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MIBio 2016

Stability of biopharmaceuticals

From molecular interactions to successful products

Wednesday 9th November 2016
Magdalene College, Cambridge

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MIBio 2016 is organised by the Formulation Science and Technology Group (FSTG) and the Joint Colloids Group of the SCI and Royal Society of Chemistry (RSC) together with the Academy of Pharmaceutical Sciences (APS).

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The Formulation Science and Technology Group is a subject group of the Royal Society of Chemistry, London. It is the leading scientific organisation dedicated to product formulation. As a charitable organisation, it works for the benefits of its members and to further the awareness of formulation science. It fosters the advancement of formulation science across many scientific disciplines and industrial applications, including pharmaceuticals, cosmetics, foods and detergents. It is a point of focus for all industrialists and academics engaged in the practice of formulation science. The FSTG organises many events during the year for the benefit of its members, including conferences, training days, and networking events.

For more information visit: **www.formulation.org.uk**

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The Academy of Pharmaceutical Sciences (APS) is the professional body for the Pharmaceutical Sciences in United Kingdom. A Pharmaceutical Scientist is an individual who contributes to bringing a new drug from concept through to a medicinal product. This includes, but is not exclusive to, individuals in academia, industry, regulation, clinical research and manufacturing. The mission of the Academy of Pharmaceutical Sciences is to champion innovation and opportunities in Pharmaceutical Sciences for the delivery of medicines. In order to achieve this mission, our aims are to:

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Colloid science today is a very broad and dynamic subject spanning a wide range of areas from classical dispersions to novel nanoparticles for drug delivery. The Colloid Group aims to act as a focus for these interests for the UK colloid community (and wider). Whether you are a chemist, physicist, engineer, student, formulation scientist, nanotechnologist, pharmacist, biologist, polymer scientist, food scientist or any other related discipline interested in colloids, we invite you to join the Colloid Group. Today the group supports the UK colloid community by organising a range of meetings ranging from one day to multiday meetings. We also invite nominations for outstanding contributions to colloid science in the UK through our three awards, the McBain Medal, the Thomas Graham Lecture and the Rideal Award.

For more information visit: **www.colloidsgroup.org.uk**

FOREWORD

Stability of biopharmaceuticals
From molecular interactions to successful products

It is a pleasure to welcome you to the 6th annual MIBio conference at Magdalene College, Cambridge. The aim of the MIBio series is to bring the biopharmaceutical formulation community together to discuss the latest developments in the field.

Over the last decade, formulation has become a critical and integral part of the biopharmaceutical development process. With the increasing number of pipeline products and off-patent biologics, the importance of formulation is even greater than ever. We believe that in order to ensure future progress the industrial and academic communities need to work together, so we are delighted to welcome a very healthy mix of academics and industrialists at our event today.

Each year, the MIBio conference has a special theme. This year, the conference will focus on discussing present and future drug-device development and the need for creative formulation to support successful product strategies. This will include formulation strategies for new product formats, use of novel excipients and the use of computational approaches in the formulation and drug delivery design, as well as regulatory and strategic implications of these new approaches. Seven key experts in the field will present on these topics during the day and, as is traditional in the MIBio series, there will be opportunities for audience participation in the discussion of these important matters.

We are very grateful to all the sponsors and exhibitors who have made this meeting possible. We also thank all the authors who sent in abstracts and are contributing to the poster session.

MIBio 2016 is a one-day event, but the discussions you start today may lead to new collaborations and discoveries that will help steer the development of the next generation biopharmaceutical products.

