen



Cancer Immunotherapy
J Couzin-Frankel Science 2013;
342:1432-1433

Thanks to



◆ Shahid Uddin



MedImmune Formulation Sciences