We hope you enjoy the event,

Jan Jezek, Nicholas Darton, Tejash Shah and Stephen Harding
on behalf of MIBio 2016

MIBio 2016

PROGRAMME

08:00 Registration opens

09:00 Opening remarks

Morning session: Formulation and drug-device development – the present and the future *chair: Prof. Stephen Harding | University of Nottingham*

09:15 Moving from drug delivery towards patient outcome improvement: a serious challenge for biologic formulation technology
Didier Pertuy | VP, Global Head Drug-Device Development, Sanofi, France

09:45 Cell and gene therapy formulation technologies: transitioning clinical therapies to medicines
Rita Majithiya | Investigator, Formulation and delivery, GSK, UK

10:15 Speed Networking

11:15 Producing protein and structures for human membrane proteins for antibody development and drug design
Liz Carpenter | Professor, University of Oxford, UK

11:45 Exhibitors highlight

12:40 Lunch Break, Exhibition and Posters

Afternoon session: Creative formulation approaches to overcome new and old challenges *chair: Bernardo Perez-Ramirez | Senior Scientific Director, Genzyme (Sanofi Company), USA*

13:45 Introduction

14:00 Development of co-formulation of monoclonal antibodies and recombinant human hyaluronidase (rHuPH20) - a case study
Astrid Pappenberger | Group leader, Senior Scientist, Roche, Switzerland

14:30 Combining computational approaches and experiments for selecting compounds with the desired properties, applied in particular to the osmolyte-like effects on the thermal stability of a monoclonal antibody
Andreas Bender | Lecturer for molecular informatics and drug design, University of Cambridge, UK

15:00 Coffee break, Exhibition and Posters

15:30 Use of math modelling to understand delivery of biopharmaceuticals to the lung
Nia Stevens | Investigator, GSK, UK

16:00 Discussion panel: Creative formulation to enable new product concepts – Current and future trends, regulatory considerations and alignment with product strategies

17:00 Concluding remarks

17:10 Conference ends

Morning Session - Lecture Abstract

Moving from drug delivery towards patient outcome improvement: a serious challenge for biologic formulation technology

Didier Pertuy - Sanofi

The R&D Pharmaceutical landscape went through a succession of interconnected evolution trends that led to a significant increase of Drug Product demand based on smart device-mediated self-administration of biologic modalities, particularly therapeutic monoclonal antibodies. These new types of Drug Products are certainly opening new opportunities to improve healthcare outcomes. But they raised as well new challenges that require new development practices under the strategic framework of a Patient-centered Integrated System Design approach. Within this strategic framework the ability to design patient friendly stable ready to use solutions containing a high concentration of proteins is a critical asset that puts formulation technology on the critical path.

didier.pertuy@sanofi.com

Morning Session - Lecture Abstract

Cell and Gene Therapy Formulation Technologies: Transitioning clinical therapies to medicines

Rita Majithiya - GSK

Cell and gene therapy medicines represent transformative treatment options for patients with a range of disorders spanning several therapy areas. Commercialisation of these programs to transform clinical successes to medicines requires a novel drug development paradigm. State of the art formulation development would be a key contributor to significantly improve product stability and shelf life, thereby developing robust medicines enabling global distribution while assuring safety and efficacy of the medicine. For ex-vivo autologous therapies, this would represent a shift from current supply paradigm of a co-located manufacturing and treatment center. This would be vital to enable reach of cell and gene therapy medicines to patients across the globe. There are significant technical, development and regulatory challenges which need to be overcome and risks mitigated to realise prospects outlined above. GSK is following a rational, risk based approach to developing these formulations and realize the potential of these novel therapeutics. The presentation will cover our approach to formulation development for cell and gene therapies.

rita.x.majithiya@gsk.com

Morning Session - Lecture Abstract

Producing protein and structures for human membrane proteins for antibody development and drug design

Liz Carpenter – University of Oxford

For human integral membrane proteins (IMPs), producing the protein sample is often the limiting factor for structural and functional studies, and for antibody generation. The SGC has created a pipeline for human IMPs production that has allowed us to solve structures of seven human IMPs, using a range of structure determination techniques, including X-ray crystallography, serial femtosecond crystallography and cryoEM. We use these methods to produce and study proteins that are identified as genetic hits for neuropsychiatric and metabolic disease, cancer and inflammation.

liz.carpenter@sgc.ox.ac.uk

Afternoon session – Lecture Abstract

Development of co-formulation of monoclonal antibodies and recombinant human hyaluronidase (rHuPH20) - a case study

Astrid Pappenberger - Roche

For patients, subcutaneous (SC) administration represents a convenient alternative to i.v. infusion. However, SC application faces limitations with regards to the drug volume that can be administered. To enable delivery of the necessary doses, increase in the concentration of the drug and/or temporary enlargement of the interstitial space at the injection site, e.g. by using recombinant human hyaluronidase (rHuPH20), are potential strategies to face this challenge.

The presentation will highlight the technical development approaches used at Roche for the drug product development of co-formulations consisting of concentrated monoclonal antibodies and rHuPH20. The presentation will focus on particular challenges for formulation and process development arising from combination of two very different proteins in order to maintain both stable and active within one formulation.

astrid.pappenberger@roche.com

Afternoon session – Lecture Abstract

Combining computational approaches and experiments for selecting compounds with the desired properties, applied in particular to the osmolyte-like effects on the thermal stability of a monoclonal antibody

Andreas Bender - University of Cambridge

More and more chemical and biological data is available both in the public domain as well as inside companies; however how to use this information efficiently to address a problem is often much less clear.

In our group, we are hence developing methods to mine such data, and to test our predictions (often related to compound effects on biological systems, such as bioactivity and others) with experimental partners.

This presentation will firstly give a general overview of the utilization of chemical and biological information to address life science problems. Subsequently, a case study will illustrate how we can use computational algorithms to design a diverse compound library to modulate the thermal stability of a monoclonal antibody, and how to rationalize the resulting effects in a structure-activity study. More specifically, to better understand the structural basis underlying the effect of additives we selected a diverse library of compounds comprising 84 compounds of the polyol, amino acid and methylamine chemical classes and determined the effect of each compound on thermal stability of a monoclonal antibody as a function of compound concentration. Thermal stabilization of the antibody was influenced by solution pH. Quantitative structure-activity relationships (QSAR) were derived by partial least squares regression for individual compound classes and globally. The global model suggests that ligands with a phenyl ring will decrease the Tm, while highly soluble, polar compounds with at least two hydrogen bond donors will increase the Tm. Hence, overall, we could show that in this case the design and rationalization of the effects of small molecules on the thermal stability of an antibody could be supported by computational methods.

ab454@cam.ac.uk

Afternoon session – Lecture Abstract

Use of math modelling to understand delivery of biopharmaceuticals to the lung

Nia E Stevens - GSK

Delivery to the lung is a widely investigated route of administration for Biopharmaceuticals, either for delivery to treat local lung effects or as a route to systemic absorption that avoids the metabolic processes of the gastrointestinal tract and the inconvenience of administration by injection.

Evaluating the dose delivered to the lung and, in particular, doses delivered to the bronchi, bronchioles and alveolated airways is difficult since the ability to make direct measurements are severely limited. Math models provide an opportunity to obtain estimates of how drug is delivered to and distributed within the lung that is based on basic physics rather than intuition based judgements.

Here examples are presented of how a math modelling approach has been applied to understand the lung delivery of biopharmaceutical molecules and for both systemic and local lung treatments.

nia.e.stevens@gsk.com

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Exhibitors Contact Details -

Adaptive Instruments Ltd
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Mail: Biopharma House, Winnall Valley Road, Winchester, SO23 0LO
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Tel: +44 (0) 1483 600 867 Web: www.merrowscientific.com

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Tel: +44 (0) 7475 783 708 Web: www.proteinsimple.com

Surface Measurement Systems Ltd
Mail: Unit 5 Wharfside, Rosemont Road, Alperton, London, HA0 4PE, UK
Tel: +44 (0) 208 795 9403 Web: www.surfacemeasurementsystems.com

TA Instruments
Mail: 730-740 Centennial Court, Centennial Park, Elstree, Herts, WD6 3SZ, UK
Tel: +44 (0) 208 238 6100 Web: www.tainstruments.com

Unchained Labs
Mail: 6870 Koll Center Parkway, Pleasanton, CA 94566, USA
Tel: +1 925 587 9800 Web: www.unchainedlabs.com

Xigo Nanotools Ltd
Mail: 8 Hoveton Gardens, St Helens, WA9 5UR, UK
Tel: +44 (0) 7578 649 439 Web: www.xigonanotools.co.uk

Poster Abstract

Development of dry powder formulations combining both a biologic therapeutic entity and a small molecule drug substance

Harriet Bridgwater, Amy Worle

Vectura Group plc, Vectura House, Bumpers Way, Chippenham, Wiltshire, SN14 6FH

A product combining a biological therapeutic entity with a small molecule drug substance is still a novel concept in inhalation. A number of small molecule drug products are co-prescribed with a biologic therapy. A combination biologic/small molecule product would potentially have significant compliance and patient benefits via simplifying and reducing the time of treatment. This case study assessed the combination of an immunomodulatory protein (Omalizumab) with a co-prescribed corticosteroid (Fluticasone Propionate).

Small molecules and biologics are typically formulated and delivered in different ways, with biologics commonly developed as liquid formulations for injection. For this case study the formulation was designed for delivery via a dry powder inhaler (DPI). Biologics can be rendered more stable in the solid state via co-formulation with specific excipients therefore a dry powder format can offer improved stability.

The development of a combination dry powder formulation presented a number of challenges that were addressed through the combined use of spray drying and low intensity blending techniques. Excipients were identified to provide protein stability and also for use as force control agents/ carrier particles. The drug substances were initially formulated independently to adopt the most appropriate approach for each molecule.

The physical stability (via aerosol performance testing) and biological integrity of the formulation was assessed for 6 months at 30^0C/65% relative humidity. Results were compared to a mono biologic formulation. The study demonstrated that a small molecule and a biologic can be combined successfully to produce a novel model dry powder formulation with good homogeneity and stability.

harriet.bridgwater@vectura.com

Poster Abstract

Improving downstream operation through formulation innovation

Arecor team: Nicholas Darton, David Gerring, Joshua Cremin, Jan Jezek, Maria Botha

Centre for Process Innovation team: Stuart Jamieson, Jonathan Welsh, Clare Trippett, Julie Anderson, Julia Leach, John Liddell

Fujifilm Diosynth Biotechnologies team: Jonathan Haigh, Tibor Nagy, Daniel Pettit, Mark Douglas

Arecor, the Centre for Process Innovation (CPI) and Fujifilm Diosynth Biotechnologies have entered into a consortium to collaborate on a two-year R&D project entitled Improved Downstream Operation through Formulation Innovation, supported by grant funding from Innovate UK under its £20 million Industrial Biotechnology Catalyst (IBC) scheme. The aim of the project is to achieve a step change in biopharmaceutical yield and quality by improving product stability during downstream processing (DSP). The program will focus on utilising Arecor's innovative and proprietary formulation technology platform. Arecor is the lead party in the consortium and has a proven track record of applying its formulation technology to develop superior liquid stable biopharmaceutical products including therapeutic proteins, peptides and novel format antibodies. In addition, the industrial bioprocessing experience and expertise of Fujifilm Diosynth Biotechnologies and CPI, will be employed to design predictive scaled down models to enable the implementation of Arecor's formulation platform to DSP and subsequent scale-up to large scale manufacturing. With a unique combination of expertise across the consortium, this collaboration is expected to deliver a novel formulation platform that can be applied to routine biopharmaceutical manufacturing to deliver significant improvements in the performance of DSP. Specific benefits being sought are improvements in yield, overall protein stability and quality. The platform will be applied to reduce the production costs of biopharmaceuticals, which will ultimately reduce the cost of therapeutics to healthcare providers. This aligns with the strategic objective of the IBC scheme to enhance the UK's position as a global leader in this sector.

nicholas.darton@arecor.com

Poster Abstract

Beware – 'equivalent' precast gels with different shelf-lives can give different gel profiles

Samantha Ide, Catherine Oliver, Sara Sefton

Vectura Group plc, Vectura House, Bumpers Way, Chippenham, Wiltshire, SN14 6FH, United Kingdom

Vectura is developing an immunomodulatory protein as a spray-dried powder formulation for delivery via a dry powder inhaler. A suite of analytical methods are required for analysis including SDS-PAGE to assess protein purity by detecting degradation products and aggregates. Development work was performed to improve a SDS-PAGE method which uses a Tris-Glycine gel with a short shelf-life by comparing alternative Tris-Glycine gels of identical percentage acrylamide gradient, but with a longer shelf-life. The longer shelf-life gels have modified chemistry to increase stability, but are intended to generate comparable results. The reduced sample profile on the longer shelf-life gels was not comparable to the short shelf-life gel profile as an extra band was observed, corresponding to the non-reduced protein molecular weight. Increasing the reducing agent concentration decreased the intensity of this band, suggesting that it was non-reduced protein. The addition of capping agent to stabilise reduced samples was investigated, but this had no effect on the amount of the extra band present. This supported the theory that the extra band was not caused by reformation of disulphide bonds during electrophoresis, but by protein which was not fully reduced prior to electrophoresis. The extra band was eliminated from long shelf-life gels by changing sample preparation conditions to give a more complete reduction of the protein. In summary, nominally equivalent gel products have produced markedly different profiles, highlighting the need for detailed comparison when introducing different gel products as absolute equivalence is of paramount importance in CMC applications.

samantha.ide@vectura.com

Poster Abstract

Experimental investigation and analysis of solvent additive effects on monoclonal antibody aggregation

Hans Kiefer, Olubukayo Oyetayo, Fabian Bickel, Martina Merg, Oscar Méndez-Lucio, Andreas Bender

Institute of Applied Biotechnology, Biberach University of Applied Sciences, Biberach, Germany (OO, FB, MM, HK) and Centre for Molecular Informatics, Department of Chemistry, University of Cambridge, United Kingdom (OM, AB)

Aggregates of biopharmaceutical proteins that form upon exposure to various stress conditions can adopt widely different molecular structures. Depending on the mechanism of formation, they also behave differently with respect to aggregation reversibility. We have established small-scale model experiments to produce aggregates of monoclonal antibodies (mAbs) by controlled shifts in pH or ionic strength as well as by exposure to various interfaces. Aggregate secondary and tertiary structure was analyzed by spectroscopic methods. Aggregation kinetics was shown to be highly reproducible and rate constants of nucleation and growth were extracted from kinetic traces. In an additive screen including compounds from three different substance classes, molecular descriptors were correlated with both aggregation rate constants and TM changes using a quantitative structure activity relationship (QSAR) approach. The analysis reveals a correlation between certain molecular properties such as relative and absolute surface polarity and the protective effect of additives tested. Negative correlation with some descriptors, i.e. destabilizing properties, were also identified. This approach will be extended to a larger compound set with the aim to obtain more detailed information, eventually enabling the design of improved additives.

kiefer@hochschule-bc.de

Poster Abstract

Assessing an interaction parameter for bioformulation stability in a single measurement: Exploiting concentration gradients from Taylor dispersion

Rachel Bott, Markos Trikeriotis, Seyi Latunde-Dada, Oksana I. Leszczyszyn

Malvern Instruments Ltd., Grovewood Road, Malvern, WR14 1XZ

The self-association characteristics of molecules in dilute solutions are thought to be good indicators of stability. One measure of the propensity for self-association is the diffusion interaction parameter (k_D). In existing methodologies the determination of this parameter requires several measurements to be undertaken over a concentration series, but here we show how this can be achieved in a single, low volume measurement using Taylor Dispersion Analysis (TDA). TDA is a fast and simple method for determining the diffusion coefficients of molecules in solution, which is achieved by monitoring the dispersion of a small plug of solute as it travels through a microcapillary. Dispersion of the solute plug results in a concentration profile, from which the k_D can be extracted by determining the solute's diffusion coefficients as a function of concentration. Here, we apply our method to solutions that display either positive or negative interaction parameters with resulting k_D values in good agreement with those from DLS measurements and literature values. In addition, we also demonstrate how the technique can be used to assess the stability of Lysozyme in a series of different buffers.

oksana.barker@malvern.com

Poster Abstract

Investigating the effects of flow on therapeutic protein aggregation

Leon F Willis

Astbury Centre for Structural Molecular Biology, Faculty of Biological Sciences, University of Leeds

Biopharmaceuticals are mainly protein-based drugs with therapeutic applications in diseases such as cancer and chronic inflammation. Unlike small-molecule drugs, therapeutic proteins can lose efficacy by unfolding, mis-folding and self-associating to form protein aggregates during their manufacture and storage. The hydrodynamic forces involved in some bioprocessing steps, e.g. nanofiltration and vial-filling, have been linked to therapeutic protein aggregation. However, the lack of clarity regarding the type of fluid flow (e.g. shear or extensional) responsible for bringing about damage to proteins means the link between hydrodynamic forces and protein aggregation remains tenuous.

Using a custom-made device, we have subjected two model monoclonal antibodies (mAbs) to stress under extensional flow. The hydrodynamic forces the proteins experience is analogous to those found in the bioprocessing arena. Following stress, the mAb solutions were biophysically characterised using Dynamic Light Scattering (DLS), Nanoparticle Tracking Analysis (NTA), Transmission Electron Microscopy (TEM) and UV-Visible spectroscopy. Our results show that one of the mAbs aggregates to a much greater extent under extensional flow than the other, despite sharing very high sequence homology. Furthermore, their behaviour is markedly different when their formulation is changed, with significantly less aggregation observed under equivalent flow conditions. Our studies could potentially inform the selection of new, aggregation-resistant mAb-based therapies during the drug development process.

bslfwi@leeds.ac.uk

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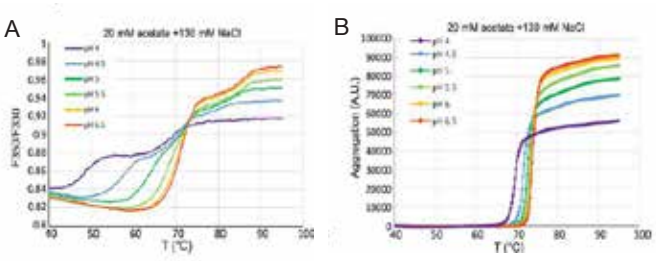

Conformational stability and aggregation of a mAb under different buffer conditions.

(A) Thermal unfolding monitored by detection of shifts in the fluorescence ratio (F350/F330)

(B) Aggregation detected by changes in backreflection in dependence of different buffer pH values

Contact us for further information:

NanoTemper Technologies, Ltd.
Sheraton House, Castle Park
Cambridge, UK
CB3 0AX
Phone: +44 1223 370033
E-Mail: info@nanotemper.co.uk

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List of Participants

This list only includes delegates who wished to be listed

Laura Arkle	CPI	laura.arkle@uk-cpi.com
Oksana Barker	Malvern Instruments	oksana.barker@malvern.com
Aurélien Baudot	Isogen Life Science	aurelien.baudot@isogen-lifescience.com
Andreas Bender	University of Cambridge	ab454@cam.ac.uk
Joanne Broadhead	Freeline Therapeutics	joanne.broadhead@freelinetx.com
Liz Carpenter	University of Oxford	liz.carpenter@sgc.ox.ac.uk
Karen Coombes	Upperton	kcoombes@upperton.com
Joshua Cremin	Arecor	Joshua.Cremin@arecor.com
Nicholas J. Darton	Arecor	nicholas.darton@arecor.com
Alan Dickson	University of Manchester	alan.dickson@manchester.ac.uk
Charlotte Dodd	Malvern Instruments	charlotte.dodd@malvern.com
Joanne Flannelly	University of Manchester	joanne.flannelly@manchester.ac.uk
Christine Hallam	Porton Biopharma	christine.hallam@portonbiopharma.com
Stephen Harding	University of Nottingham	Steve.Harding@nottingham.ac.uk
Rebecca Horlock	Fujifilm Diosynth Biotechnologies Ltd	rebecca.horlock@fujifilm.com
James Humphrey	Croda Europe Ltd	james.humphrey@croda.com
Dan Jenkins	Adaptive Instruments	danjenkins@adaptive-instruments.com
Jan Jezek	Arecor	Jan.Jezek@arecor.com
Rose Keeling	Arecor	Rose.Keeling@arecor.com
Matt Kettle	Protein Simple	matt.kettle@proteinsimple.com
Hans Kiefer	Biberach University of Applied Sciences	kiefer@hochschule-bc.de
Anne-Laure Laine	MedImmune	lainean@medimmune.com
Julia Leach	CPI	julia.leach@uk-cpi.com
Richard Lewis	Biopharma Process Systems	rlewis@biopharma.co.uk
Daniel Lund	Unchained Labs	dan.lund@unchainedlabs.com
Jas Mahey	TA Instruments	jmahey@tainstruments.com
Rita Majithiya	GSK	rita.x.majithiya@gsk.com
Natalia Markova	Malvern Instruments	natalia.markova@malvern.com
Sharad Menon	LGC	sharad.menon@lgcgroup.com
Astrid Pappenberger	Roche	astrid.pappenberger@roche.com
James Parry	Unchained Labs	james.parry@unchainedlabs.com

List of Participants

This list only includes delegates who wished to be listed

Bernardo Perez-Ramirez	Genzyme	Bernardo.Perez-Ramirez@genzyme.com
Didier Pertuy	Sanofi	Didier.Pertuy@sanofi.com
Daniel Pettit	Fujifilm Diosynth Biotechnologies Ltd	daniel.pettit@fujifilm.com
Jorge Pinto	Arecor	Jorge.Pinto@arecor.com
Mary Phillips-Jones	University of Central Lancashire	mphillips-jones@uclan.ac.uk
Lea Pickering	Illumina	lpickering@illumina.com
Jade Powell	Marks & Clerk LLP	jpowell@marks-clerk.com
Ben Proudlove	Merrow Scientific Ltd	ben@merrowscientific.com
Rachael Rowlands-Jones	KTN	rachael.rowlandsjones@ktn-uk.org
Keith Sanderson	Xigo Nanotools Ltd	keith@xigonanotools.co.uk
NektariaServi	Surface Measurement Systems	nservi@surfacemeasurementsystems.com
Tejash Shah	GSK	tejash.2.shah@gsk.com
Vincent Smith	Illumina UK Ltd	vpsmith@illumina.com
Neil Stainton	Croda	neil.stainton@croda.com
Nia Stevens	GSK	nia.e.stevens@gsk.com
Cathy Styles	Unchained Labs	cathy.styles@unchainedlabs.com
Bowen Tian	University of Nottingham	bowen.tian@nottingham.ac.uk
Malgorzata Tracka	Polpharma Biologics	malgorzata.tracka@polpharma.com
Maria Walton	Malvern Instruments	maria.walton@malvern.com
Nicola Watts	Arecor	Nicola.Watts@arecor.com
Martin Westcott	LGC	martin.westcott@lgcgroup.com
Leon Willis	University of Leeds	bslfwi@leeds.ac.uk

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